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Congenital stationary night blindness: An analysis and update of genotype–phenotype correlations and pathogenic mechanisms

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ABSTRACT

Congenital stationary night blindness (CSNB) refers to a group of genetically and clinically heterogeneous retinal disorders. Seventeen different genes with more than 360 different mutations and more than 670 affected alleles have been associated with CSNB, including genes coding for proteins of the phototransduction cascade, those important for signal transmission from the photoreceptors to the bipolar cells or genes involved in retinoid recycling in the retinal pigment epithelium. This article describes the phenotypic characteristics of different forms of CSNB that are necessary for accurate diagnosis and to direct and improve genetic testing. An overview of classical and recent methods used to identify specific CSNB genotypes is provided and a meta-analysis of all previously published and novel data is performed to determine the prevalence of disease-causing mutations. Studies of the underlying molecular pathogenic mechanisms based on cell culture techniques and animal studies are outlined. The article highlights how the study of CSNB has increased understanding of the mechanisms of visual signalling in the retina, likely to prove important in developing future treatments for CSNB and other retinal disorders.

Contents

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1. Introduction

Congenital stationary night blindness (CSNB) refers to a genetically determined largely non-progressive group of retinal disorders that predominantly affect signal processing within photoreceptors, retinoid recycling in the retinal pigment epithelium (RPE) or signal transmission via retinal bipolar cells (Zeitz, 2007). CSNB is clinically and genetically heterogeneous. Patients often complain of night or dim light vision disturbance or delayed dark adaptation, but photophobia is also reported in a subgroup of patients. Some forms may be associated with other ocular signs such as poor visual acuity, myopia, nystagmus, strabismus and fundus abnormalities (Zeitz, 2007). The night vision disturbance may be overlooked since it is highly subjective especially for individuals living in an urban or well-lit environment. Vision problems may also be denied (Dryja, 2000). Scotopic vision is rarely tested routinely and CSNB is likely under-diagnosed by clinicians, confounding estimates of prevalence.

To our knowledge, the first individuals diagnosed with CSNB were the descendants of Jean Nougaret, who was born 1637 in southern France. Since then many clinicians and researchers have contributed to the understanding of different CSNB phenotypes, genetic causes and pathogenic mechanisms. The purpose of this article is to summarise these findings and to extend current knowledge by inclusion of novel data and interpretation.

2. Phenotypic characteristics of CSNB

2.1. Clinical classification

CSNB can be subdivided according to the pattern of inheritance which may be X-linked, autosomal recessive or autosomal dominant (see also: 3. CSNB genes and mutations). Fundus appearance may be normal or abnormal but in all cases the full field electroretinogram (FF-ERG) is critical for functional phenotyping and precise diagnosis.

2.1.1. Electroretinography

FF-ERG is a non-invasive technique which detects, using corneal electrodes, the electrical responses generated within the retina upon flash stimulation. It allows the distinction between generalised rod and cone system activity and between photoreceptor and inner retinal function. Standard recording procedures and recommendations are regularly updated by the International Society for Clinical Electrophysiology of Vision (ISCEV, http://www.iscev.org/, (Marmor et al., 2009)). Current recommendations include a minimum recording of five basic responses to flashes of light delivered by a Ganzfeld stimulator, required to evenly illuminate the maximal area of retina after mydriasis. Three basic responses are recorded after a minimum of 20 min of dark adaptation (DA; scotopic conditions) and two are recorded after at least 10 min of light adaptation (LA; photopic conditions) to a background luminance of 30 cd.m^{-2}. The dark-adapted dim flash ERG is recorded to a flash strength of 0.01 cd.s.m^{-2} which is below cone system threshold (named the DA 0.01 ERG). This ERG is dominated by a positive polarity b-wave generated mainly at the level of rod depolarizing bipolar cells (DBCs or rod ON-bipolar cells) (Hood and Birch, 1996; Robson and Frishman, 1995; Shiells and Falk, 1999). A brighter flash (3 cd.s.m^{-2}) is used to elicit the standard ERG (formerly called the combined or mixed rod-cone response; now named DA 3.0 ERG). The DA 3.0 ERG shows a negative a-wave, some of which is generated in the photoreceptors, followed by a larger positive b-wave, originating in the inner nuclear layer. There is a contribution from the dark-adapted cone system to the scotopic ERG a- and b-waves, which is proportionately reduced to brighter flashes. An additional dark-adapted ERG is therefore recommended by ISCEV in response to a 10 or 30 cd.s.m^{-2} flash (DA10.0 ERG or DA30.0 ERG respectively) to better demonstrate the a-wave and to give a better measure of generalised rod photoreceptor function (see for review

Table 1
Novel and known mutations implicated in congenital stationary night blindness.

Exon	Changes at DNA level	Changes at RNA or protein level	Frequency (dbSNP)	Exome variant server	Polyphen2	Sift	Mutation taster	Frequency (index cases)	Frequency (allele)	Different mutations	Comment	Reference or origin of clinical center
1.1: *GNAT1* (NM_144499.2)												
2	c.113G>A	p.Gly38Asp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs104893740	(Dryja et al., 1996)
4	c.386A>G	p.Asp129Gly	No	No	Probably damaging	Deleterious	Disease causing	1	2	1	arCSNB Riggs	(Naeem et al., 2012)
6	c.598C>G	p.Gln200Glu	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Szabo et al., 2007)
Sum								3	4	3		
1.2: *PDE6B* (NM_000283)												
4	c.772C>A	p.His258Asn	No	No	Probably damaging	Tolerated	Disease causing	1	1	1	rs121918582	(Gal et al., 1994a)
6	c.940_941ins GCTTCTCAGG AAATTGTCTTCT	p.Tyr314Cysfs*50	No	No	No	No	No	1	1	1		(Manes et al., 2014)
Sum								2	2	2		
1.3: *RHO* (NM_000539)												
1	c.269G>A	p.Gly90Asp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs104893790	(Rao et al., 1994)
1	c.281C>T	p.Thr94Ile	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs104893796	(al-Jandal et al., 1999)
4	c.875C>A	p.Ala292Glu	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs104893789	(Dryja et al., 1993)
4	c.884C>T	p.Ala295Val	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2008)
Sum								4	4	4		
1.4: *SLC24A1* (NM_004727.2)												
2	c.1613_1614del	p.Phe538Cysfs*23	No	No	No	No	No	1	2	1		(Riazuddin et al., 2010)
Sum								1	2	1		
1.5: *NYX* (AJ278865)												
1_2	Microdeletion	no	No	No	No	No	No	1	1	1		(Pusch et al., 2000)
2	Microdeletion	no	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
IVS2	c.37+1G>C	r.spl?	No	No	No	No	No	1	1	1		(Zito et al., 2003)
3	c.48_64del17nt	p.Leu18Argfs*91	No	No	No	No	No	1	1	1		(Zito et al., 2003)
3	c.65G>A	p.Trp22*	No	No	No	No	No	1	1	1		(Zeitz et al., 2009)
3	c.85_108del24nt	p.Arg29_Ala36del	No	No	No	No	No	8	8	1		(Bech-Hansen et al., 2000) and this study: Philadelphia and Michigan, USA
3	c.92G>C	p.Cys31Ser	No	No	Probably damaging	Deleterious	Disease causing	3	3	1	rs62637020	(Pusch et al., 2000)
3	c.92G>A	p.Cys31Tyr	No	No	Probably damaging	Deleterious	Disease causing	2	2	1		(Wang et al., 2012b) and this study: Leuven, Belgium
3	c.105C>A	p.Cys35*	No	No	No	No	No	2	2	1	rs62637021	(Pusch et al., 2000)
3	c.137T> G	p.Val46Gly	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Philadelphia, USA
3	c.140G>C	p.Arg47Pro	No	No	Probably damaging	Tolerated	Disease causing	1	1	1		This study: Nantes France
3	c.143G>A	p.Cys48Tyr	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2009)
3	c.149G>C	p.Arg50Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wang et al., 2012b)
3	c.169C>A	p.Pro57Thr	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2005a)
3	c.187G>T	p.Glu63*	No	No	No	No	No	1	1	1		(Zeitz et al., 2009)
3	c.191C>A	p.Ala64Glu	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2005a)
3	c.272T>A	p.Leu91Gln	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wang et al., 2012b)
3	c.281G>C	p.Arg94Pro	No	No	Probably damaging	Tolerated	Disease causing	1	1	1	rs104894910	(Xiao et al., 2006)
3	c.293T>C	p.Leu98Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Simonsz et al., 2009)
3	c.302_304delTCA	p.Ile101del	No	No	No	No	No	1	1	1		(Pusch et al., 2000)
3	c.302T>C	p.Ile101Thr	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs104894911	(Xiao et al., 2006)
3	c.339_353del15nt	p.Glu114_Ala118del	No	No	No	No	No	3	3	1		(Pusch et al., 2000; Zito et al., 2003) and this study: Paris, France
3	c.350T>C	p.Leu117Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Ghent, Belgium

3	c.350T>A	p.Leu117Gln	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Jerusalem, Israel
3	c.368T>G	p.Leu123Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Leuven, Belgium
3	c.425T>C	p.Leu142Pro	No	No	Probably damaging	Deleterious	Disease causing	2	2	1		This study: Montpellier, France and Jerusalem, Israel
3	c.427G>C	p.Ala143Pro	No	No	Probably damaging	Tolerated	Disease causing	1	1	1	rs62637023	(Pusch et al., 2000)
3	c.445_465dup	p.Ser149_Leu155dup	No	No	No	No	No	1	1	1		(Bech-Hansen et al., 2000)
3	c.452C>T	p.Pro151Leu	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637024	(Bech-Hansen et al., 2000)
3	c.482T>G	p.Leu161Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Paris, France
3	c.485G>C	p.Arg162Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Bijveld et al., 2013a)
3	c.518G>C	p.Arg173Pro	No	No	Probably damaging	Tolerated	Disease causing	1	1	1		(Zeitz et al., 2009)
3	c.524C>G	p.Pro175Arg	No	No	Probably damaging	Deleterious	Disease causing	5	5	1	rs62637025	(Pusch et al., 2000; Zeitz et al., 2009)
3	c.551T>C	p.Leu184Pro	No	No	Probably damaging	Deleterious	Disease causing	2	2	1	rs62637026	(Bech-Hansen et al., 2000)
3	c.559_560delinsAA	p.Ala187Lys	No	No	Possibly damaging	Tolerated	Disease causing	3	3	1		(Pusch et al., 2000)
3	c.556_618del50ins3nt	Frameshift with stop at codon 259	No	No	No	No	No	1	1	1		(Bech-Hansen et al., 2000)
3	c.557_558dup	p.Ala187Thrfs*162	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
3	c.573_574insATCGA_577delC	p.Gly192Ifs*86	No	No	No	No	No	1	1	1		This study: Montpellier, France
3	c.607C>T	p.Gln203*	No	No	No	No	No	2	2	1		(Zeitz et al., 2009) and this study: Paris, France
3	c.621_622ins9nt	p.Arg207_Leu208ins LeuLeuArg	No	No	No	No	No	2	2	1		(Bech-Hansen et al., 2000; Pusch et al., 2000)
3	c.628_629ins9nt	p.Arg209_Ser210ins CysLeuArg	No	No	No	No	No	1	1	1		(Bech-Hansen et al., 2000)
3	c.638T>A	p.Leu213Gln	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637028	(Bech-Hansen et al., 2000)
3	c.647A>G	p.Asn216Ser	No	No	Probably damaging	Deleterious	Disease causing	4	4	1		(Bech-Hansen et al., 2000; Zeitz et al., 2009; Zito et al., 2003)
3	c.695T>C	p.Leu232Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637030	Bech-Hansen et al., 2000
3	c.704T>C	p.Leu235Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Bijveld et al., 2013a)
3	c.732_743del12	p.Glu244_Ala247del	No	No	No	No	No	1	1	1	rs63749062	(Pusch et al., 2000)
3	c.770G>C	p.Arg257Pro	No	No	Benign	Deleterious	Disease causing	1	1	1		Rigaudière et al., 2012 http://lodel.irevues.inist.fr/oeiletphysiologiedelavision/?id=162#tocto3n14
3	c.782T>C	p.Leu261Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This Study: Ghent, Belgium
3	c.792C>G	p.Asn264Lys	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637032	(Bech-Hansen et al., 2000)
3	c.838C>T	p.Leu280Phe	No	No	Probably damaging	Deleterious	Disease causing	2	2	1		(Bijveld et al., 2013a)
3	c.848_849insAT	p.Tyr284Serfs*65	No	No	No	No	No	1	1	1		This study: Ghent, Belgium
3	c.854T>C	p.Leu285Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637033	(Bech-Hansen et al., 2000)
3	c.854T>G	p.Leu285Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Freiburg, Germany
3	c.855delG	p.Asp286Thrfs*62	No	No	No	No	No	3	3	1		(Leroy et al., 2009)
3	c.893T>C	p.Phe298Ser	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637034	(Bech-Hansen et al., 2000)
3	c.895C>T	p.Gln299*	No	No	No	No	No	1	1	1		(Zito et al., 2003)
3	c.920T>C	p.Leu307Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Pusch et al., 2000)
3	c.935A>G	p.Asn312Ser	No	No	Probably damaging	Deleterious	Disease causing	2	2	1	rs62637035	(Pusch et al., 2000)
3	c.1038G>T	p.Trp346Cys	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Paris, France
3	c.1040T>C	p.Leu347Pro	No	No	Probably damaging	Deleterious	Disease causing	2	2	1	rs62637036	(Pusch et al., 2000)
3	c.1049G>A	p.Trp350*	No	No	No	No	No	2	2	1	rs62637037	(Bech-Hansen et al., 2000)
3	c.1109G>T	p.Gly370Val	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs62637038	(Pusch et al., 2000)
3	c.1122_*11del	p.Gln375Leufs*77	No	No	No	No	No	2	2	1		(Zito et al., 2003)
3	c.1143_1155del	p.Ser382Valfs*7	No	No	No	No	No	1	1	1		This study, Tubingen, Germany
3	c.1309delC	p.Leu437Trpfs*123	No	No	No	No	No	1	1	1		(Zito et al., 2003)
3	c.1370_1387del18	p.Gln457_Ala463 delinsPro	No	No	No	No	No	1	1	1		(Zeitz et al., 2009)
3	c.1399_1400insGA	p.Leu467Argfs*17	No	No	No	No	No	1	1	1		This study: Paris, France
3	c.1429G>C	p.Gly477Arg	No	No	Benign	Tolerated	Polymorphism	1	1	1		(Wang et al., 2012b)

(*continued on next page*)

Table 1 (*continued*)

Exon	Changes at DNA level	Changes at RNA or protein level	Frequency (dbSNP)	Exome variant server	Polyphen2	Sift	Mutation taster	Frequency (index cases)	Frequency (allele)	Different mutations	Comment	Reference or origin of clinical center
3′UTR	Microdeletion	?	No	No	No	No	No	1	1	1		(Pusch et al., 2000)
Sum								102	102	69		
1.6: *GRM6* (NM_000843)												
1	c.3G>T	p.Met1? (Start loss)	No	No	No	No	No	1	2	1	Co-segregation and clinic to be done	This study, Brussels, Belgium
1	c.57_75dupl19	p.Leu26Valfs*169	No	No	No	No	No	0.5	1	1	rs63749063	(Zeitz et al., 2005b)
1	c.137C>T	p.Pro46Leu	No	No	Possibly damaging	Deleterious	Disease causing	0.5	1	1	rs62638197	(Zeitz et al., 2005b)
1	c.172G>C	p.Gly58Arg	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs62638198	(Zeitz et al., 2005b)
1	c.448G>A	p.Gly150Ser	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs62638202	(Dryja et al., 2005)
2	c.577delG	p.Val193Trpfs*16	No	No	No	No	No	1	2	1		(Sergouniotis et al., 2011b)
2	c.712C>T	p.Arg238*	No	No	No	No	No	1	2	1	rs199663175	(O'Connor et al., 2006; Sergouniotis et al., 2011b)
3	c.727dupG	p.Val243Glyfs*40	No	Eur. Am.: AC = 0.02% – Afr. Am.: AC = 0.00%	No	No	No	0.5	1	1		(Zeitz et al., 2005b)
3	c.824G>A	p.Gly275Asp	No	No	Probably damaging	Deleterious	Disease causing	1	2	1	het unclear	(Sergouniotis et al., 2011b; Zeitz et al., 2009)
5	c.1054C>T	p.Arg352Cys	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Sergouniotis et al., 2011b)
6	c.1214T>C	p.Ile405Thr	No	Eur. Am.: *G* = 0.03% – Afr. Am.: *G* = 0.00%	Possibly damaging	Deleterious	Disease causing	1	2	1	rs121434304	(Zeitz et al., 2007)
6	c.1227C/T>A/T	p.Tyr409*	No	No	No	No	No	0.5	1	1		(O'Connor et al., 2006)
6	c.1267T>C	p.Cys423Arg	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1	het unclear	(Wang et al., 2012b)
6	c.1336C>T	p.Arg446*	No	No	No	No	No	1	2	1		This study: Leeds, United Kingdom
8	c.1565G>A	p.Cys522Tyr	No	Eur. Am.: *T* = 0.01% – Afr. Am.: *T* = 0.00%	Probably damaging	Deleterious	Disease causing	1	2	1	rs62638208	(Zeitz et al., 2005b)
8	c.1861C>T	p.Arg621*	No	Eur. Am.: *A* = 0.05% – Afr. Am.: *A* = 0.00%	No	No	No	1	2	1	rs62638214	(Dryja et al., 2005)
8	c.2029C>T	p.Arg677Cys	*A* = 0.001/1	Eur. Am.: *A* = 0.00% – Afr. Am.: *A* = 0.02%	Probably damaging	Deleterious	Disease causing	1	2	1	rs138551288	(Sergouniotis et al., 2011b)
8	c.2030G>A	p.Arg677His	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Sergouniotis et al., 2011b)
8	c.2062delC	p.Pro689Leufs*24	No	No	No	No	No	0.5	1	1		(Sergouniotis et al., 2011b)
8	c.2122C>T	p.Gln708*	No	No	No	No	No	1	2	1	rs62638624	(Dryja et al., 2005; Sergouniotis et al., 2011b)
8	c.2267G>A	p.Gly756Asp	No	No	Benign	Deleterious	Disease causing	1.5	3	1		(Malaichamy et al., 2014; Sergouniotis et al., 2011b)
9	c.2341G>A	p.Glu781Lys	No	No	Probably damaging	Deleterious	Disease causing	1	2	1	rs62638625	(Dryja et al., 2005)
Sum								18	36	22		
1.7: *TRPM1* (NM_002420.4)												
2	c.1-27C>T (70 + TRPM1) or c.40C>T (92 + TRPM1)	5'UTR expression defect or p.Arg14Trp	No	No	No	No	No	1	2	1		(Audo et al., 2009)

2-7	chr15: 31355203-31391647del	No functional protein	No	No	No	No	No	2	4	1		(van Genderen et al., 2009) and this study: Philadelphia, USA
IVS2	c.18-3C>T	r.spl?	No	No	No	No	No	0.5	1	1		(Nakamura et al., 2010)
3	c.20G>A	p.Cys7Tyr	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		This study: Leeds, United Kingdom
3	c.31C>T	p.Gln11*	No	No	No	No	No	0.5	1	1		(Audo et al., 2009)
3	c.83delA	p.Asn28Metf*62	No	No	No	No	No	0.5	1	1		(van Genderen et al., 2009)
4	c.215A>G	p.Tyr72Cys	No	Eur. Am.: C = 0.04% – Afr. Am.: C = 0.02%	Probably damaging	Deleterious	Disease causing	1.5	3	1	rs200514769	(Audo et al., 2009) and this study, Leuven, Belgium
4	c.220C>T	p.Arg74Cys	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Li et al., 2009; van Genderen et al., 2009)
4	c.296T>C	p.Leu99Pro	G = 0.001/2	Eur. Am.: G = 0.04% – Afr. Am.: G = 0.00%	Probably damaging	Deleterious	Disease causing	2	4	1	In one patient only 1 het rs191205969	(Audo et al., 2009; van Genderen et al., 2009) and this study: Philadelphia, USA
4	c.398C>A	p.Ala133Asp	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Malaichamy et al., 2014)
4	c.416delG	p.Gly139Valfs*10	No	No	No	No	No	0.5	1	1		(Li et al., 2009)
4	c.416G>T	p.Gly139Val	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Malaichamy et al., 2014)
IVS4	c.428-1G>C	r.spl?	No	No	No	No	No	1	2	1		(Bijveld et al., 2013a)
I VS4	c.428-3C>G	r.spl?	No	No	No	No	No	0.5	1	1		(Audo et al., 2009)
5	c.470C>T	p.Ser157Phe	A = 0.001/3	Eur. Am.: A = 0.32% – Afr. Am.: A = 0.10%	Probably damaging	Deleterious	Disease causing	0.5	1	1	Patient only het	This study: Paris, France
6	c.664G>A	p.Ala222Thr	No	No	Possibly damaging	Deleterious	Disease causing	0.5	1	1		This study: Philadelphia, USA
7	c.857C>T	p.Ser286Leu	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Malaichamy et al., 2014)
7	c.880A>T	p.Lys294*	No	No	No	No	No	1	2	1		This study, Jerusalem, Israel
7	c.897C>T	p.Gly299Gly	No	No	No	No	No	1.5	3	1	Splicing? one patient only het	This study, Brussels, Belgium
IVS8	c.1023+3_6delAAGT	r.spl?	No	No	No	No	No	0.5	1	1		(Nakamura et al., 2010)
9	c.1091T>G	p.Leu364Arg	No	Eur. Am.: C = 0.00% – Afr. Am.: C = 0.05%	Probably damaging	Deleterious	Disease causing	0.5	1	1		(van Genderen et al., 2009)
10	c.1197G>A	c.Pro399Pro/ r.spl?	No	No	No	No	No	0.5	1	1		(Audo et al., 2009)
12	c.1418G>C	p.Arg473Pro	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Audo et al., 2009)
13	c.1557G>T	p.Lys519Asn	No	No	Benign	Deleterious	Disease causing	1	2	1		This study, Monreal, Canada
14	c.1600G>A	p.Gly534Arg	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(van Genderen et al., 2009)
14	c.1622T>A	p.Met541Lys	No	No	Probably damaging	Deleterious	Disease causing	1	2	1	Audo et al., 2009, patient only het	(Audo et al., 2009; Bijveld et al., 2013a)
16	c.1832C>A	p.Pro611His	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(van Genderen et al., 2009)
16	c.1870C>T	p.Arg624Cys	No	No	Probably damaging	Deleterious	Disease causing	2.5	5	1		(Malaichamy et al., 2014; Nakamura et al., 2010)
16	c.1871G>A	p.Arg624His	No	Eur. Am.: T = 0.00% – Afr. Am.: T = 0.02%	Probably damaging	Deleterious	Disease causing	1.5	3	1		This study: Leeds, United Kingdom
16	c.1961A>C	p.His654Pro	No	No	Possible damaging	Tolerated	Disease causing	0.5	1	1	Patient only het but co-segregated with adcCSNB	(Audo et al., 2012b)
IVS16	c.2021+2T>C	r.spl?	No	No	No	No	No	1	2	1		(Li et al., 2009)
17	c.2083G>C	p.Ala695Pro	G = 0.007/16	Eur. Am.: G = 0.11% – Afr. Am.: G = 0.14%	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs138944426	This study: Gießen/Marburg, Germany

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Table 1 (*continued*)

Exon	Changes at DNA level	Changes at RNA or protein level	Frequency (dbSNP)	Exome variant server	Polyphen2	Sift	Mutation taster	Frequency (index cases)	Frequency (allele)	Different mutations	Comment	Reference or origin of clinical center
17	c.2128A>G	p.Thr710Ala	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		This study: Leuven, Belgium
IVS17	c.2250+1G>A	Absence of exon 17?/r.spl?	No	No	No	No	No	0.5	1	1	Patient only het	(van Genderen et al., 2009)
18	c.2322T>A	p.Tyr774*	No	No	No	No	No	0.5	1	1	patient only het	(Audo et al., 2009)
20	c.2567G>A	p.Trp856*	No	No	No	No	No	1.5	3	1	patient only het	(Audo et al., 2009)
20	c.2629C>T	p.Arg877*	No	No	No	No	No	1	2	1		This study: Jerusalem, Israel
20	c.2634+1G>A	r.spl?	No	No	No	No	No	0.5	1	1	Patient only het combined with silent mutation	(Audo et al., 2009)
21	c.2645C>A	p.Ser882*	No	No	No	No	No	0.5	1	1		(Nakamura et al., 2010)
21	c.2783G>A	p.Arg928Gln	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Malaichamy et al., 2014) and this study: Jerusalem, Israel
22	c.2951G>A	p.Arg984His	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		This study: Gieβen/Marburg, Germany
22	c.3004A>T	p.Ile1002Phe	No	Eur. Am.: $A = 0.01\%$ – Afr. Am.: $A = 0.00\%$	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Li et al., 2009)
IVS22	c.3061+1G>A	Absence of exon 22?/r.spl?	No	No	No	No	No	0.5	1	1		(van Genderen et al., 2009)
IVS23	c.3082+2dup	?	No	No	No	No	No	0.5	1	1		(Bijveld et al., 2013a)
24	c.3094G>T	p.Glu1032*	No	No	No	No	No	0.5	1	1		(Audo et al., 2009)
24	c.3105T>A	p.Tyr1035*	No	No	No	No	No	0.5	1	1		(Li et al., 2009)
24	c.3142G>A	p.Gly1048Ser	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Bijveld et al., 2013a)
24	c.3224T>C	p.Phe1075Ser	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Nakamura et al., 2010)
25	c.3326_3327insC	p.Pro1110Thrfs*39	No	No	No	No	No	1	2	1		(Malaichamy et al., 2014)
26	c.3491delA	p.Gln1164Argfs*31	No	No	No	No	No	0.5	1	1		(Audo et al., 2009)
27	c.3834C>T	p.Asn1278Asn/r.spl?	No	No	No	No	No	0.5	1	1	Patients has also splice site mutation	(Audo et al., 2009)
Sum								39.5	82	51		
1.8: *GPR179* (NM_001004334.2)												
1	c.187delC	p.Leu63Serfs*12	No	No	No	No	No	0.5	1	1		(Peachey et al., 2012b)
1	c.278delC	p.Pro93Glnfs*57	No	No	No	No	No	1	2	1		(Audo et al., 2012a)
1	c.376G>C	p.Asp126His	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Audo et al., 2012a)
1	c.479_501del	p.Leu160Profs*38	No	No	No	No	No	0.5	1	1		(Audo et al., 2012a)
1	c.598C>T	p.Arg200*	No	No	No	No	No	0.5	1	1		(Audo et al., 2012a)
1	c.659A>G	p.Tyr220Cys	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Peachey et al., 2012b)
2	c.870_871dup	p.Asn291Ilefs*43	No	No	No	No	No	0.5	1	1		This study: London, United Kingdom
3	c.984delC	p.Ser329Leufs*4	No	Eur. Am.: $A = 0.61\%$ – Afr. Am.: $A = 0.48\%$	No	No	No	1.5	3	1		(Audo et al., 2012a; Peachey et al., 2012b)
6	c.1364G>A	p.Gly455Asp	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Audo et al., 2012a)
6	c.1368del	p.Phe456Leufs*30	No	No	No	No	No	0.5	1	1		This study: London, United Kingdom
7	c.1376T>C	p.Val459Ala	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1	not clear	(Audo et al., 2012a)
IVS8	c.1784+1G>A	r.spl?	No	No	No	No	No	0.5	1	1		(Audo et al., 2012a)
9	c.1807C>T	p.His603Tyr	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Audo et al., 2012a)
9	c.1811C>T	p.Pro604Leu	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Malaichamy et al., 2014)
Sum								9.5	19	14		

1.9: *LRIT3* (NM_198506.4)												
4	c.983G>A	p.Cys328Tyr	No	Eur. Am.: $A = 0.01\%$ – Afr. Am.: $A = 0.00\%$	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Zeitz et al., 2013)
4	c.1151C>G	p.Ser384*	No	No	No	No	No	0.5	1	1		(Zeitz et al., 2013)
4	c.1318C>T	p.Arg440*	No	No	No	No	No	0.5	1	1		(Zeitz et al., 2013)
4	c.1538_1539del	p.Ser513Cysfs*59	No	No	No	No	No	0.5	1	1		(Zeitz et al., 2013)
1	c.345T>A	p.Asn115Lys	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		This study: Philadelphia, USA
Sum								3	6	5		
1.10: *CACNA1F* (AJ006216)												
2	c.148C>T	p.Arg50*	No	No	No	No	No	1	1	1		(Boycott et al., 2001)
2	c.151_155del AGAAA	p.Arg51Profs*65	No	No	No	No	No	1	1	1		(Wutz et al., 2002)
2	c.208C>T	p.Arg70Trp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Bijveld et al., 2013a)
2	c.220T>C	p.Cys74Arg	No	No	Probably damaging	Deleterious	Disease causing	2	2	1		(Simonsz et al., 2009; Wutz et al., 2002)
2	c.244C>T	p.Arg82*	No	No	No	No	No	6	6	1		(Boycott et al., 2001; Wutz et al., 2002; Zeitz et al., 2009) and this study Paris, France and Montpellier, France
2	c.245dup	p.Arg83Thrfs*35	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
2	c.245G>A	p.Arg82Gln	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Ghent, Belgium
2	c.263T>A	p.Ile88Asn	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Ghent, Belgium
3	c.281dup	p.Asp95Argfs*23	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
3	c.299T>C	p.Leu100Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Montpellier, France
3	c.299T>G	p.Leu100Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Leicester, United Kingdom
3	c.371dup	p.Asn124Lysfs*175	No	No	No	No	No	1	1	1		This study: Tübingen, Germany
IVS3	c.382-2A>G	r.spl?	No	No	No	No	No	1	1	1		(Boycott et al., 2001)
4	c.396C>A	p.Tyr132*	No	No	No	No	No	1	1	1		This study: Tübingen, Germany
4	c.413del	p.Phe138Serfs*65	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
4	c.448G>C	p.Gly150Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Weleber, 2002)
4	c.466_469del AGCGins34nt	p.Ser156_Ala157 delins12	No	No	No	No	No	3	3	1		(Boycott et al., 2001; Nakamura et al., 2003a; Nakamura et al., 2001)
4	c.469G>C	p.Ala157Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Bijveld et al., 2013a)
5–11	c.621_1392delins CTCATTG	p.Phe208_Leu1977 delins20	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
5	c.647T>G	p.Leu216Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Paris, France
6	c.685T>C	p.Ser229Pro	No	No	Probably damaging	Tolerated	Disease causing	1	1	1		(Wutz et al., 2002)
6	c.764G>A	p.Gly255Glu	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	Het carrier affected	(Michalakis et al., 2014)
6	c.796_797 delinsGAACTT	p.Thr266Glufs*34	No	No	No	No	No	1	1	1		This study: Paris, France
6	c.781G>A	p.Gly261Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wutz et al., 2002)
6	c.808del	p.Leu270Trpfs*25	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
7	c.832G>T	p.Glu278*	No	No	No	No	No	1	1	1		(Zito et al., 2003)
7	c.903_904insG	p.Arg302Alafs*13	No	No	No	No	No	1	1	1		(Nakamura et al., 2001)
7	c.926G>A	p.Gly309Asp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Tours, France
7	c.935delA	p.Asn312Thrfs*10	No	No	No	No	No	1	1	1		(Zeitz et al., 2009)
7	c.943_945delAAC	p.Asn315del	No	No	No	No	No	2	2	1		This study: Freiburg, Germany and Paris, France
7	c.945_947delCTT	p. Phe318del	No	No	No	No	No	1	1	1		(Boycott et al., 2001)

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Table 1 (*continued*)

Exon	Changes at DNA level	Changes at RNA or protein level	Frequency (dbSNP)	Exome variant server	Polyphen2	Sift	Mutation taster	Frequency (index cases)	Frequency (allele)	Different mutations	Comment	Reference or origin of clinical center
7	c.973C>T	p.Gln325*	No	No	No	No	No	1	1	1	NGS	(Audo et al., 2012b)
7	c.985_986insC	p.Met329Thrfs*18	No	No	No	No	No	1	1	1		This study: Paris France
7	c.1004_1009 delTGCTCT	p.Val335_Tyr337 delinsAsp	No	No	No	No	No	1	1	1		This study: Montpellier, France
8	c.1046G>A	p.Trp349*	No	No	No	No	No	2	2	1		(Simonsz et al., 2009) and this study: Freiburg, Germany
8	c.1075G>A	p.Gly359Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Simonsz et al., 2009)
8	c.1106G>A	p.Gly369Asp	No	No	Probably damaging	Deleterious	Disease causing	4	4	1	rs122456133	(Boycott et al., 2001; Strom et al., 1998; Wutz et al., 2002) and this study: Paris, France
IVS8_IVS46	c.1118+ 207_5472 +306del	p.Glu374Valfs*96	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
9	c.1135A>T	p.Arg379*	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
9	c.1213delC	Leu405Trpfs*28	No	No	No	No	No	2	2	1		(Bech-Hansen et al., 1998; Zito et al., 2003)
10	c.1282C>T	p.Gln428*	No	No	No	No	No	1	1	1		(Wutz et al., 2002)
IVS11	c.1463+1G>A	r.spl?	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
13	c.1504C>T	p.Arg502*	No	No	No	No	No	1	1	1		This study: Montpellier, France
IVS13	c.1651+1G>A	r.spl?	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
14	c.1761C>A	p.Cys587*	No	No	No	No	No	1	1	1		This study: Tübingen, Germany
14	c.1816C>T	p.Gln606*	No	No	No	No	No	1	1	1		This study, Montreal, Canada
IVS14	c.1877+2T>G	r.spl?	No	No	No	No	No	1	1	1		This study, Tübingen, Germany
14	c.1840C>T	p.Arg614*	No	No	No	No	No	3	3	1		(Boycott et al., 2001; Wutz et al., 2002) and this study: Strasbourg, France
14	c.1870G> A	p.Val624Ile	$T = 0.003/5$	Eur. Am.: $T = 0.33\% -$ Afr. Am.: $T = 0.10\%$	Probably damaging	Tolerated	Polymorphism	1	1	1	rs141010716	(Weleber, 2002)
15	c.1954_1956del	p.Leu652del	No	No	No	No	No	1	1	1		(Wang et al., 2012b)
15	c.1988G>A	p.Gly663Asp	No	No	Probably damaging	Deleterious	Disease causing	2	2	1		(Boycott et al., 2001; Nakamura et al., 2001)
15	c.2038C>T	p.Arg680*	No	No	No	No	No	3	3	1		(Zeitz et al., 2009; Zeitz et al., 2005a) and this study: Montpellier, France
16	c.2090T> C	p.Leu697Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	het carrier affected	(Michalakis et al., 2014)
17	c.2213del	p.Leu738Argfs*2	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
17	c.2225T>G	p.Phe742Cys	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wutz et al., 2002)
17	c.2234T>C	p.Ile745Thr	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	rs122456136	(Hemara-Wahanui et al., 2005)
IVS17	c.2288+1G>A	r.spl?	No	No	No	No	No	1	1	1		This study: Tübingen, Germany
IVS17	c.2288+5G>T	r.spl?	No	No	No	No	No	1	1	1		This study: Montpellier, France
IVS19	c.2387-1G>C	r.spl?	No	No	No	No	No	1	1	1		(Wutz et al., 2002)
IVS20	c.2544-1G>A	r.spl?	No	No	No	No	No	2	2	1		This study: Paris, France
IVS20	c.2544-2A>T	r.spl?	No	No	No	No	No	1	1	1		This study: Tübingen, Germany
21	c.2546T>C	p.Leu849Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wutz et al., 2002)
21	c.2590_2591del	p.Asn864Serfs*16	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)

21	c.2650C>T	p.Arg884*	No	No	No	No	No	6	6	1	rs122456135	(Bech-Hansen et al., 1998; Boycott et al., 2001; Zeitz et al., 2005a) and this study Lille, France, Brussel, Belgium and Paris, France
IVS21	c.2674-2_2674-3delCA	r.spl?	No	No	No	No	No	1	1	1		(Wutz et al., 2002)
IVS22	c.2733+1G>C	r.spl?	No	No	No	No	No	1	1	1		(Nakamura et al., 2001)
23	c.2747G>C	p.Gly916Ala	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Bijveld et al., 2013a)
23	c.2750C>A	p.Ala917Asp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Boycott et al., 2001)
23	c.2779A>G	p.Ser927Gly	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Tübingen, Germany
23	c.2789A>C	p.Asn930Thr	No	No	Possibly damaging	Deleterious	Disease causing	1	1	1		This study: Tübingen, Germany
23	c.2796_2797delinsCT	p.Leu932_Asp933delinsPheTyr	No	No	No	No	No	1	1	1		This study: Montpellier, France
23	c.2797G>T	p.Asp933Tyr	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2009)
23	c.2821dup	p.Leu941Profs*115	No	No	No	No	No	1	1	1	het carrier affected	(Michalakis et al., 2014)
24	c.2872C>T	p.Arg958*	No	No	No	No	No	3	3	1	rs122456134	(Strom et al., 1998; Zeitz et al., 2009) and this study: Freiburg, Germany
24	c.2881C>T	p.Arg961*	No	No	No	No	No	1	1	1		(Zito et al., 2003)
24	c.2899C>T	p.Arg967*	No	No	No	No	No	6	6	1		(Bijveld et al., 2013a; Nakamura et al., 2002; Strom et al., 1998; Zeitz et al., 2009) and this study: Gießen/Marburg, Germany and Paris, France
IVS24	c.2928+1G>A	r.spl?	No	No	No	No	No	1	1	1	First thought SNP, but female carriers show also phenotype	(Boycott et al., 2001; Michalakis et al., 2014; Zeitz et al., 2009)
25	c.2968G>A	p.Gly990Arg	No	No	Probably damaging	Deleterious	Disease causing			1		(Wang et al., 2012b)
25	c.2973_2975delCAT	p. Ile992del	No	No	No	No	No	1	1	1		(Boycott et al., 2001)
25	c.3019G>A	p.Gly1007Arg	No	No	Probably damaging	Deleterious	Disease causing	5	5	1		(Wutz et al., 2002; Zeitz et al., 2009) and this study: 2x Ghent, Belgium and Leuven, Belgium
26	c.3088_3089+2delAAGT	p.Lys1030Glyfs*25 r.spl?	No	No	No	No	No	1	1	1		This study: Paris, France
27	c.3118delG	p.Asp1040Thrfs*26	No	No	No	No	No	1	1	1		(Boycott et al., 2001)
27	c.3133dup	p.Leu1045Profs*11	No	No	No	No	No	5	5	1	rs80359870	(Bech-Hansen et al., 1998; Boycott et al., 2001; Strom et al., 1998) and this study: Tübingen, Germany and Gießen/Marburg, Germany
27	c.3145C>T	p.Arg1049Trp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Strom et al., 1998)
27	c.3203T>C	p.Leu1068Pro	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wutz et al., 2002)
28	c.3308C>A	p.Ser1103*	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
28	c.3400G>A	p.Glu1134Lys	No	Eur. Am.: $T = 0.00\%$ – Afr. Am.: $T = 0.05\%$	Probably damaging	Deleterious	Disease causing	1	1	1	rs138447882	(Zeitz et al., 2009)
28	c.3407del	p.Glu1136Glyfs*41	No	No	No	No	No	1	1	1		This study: Montpellier, France
29	c.3458C>A	p.Ala1153Asp	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Montpellier, France
29	c.3471_3472delGC	p.Gln1157His*25	No	No	No	No	No	1	1	1		(Zeitz et al., 2009)
30	c.3640delC	p.Leu1214Serfs*42	No	No	No	No	No	1	1	1		(Bech-Hansen et al., 1998)

(*continued on next page*)

Table 1 (*continued*)

Exon	Changes at DNA level	Changes at RNA or protein level	Frequency (dbSNP)	Exome variant server	Polyphen2	Sift	Mutation taster	Frequency (index cases)	Frequency (allele)	Different mutations	Comment	Reference or origin of clinical center
30	c.3658_3669del	p.Gly1220_Thr1223del	No	No	No	No	No	2	2	1		(Bech-Hansen et al., 1998; Wutz et al., 2002)
30	c.3662T>G	p.Leu1221Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1	Aland Island Eye Disease?	This study: Montpellier, France
31	c.3718_3792+54del	p.Thr1240_Asn1264 del r.spl?	No	No	No	No	No	1	1	1		This study: Jerusalem, Israel
31	c.3761G>T	p.Ser1254Ile	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2005a)
33	c.3853C>A	p.Arg1285Ser	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Zeitz et al., 2005a)
33	c.3853C>T	p.Arg1285Cys	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Paris, France
33	c.3862C>T	p.Arg1288*	No	No	No	No	No	3	3	1		(Bech-Hansen et al., 1998; Wutz et al., 2002; Zeitz et al., 2009)
IVS33	c.3942+2T>C	r.spl?	No	No	No	No	No	1	1	1		(Wutz et al., 2002)
IVS33	c.3942+2T>A	r.spl?	No	No	No	No	No	1	1	1		(Wutz et al., 2002)
35	c.4016G>T	p.Gly1339Val	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Lille, France
35	c.4042C>T	p.Gln1348*	No	No	No	No	No	1	1	1		(Strom et al., 1998; Wutz et al., 2002)
35	c.4051C>T	p.Arg1351*	No	No	No	No	No	1	1	1		This study: Ghent, Belgium
34-36	c.3943-?_c.4260+?	?	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
35	c.4091T>A	p.Leu1364His	No	No	Possibly damaging	Deleterious	Disease causing	2	2	1		(Strom et al., 1998; Zeitz et al., 2009)
IVS35	c.4101-1G>C	r.spl?	No	No	No	No	No	2	2	1		(Wutz et al., 2002) and this study: Montpellier, France
36	c.4226A>G	p.Tyr1409Cys	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study, Brussels, Belgium
37	c.4320G>A	p.Trp1440*	No	No	No	No	No	1	1	1		(Bech-Hansen et al., 1998)
37	c.4364G>T	p.Trp1455Leu	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Freiburg, Germany
38	c.4424T>C	p.Leu1475Pro	No	No	Probably damaging	Deleterious	disease causing	1	1	1		(Zeitz et al., 2009)
38	c.4433del	p.Ile1478Thrfs*23	No	No	No	No	No	1	1	1		This study, Nantes, France
38	c.4441C>G	p.Pro1481Ala	No	No	Probably damaging	Deleterious	Disease causing	3	3	1		(Zeitz et al., 2009) and this study: 2x Ghent, Belgium
38	c.4447G>A	p.Gly1483Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		This study: Lille, France
38	c.4462T>C	p.Cys1488Arg	No	No	Probably damaging	Deleterious	Disease causing	1	1	1		(Wutz et al., 2002)
38	c.4466C>G	p.Pro1489Arg	No	No	Probably damaging	Deleterious	Disease causing	3	3	1		(Simonsz et al., 2009; Wutz et al., 2002)
IVS38	c.4485+2T>A	r.spl?	No	No	No	No	No	1	1	1		This study: Brussels, Belgium
39	c.4490T>C	p.Leu1497Pro	No	No	Probably damaging	Deleterious	Disease causing	2	2	1		(Wutz et al., 2002; Zeitz et al., 2009)
39	c.4547_4549delinsCC	p.Leu1516Profs*9	No	No	No	No	No	1	1	1	het carrier affected	(Michalakis et al., 2014)
39	c.4548delC	p.Phe1517Leufs*8	No	No	No	No	No	1	1	1		(Jacobi et al., 2003)
IVS39	c. 4590-2A>G	r.spl?	No	No	No	No	No	1	1	1		(Boycott et al., 2001)
41	c.4735C>T	p.Gln1579*	No	No	No	No	No	1	1	1		This study: Paris, France
41	c.4771A>T	p.Lys1591*	No	No	No	No	No	1	1	1		(Strom et al., 1998)
41	c.4812delC	p.Ala1605Profs*144	No	No	No	No	No	1	1	1		This study: Nantes, France
45	c.5304_5305insG	p.Tyr1769Val*36	No	No	No	No	No	1	1	1		(Bijveld et al., 2013a)
46	c.5446C>T	p.Arg1816*	No	No	No	No	No	2	2	1		(Wutz et al., 2002) and this study: Ghent, Belgium
47	c.5632delC	p.His1878Metfs*43	No	No	No	No	No	1	1	1		(Boycott et al., 2001)
Sum								176	176	126		
1.11: *CABP4* (NM_145200.3)												
1	c.81_82insA	p.Pro28Thrfs*4	No	No	No	No	No	4	8	1		(Aldahmesh et al., 2010; Khan et al., 2013)
1	c.154C>T	p.Arg52*	No	No	No	No	No	1	2	1		This study: Gießen/Marburg, Germany

2	c.370C>T	p.Arg124Cys	*T* = 0.001/1	Eur. Am.: *T* = 0.03% – Afr. Am.: *T* = 0.02%	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs121917828	(Zeitz et al., 2006)
4	c.646C>T	p.Arg216*	No	Eur. Am.: *T* = 0.01% – Afr. Am.: *T* = 0.00%	No	No	No	1	2	1	rs150115958	(Littink et al., 2009)
6	c.800_801delAG	p.Glu267Valfs*92	No	Eur. Am.: C = 0.01% – Afr. Am.: C = 0.00%	No	No	No	1.5	3	1		(Zeitz et al., 2006)
Sum								8	16	5		
1.12: *CACNA2D4* (NM_172364)												
25	c.2406C>A	p.Tyr802*	No	Eur. Am.: *T* = 0.08% – Afr. Am.: *T* = 0.07%	No	No	No	1	2	1	rs71454844	(Wycisk et al., 2006a,b)
25	c.2452C>T	p.Arg818Cys	No	No	Probably damaging	Tolerated	Polymorphism	0.5	1	1	unclear	(Zeitz et al., 2009)
Sum								1.5	3	2		
1.13: *RDH5* (NM_001199771.1)												
2	c.71_74del	p.Leu24Profs*36	No	No	No	No	No	3	6	1		(Pras et al., 2012)
2	c.95delT	p.Phe32Serfs*29	No	No	No	No	No	0.5	1	1		(Schatz et al., 2010)
2	c.98T>A	p.Ile33Asn	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Ruther et al., 2004)
2	c.98T>C	p.Ile33Thr	No	Eur. Am.: C = 0.01% – Afr. Am.: C = 0.00%	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs146059919	(Sergouniotis et al., 2011c)
2	c.103G>A	p.Gly35Ser	No	No	Probably damaging	Deleterious	Disease causing	2.5	5	1	rs62638182	(Nakamura et al., 2000; Wada et al., 2001)
2	c.124C>T	p.Arg42Cys	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Niwa et al., 2005)
2	c.129del	p.Leu44Trpfs*17	No	No	No	No	No	1	2	1	rs62638183	(Driessen et al., 2000)
2	c.160C>T	p.Arg54*	No	No	No	No	No	7	14	1	Buchara, Iraq, Morocco, Iran = Jewish from different ethnicity	(Pras et al., 2012)
2	c.175T>A	p.Cys59Ser	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Wang et al., 2012a)
2	c.211_214dup	p.Ala72Glyfs*15	No	No	No	no	No	0.5	1	1		(Driessen et al., 2000)
2	c.218C>T	p.Ser73Phe	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs62638185 not clear which patients are new	(Nakamura et al., 2003b; Yamamoto et al., 1999)
2	c.285G>A	p.Trp95*	No	No	No	No	No	0.5	1	1		(Wang et al., 2012a)
IVS2	c.310+1G>A	r.spl?	No	No	No	No	No	0.5	1	1		(Sergouniotis et al., 2011c)
3	c.319G>C	p.Gly107Arg	No	No	Probably damaging	Deleterious	Disease causing	2.5	5	1	rs62638186	(Hotta et al., 2003; Nakamura et al., 2000; Sato et al., 2004)
3	c.346G>C	p.Gly116Arg	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Sergouniotis et al., 2011c)
3	c.347_348insCAG	p.Gly116_Ile117insSer	No	No	No	No	No	1	2	1	Nomenclature after LOVD	Sergouniotis et al., 2011b)
3	c.382G>A	p.Asp128Asn	No	Eur. Am.: *A* = 0.01% – Afr. Am.: *A* = 0.00%	Probably damaging	Deleterious	Disease causing	2.5	5	1		(Iannaccone et al., 2007; Pras et al., 2012; Schatz et al., 2010)
3	c.394G>A	p.Val132Met	*A* = 0.001/1	No	Probably damaging	Deleterious	Polymorphism	1.5	3	1	rs62638187	(Nakamura et al., 2000; Nakamura et al., 2004a; Niwa et al., 2005)
3	c.416G>T	p.Gly139Val	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Sergouniotis et al., 2011c)

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Table 1 (*continued*)

Exon	Changes at DNA level	Changes at RNA or protein level	Frequency (dbSNP)	Exome variant server	Polyphen2	Sift	Mutation taster	Frequency (index cases)	Frequency (allele)	Different mutations	Comment	Reference or origin of clinical center
3	c.469C>T	p.Arg157Trp	No	Eur. Am.: $T = 0.00\%$ – Afr. Am.: $T = 0.02\%$	Probably damaging	Deleterious	Disease causing	1.5	3	1	rs104894374	(Cideciyan et al., 2000; Ruther et al., 2004)
3	c.470G>A	p.Arg157Gln	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Hajali et al., 2009; Sergouniotis et al., 2011c)
3	c.490G>T	p.Val164Phe	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Yamamoto et al., 2003)
3	c.500G>A	p.Arg167His	No	Eur. Am.: $A = 0.01\%$ – Afr. Am.: $A = 0.02\%$	Probably damaging	Deleterious	Disease causing	0.5	1	1	rs199877211	(Sekiya et al., 2003)
3	c.530T>G	p.Val177Gly	No	No	Probably damaging	Deleterious	Disease causing	1	2	1	rs104894373 (more familial fleck retina with night blindness … ?)	(Hayashi et al., 2006; Kuroiwa et al., 2000)
4	c.572G>A	p.Arg191Gln	No	Eur. Am.: $A = 0.00\%$ – Afr. Am.: $A = 0.02\%$	Probably damaging	Tolerated	Disease causing	0.5	1	1	only het	(Pras et al., 2012)
4	c.625C>T	p.Arg209*	No	Eur. Am.: $T = 0.02\%$ – Afr. Am.: $T = 0.00\%$	No	No	No	1	2	1		(Schatz et al., 2010)
4	c.689_690 delinsGG	p.Pro230Arg	No	No	Benign	Tolerated	Disease causing	0.5	1	1		(Wang et al., 2008)
4	c.710A>C	p.Tyr237Ser	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Sergouniotis et al., 2011c)
4	c.712G>T	p.Gly238Trp	$T = 0.001/2$	No	Probably damaging	Deleterious	Disease causing	6	12	1	founder mutation Japan	(Gonzalez-Fernandez et al., 1999; Hajali et al., 2009; Iannaccone et al., 2007; Schatz et al., 2010; Sergouniotis et al., 2011c; Yamamoto et al., 1999)
4	c.718dup	p.Ala240Glyfs*19	No	No	No	No	No	0.5	1	1	rs62638192	(Nakamura et al., 2000)
4	c.718del	p.Ala240Profs*7	No	No	No	No	No	1	2	1		(Makiyama et al., 2014)
5	c.791T>G	p.Val264Gly	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Hirose et al., 2000)
5	c.801C>G	p.Cys267Trp	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1		(Driessen et al., 2000)
5	c.824_825delGA	p.Arg275Profs*60	No	No	No	No	No	1	2	1		(Sergouniotis et al., 2011c)
5	c.833G>A	p.Arg278Gln	No	No	Probably damaging	Deleterious	Disease causing	0.5	1	1	Only het	(Pras et al., 2012)
5	c.839G>A	p.Arg280His	No	No	Probably damaging	Deleterious	Disease causing	5	10	1	rs62638193 Founder mutation in Japan	(Gonzalez-Fernandez et al., 1999; Kuroiwa et al., 2000; Miyazaki et al., 2001; Nakamura et al., 2000; Nakamura et al., 2004a; Niwa et al., 2005; Sato et al., 2004)
5	c.841T>C	p.Tyr281His	No	No	Probably damaging	Deleterious	Disease causing	1.5	3	1	rs62638194	Nakamura et al., 2000, Nakamura et al., 2002, Niwa et al., 2005
5	c.880G>C	p.Ala294Pro	No	Eur. Am.: C = 0.01% – Afr. Am.: C = 0.00%	Probably damaging	Tolerated	Disease causing	1	2	1	rs111033593	(Gonzalez-Fernandez et al., 1999; Schatz et al., 2010)

5	c.928delinsGAAG	p.Leu310delins GluVal	No	No	No	No	No	28	56	1	Founder mutation in Japan Hayashi et al., 2006: more familial fleck retina with night blindness… ?	(Hayashi et al., 2006; Hirose et al., 2000; Makiyama et al., 2014; Nakamura et al., 2000; Nakamura and Miyake, 2002; Niwa et al., 2005; Sato et al., 2004; Sekiya et al., 2003; Wada et al., 2000; Wang et al., 2008)
5	c.955T>C	p.*319Argext*32	No	No	No	No	No	0.5	1	1		Sergouniotis et al., 2011a,b,c
Sum								80	161	40		
1.14: *RLBP1* (NM_000326.4)												
5	c.346G>C	p.Gly116Arg	No	No	Probably damaging	Tolerated	Disease causing	0.5	1	1		(Naz et al., 2011)
6	c.452G>A	p.Arg151Gln	No	No	Probably damaging	Tolerated	Disease causing	1	2	1	rs137853290 published p.Arg150 Gln	(Katsanis et al., 2001)
6	c.466C>T	p.Arg156*	No	No	No	No	No	0.5	1	1		(Naz et al., 2011)
Sum								2	4	3		
1.15: *RPE65* (NM_000329.2)												
IVS1	c.11+5G>A	r.spl?	No	Eur. Am.: $T = 0.02\%$ – Afr. Am.: $T = 0.05\%$	No	No	No	0.5	1	1	rs61751276	(Schatz et al., 2011)
4	c.344T>C	p.Ile115Thr	No	No	Probably damaging	Tolerated	Disease causing	0.5	1	1		(Schatz et al., 2011)
Sum								1	2	2		
1.16: *SAG* (NM_000541)												
2	Microdeletion		No	No	No	No	No	0.5	1	1		(Huang et al., 2012)
8	c.523C>T	p.Arg175*	No	No	No	No	No	0.5	1	1		(Nakamura et al., 2004b)
8	c.577C>T	p.Arg193*	No	Eur. Am.: $T = 0.04\%$ – Afr. Am.: $T = 0.00\%$	No	No	No	1.5	3	1	rs201153410	(Huang et al., 2012; Maw et al., 1998)
11	c.874C>T	p.Arg292*	No	No	No	No	No	2	4	1		(Nakamura et al., 2004b; Sergouniotis et al., 2011a)
11	c.916G>T	p.Glu306*	No	No	No	No	No	2	2	1		(Waheed et al., 2012)
11	c.926delA	p.Asn309Thrfs*12	No	No	No	No	No	16	31	1	founder mutation in Japan once het	(Fuchs et al., 1995; Fujinami et al., 2011; Saga et al., 2004; Yoshii et al., 1998)
Sum								21.5	42	6		
1.17: *GRK1* (NM_002929.2)												
1	c.614C>A	p.Ser205*	No	No	No	No	No	1	2	1		(Azam et al., 2009)
2	c.971delT (previously c.1079delT)	p.Leu324Argfs*62	No	No	No	No	No	1	2	1		(Oishi et al., 2007)
3	microdeletion	?	No	No	No	No	No	1	2	1		(Zhang et al., 2005)
5	microdeletion	?	No	No	No	No	No	2	4	1		(Yamamoto et al., 1997)
5	c.1129G>C	p.Ala377Pro	No	No	Probably damaging	Deleterious	Polymorphism	0.5	1	1		(Godara et al., 2012)
5	c.1139T>A	p.Val380Asp	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Godara et al., 2012; Yamamoto et al., 1997)
5	c.1172C>A	p.Pro391His	No	No	Probably damaging	Deleterious	Disease causing	1	2	1		(Hayashi et al., 2007)
6	c.1411_1412del	p.Pro471Phefs*28	No	No				1	2	1		(Oishi et al., 2007)
7	c.1607_1610del CGGA	p.Asp537Valfs*7	No	No				0.5	1	1		(Yamamoto et al., 1997)
Sum								9	18	9		

on origins of ERG components (Frishman, 2006)). The slope of the isolated a-wave has been linked to the kinetics of rod phototransduction (Hood and Birch, 1990) and an approximation can be achieved using the DA 10.0 or 30.0 ERG. The brighter flash ERG may additionally be more sensitive to inner retinal dysfunction, manifest as a reduced ERG b/a ratio. Oscillatory potentials (DA 3.0 oscillatory potentials) on the ascending limb of the b-wave are usually examined after low frequency filtering and are at least partly generated by amacrine cells (Wachtmeister, 1998), also better seen to a brighter (DA 10.0 or DA 30.0) flash. Light adaptation saturates the rod system allowing specific cone system recordings. Photopic ERGs are recorded under conditions of light adaptation to a flash strength of 3 cd.s.m^{-2} (LA 3.0 ERG) at two temporal frequencies; 30 Hz and 2 Hz. The LA 3.0 30 Hz ERG is a steady-state response arising predominantly in the inner retina from the L- and M-cone systems, the S-cones being less sensitive to high temporal frequencies. The LA 3.0 ERG is a single flash response with an initial negative polarity a-wave followed by a positive polarity b-wave. Cellular origins of these components are different from those recorded under scotopic conditions: the photopic a-wave is generated by cone photoreceptor hyperpolarisation after light stimulation with an additional post-photoreceptoral contribution from OFF-bipolar cells (also called hyperpolarizing bipolar cells or HBCs) (Bush and Sieving, 1994, 1996). The photopic b-wave is generated from DBCs and HBCs through a push–pull mechanism (Shiells et al., 1981; Sieving et al., 1994; Stockton and Slaughter, 1989; Ueno et al., 2004). Additional non-standard recordings may be added to the minimum ISCEV protocol to further characterize retinal function. These include the use of prolonged dark adaptation, varied interstimulus intervals and intermediate flash strengths (Vincent et al., 2013). Scotopic red flash ERG allows assessment of both dark-adapted cone and rod system function and may aid interpretation of other ERGs, particularly when there is predominant rod or cone dysfunction. Short-wavelength stimulation may be used to better isolate the S-cone system (Arden et al., 1999) or long-duration stimulation (e.g. 200 ms) to better distinguish responses from the ON- and OFF-bipolar cone pathways (Audo et al., 2008; Sieving et al., 1994). The combination of ERG, fundus examination, and clinical findings allows comprehensive phenotyping and differential diagnosis that can help direct the genetic investigations.

2.2. Clinical characteristics of CSNB with largely normal fundus appearance

Patients with CSNB associated with normal fundi may be subdivided into Riggs (Riggs, 1954) and Schubert-Bornschein (Schubert and Bornschein, 1952) sub-types based on the FF-ERG findings.

2.2.1. Riggs-type of CSNB (Riggs, 1954) (CSNB with photoreceptor dysfunction)

Riggs reported a sporadic case of CSNB as well as two siblings most likely affected with autosomal dominant CSNB showing severely reduced scotopic responses, presumed to reflect residual dark-adapted cone function (Riggs, 1954). The ERG findings in this rare type of CSNB are characterized by decreased a-wave amplitude in response to bright flash under dark adaptation in keeping with rod photoreceptor dysfunction, and possible additional reduction of b/a ratio giving an electronegative waveform. Photopic ERGs are preserved consistent with normal cone system function. This should be distinguished from the Schubert-Bornschein type of ERG abnormalities in which scotopic a-wave amplitude is normal or minimally subnormal. In cases of Riggs-type CSNB, an electronegative waveform likely represents the dark-adapted cone system contribution to the bright flash ERG, exposed in the absence of rod function, similar to ERGs associated with sub-acute vitamin A deficiency (McBain et al., 2007). A similar ERG characteristic to bright flashes may be seen in healthy subjects under LA conditions (photopic hill phenomenon) (Rufiange et al., 2003; Wali and Leguire, 1992); the b-wave attenuates relative to the a-wave at high flash intensities due to progressive reduction of the ON-component and delay in the OFF-component (Ueno et al., 2004). The scotopic red flash ERG may be informative in Riggs-type CSNB by revealing preserved dark-adapted cone function and absent rod function, with a waveform that may be of short peak time and similar to that obtained using the bright white flash. Riggs-type ERGs have been reported in autosomal dominant and autosomal recessive forms of CSNB linked to gene defects in the rod phototransduction cascade and have a relatively mild phenotype, including night blindness but no high myopia, no nystagmus and normal photopic visual acuity. For these reasons, this form of CSNB may be overlooked although it is rare with few cases reported.

The above described functional abnormalities were historically reported in the large southern French pedigree of the Nougaret family, with dominantly inherited night blindness (Cunier, 1838). The first ERG report and ERGs subsequently described by Berson and co-workers in 1998 (Sandberg et al., 1998) and reviewed by Dryja in 2000 (Dryja, 2000) suggested complete loss of rod function (De Rouck et al., 1956). Patients have normal visual acuity, visual fields, colour vision and normal fundus appearance but elevated final thresholds on dark adaptometry. A heterozygous missense mutation, p.Gly38Asp, in the gene encoding rod transducin alpha-subunit, *GNAT1* has been identified in the Nougaret family (Dryja et al., 1996) (see also: 3. CSNB genes and mutations) (Table 1.1). In 2007, Szabo and co-workers report a distinct mutation in *GNAT1*, p.Gln200Glu, underlying the same autosomal dominant phenotype in a Danish pedigree (Szabo et al., 2007) (Table 1.1). More recently, typical Riggs phenotype of autosomal recessive CSNB has been reported with a homozygous missense change in *GNAT1* in a consanguineous Pakistani pedigree (Naeem et al., 2012).

Another historical family of autosomal dominant Riggs-type CSNB was reported by Rambusch, a Danish surgeon in 1909 and fully assessed by Rosenberg et al. (1991). The CSNB phenotype of this large Danish “Rambusch family” is similar to the “Nougaret family” and a heterozygous missense mutation, p.His258Asn, in the gene encoding the beta subunit of the phosphodiesterase, *PDE6B*, has been reported (Gal et al., 1994a) (Table 1.2) (see also: 3. CSNB genes and mutations). More recently, Manes and co-workers reported a Riggs-type of CSNB with the same phenotype (i.e. normal daylight vision and prolonged dark adaptation) in association with a truncating mutation in *PDE6B* (Manes et al., 2014) (see also: 3. CSNB genes and mutations). Another autosomal dominant Riggs-type form of CSNB has been linked to mutations in rhodopsin, *RHO* (al-Jandal et al., 1999; Dryja et al., 1993; Rao et al., 1994; Sieving et al., 1995; Zeitz et al., 2008) (Table 1.3) (see also: 3. CSNB genes and mutations). The phenotype in these patients is similar to those in the “Nougaret family” although there are some reports of progression with age similar to rod-cone dystrophy (retinitis pigmentosa RP) (Dryja, 2000; Singhal et al., 2013). In addition, autosomal recessive Riggs-type of CSNB has been reported with a homozygous frameshift mutation in *SLC24A1* encoding a sodium–calcium exchanger (Riazuddin et al., 2010) (Table 1.4) (see also: 3. CSNB genes and mutations).

2.2.2. Schubert-Bornschein-type of CSNB (CSNB with bipolar cell dysfunction)

Schubert and Bornschein reported a form of CSNB in which the scotopic ERG a-wave was normal but the b-wave severely reduced giving an electronegative waveform (Schubert and Bornschein, 1952). This ERG phenotype reflects the underlying pathogenic

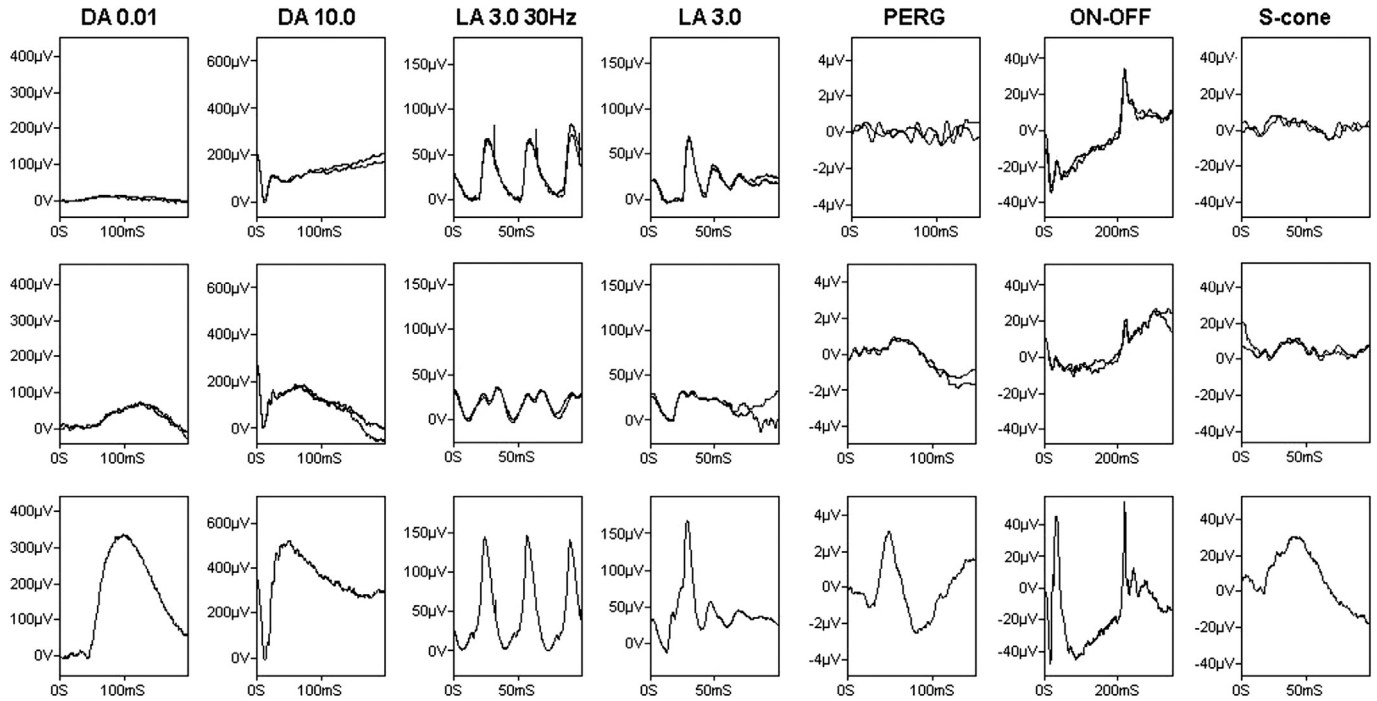

Fig. 1. Electrophysiological findings in complete and incomplete CSNB. The electrophysiological findings in complete (top row) and incomplete (middle row) CSNB and representative normal traces for comparison (bottom row). Full-field ERGs showed a high degree of inter-ocular symmetry and are shown for one eye only. Dark-adapted ERGs are shown for white flash strengths of 0.01 and 10.0 cd.s.m^{-2} (DA 0.01; DA 10.0), recorded after 25 min dark adaptation. Standard light-adapted full-field ERGs are shown for a flash intensity of 3.0 cd.s.m^{-2} (LA 3.0; 30 Hz and 2 Hz). ON–OFF ERG, S-cone ERG and pattern ERG (PERG) were performed as previously described (Audo et al., 2008).

mechanism, consistent with dysfunction occurring post-phototransduction and affecting signal transmission between photoreceptors and bipolar cells. Both autosomal recessive and X-linked inheritance forms have been reported. The "Schubert-Bornschein" or negative ERG is the most common type of ERG abnormality associated with CSNB. Miyake and co-workers in 1986 proposed a new classification dividing the subgroup of Schubert-Bornschein type of ERG into the complete and incomplete forms, respectively characterized by ON- or both ON- and OFF-bipolar pathway dysfunction (Miyake et al., 1987, 1986). Miyake further emphasized in 2002 that complete and incomplete CSNB are two distinct disorders with a good phenotype/genotype correlation (Miyake, 2002).

2.2.2.1. Complete form of Congenital Stationary Night blindness (cCSNB or CSNB1) (CSNB with ON-bipolar cell dysfunction). This form is characterized by specific full field ERG abnormalities in keeping with ON-bipolar dysfunction (Fig. 1). Under scotopic conditions, there is no detectable ERG to a dim flash (thus the term "complete") and there is an electronegative scotopic bright flash ERG (e.g. DA 3.0 or DA 10.0 ERG) with a normal a-wave and severely reduced b-wave (Fig. 1) (Miyake et al., 1986). Some mildly subnormal a-waves have been reported and this change may relate to myopia or be age-related (Dryja et al., 2005; Sergouniotis et al., 2011b). Under photopic conditions, the LA 3.0 30 Hz ERG, although often of normal amplitude may have a flattened trough and may show mild implicit time shift. The photopic single flash response (LA 3.0 ERG) frequently has normal a-wave amplitude but with a broadened trough; the waveform has a sharply rising b-wave with no oscillatory potentials and a mildly reduced b/a ratio (Fig. 1), although there is mild variability (Miyake et al., 1986; Sergouniotis et al., 2011b). These photopic ERG appearances are characteristic of loss of ON-pathway function with OFF-pathway preservation. This is confirmed by long-duration stimulation, which reveals an electronegative ON response but a normal OFF response (Fig. 1). The S-cone ERG b-wave is also markedly abnormal (Fig. 1) (Kamiyama et al., 1996; Sergouniotis et al., 2011b) consistent with S-cones connecting only to ON-bipolar cells (Kolb et al., 1997). It is of interest that a similar ERG phenotype is encountered in Melanoma-associated retinopathy (MAR), a rare acquired paraneoplastic syndrome generally associated with metastatic melanoma (Alexander et al., 1992; Berson and Lessell, 1988). Antibodies against TRPM1, one of the dysfunctional proteins in cCSNB (see also: 3. CSNB genes and mutations), have been identified in the serum of some patients affected with MAR (Dhingra et al., 2011; Kondo et al., 2011).

Complete CSNB can be inherited as an X-linked trait due to mutation in *NYX* (Bech-Hansen et al., 2000; Pusch et al., 2000) (Table 1.5) or as an autosomal recessive disorder with underlying mutations in *GRM6* (Table 1.6) (Dryja et al., 2005; Zeitz et al., 2005b), *TRPM1* (Audo et al., 2009; Li et al., 2009; van Genderen et al., 2009) (Table 1.7), *GPR179* (Audo et al., 2012a; Peachey et al., 2012b) (Table 1.8) or *LRIT3* (Zeitz et al., 2013) (Table 1.9), all gene products being localized at the dendritic tips of ON-bipolar cells (see also: 3. CSNB genes and mutations). It has been reported that the ERG intensity-response function to dark adapted 15 Hz flicker in patients with *NYX*, *TRPM1* and *GPR179* mutations differs from those with *GRM6* mutations (Klooster et al., 2013; Scholl et al., 2001; Zeitz et al., 2005b).

Patients with cCSNB typically have a history of congenital night blindness, have decreased visual acuity with a median of 0.30 logMAR (about 20/40) (Bijveld et al., 2013a), moderate to high myopia with a median refractive error of −7.4 D (Bijveld et al., 2013a) and nystagmus that tends to lessen with time. There may be a relative null-point with careful head positioning, which can often optimise visual acuity, as in patients with other causes of nystagmus (Pieh et al., 2008). Pieh and co-workers described the nystagmus as being dysconjugate and pendular with a lower amplitude and higher frequency than in idiopathic nystagmus; there is no distinction between the two Schubert-Bornschein types of CSNB and no clear distinction between other causes of nystagmus highlighting the importance of electrophysiology for diagnosis (Table 2). Strabismus is also frequently reported and

Table 2
Main differential diagnosis for CSNB with normal fundus appearance.

- **Of Night blindness**
  - *Inherited:*
    - Rod-cone dystrophies (also known as retinitis pigmentosa)
    - Choroideremia
    - Enhanced S cone syndrome allied disorders schoroideremia
  - *Acquired:*
    - Vitamin A deficiency
    - Paraneoplastic syndrome: melanoma-associated retinopathy characterized by an ON-bipolar defect with anti-TRPM1 antibodies found in the sera of some patients (Dhingra et al., 2011; Kondo et al., 2011; Morita et al., 2014; Xiong et al., 2013)
- **Of infantile nystagmus** (Gottlob and Proudlock, 2014; Pieh et al., 2008)
  - CSNB
  - Leber congenital amaurosis
  - Cone dysfunction syndrome, i.e. complete and incomplete achromatopsia
  - Oculocutaneous or ocular albinism
  - Foveal hypoplasia
  - Optic nerve hypoplasia
  - First manifestation of an early childhood intracranial tumour
  - Congenital cataract
  - Idiopathic motor nystagmus
- **Of electronegative ERG** (Audo et al., 2008)
  - *Inherited:*
    - Schubert-Bornschein type of CSNB
    - X-linked retinoschisis
    - Snowflake vitreoretinal degeneration
    - Autosomal Dominant Neovascular Inflammatory Vitreoretinopathy
    - Few reports of rod-cone or cone-rod dystrophies (reviewed in (Audo et al., 2008))
    - Juvenile Batten disease (Ceroid Neuronal Lipofuscinosis 3; CLN3)
    - Infantile Refsum disease
    - Mucolipidosis IV
    - Duchenne-Becker muscular dystrophy
  - *Acquired:*
    - Retinal ischemia due to central retinal artery occlusion or ischemic central vein occlusion
    - Some posterieor uveitis such as birdshot chorioretinopathy, diffuse unilateral subacute neuroretinitis
    - Melanoma-associated retinopathy and other autoimmune disorders
    - Retinal toxicity (e.g. vigabatrin, quinine toxicity, methanol toxicity, ocular siderosis)

should be recognized and managed to avoid additional amblyopia. Colour vision and visual fields are usually normal although there is one report of abnormal colour vision in cCSNB that may be coincidental (Tan et al., 2013). The fundus appearance is usually normal other than myopic changes although myopic maculopathy (Sergouniotis et al., 2011b), tilted disc and possible disc pallor (Heckenlively et al., 1983) have been documented. Using spectral domain Optical Coherence Tomography (SD-OCT), to study retinal structure, Godara and co-workers reported retinal thinning outside the foveal region in 3 patients with *GRM6* mutations due to changes in the inner retina, including the ganglion cell layer, with preservation of the outer retina (Godara et al., 2012). These data were compared to 93 controls although the authors do not mention whether the findings were compared to a myopic population. As far as we are aware, there are no other reports of SD-OCT in cCSNB, nor is there histological analysis of human cCSNB *post mortem* eyes and further studies are needed to confirm these findings.

Complete CSNB usually only affects visual function with no recognized associated systemic involvement whatever the underlying gene defect. However, cCSNB has been reported in patients with homozygous microdeletions on chromosome 15q13.3, a region that includes *TRPM1*. These patients usually display syndromic abnormalities with convulsive encephalopathy in which CSNB is often overlooked and a recent study outlines differences between this syndrome and neuronal ceroid-lipofuscinosis (Masurel-Paulet et al., 2014). A *CHRNA7* deletion has been identified as the genetic cause of the neurological phenotype in this microdeletion.

2.2.2.2. Incomplete form of Congenital Stationary Night blindness (icCSNB or CSNB2) (CSNB with ON- and OFF-bipolar cell dysfunction). The scotopic dim flash ERG is present in this form of CSNB (thus the term "incomplete") but of subnormal amplitude; there is a normal a-wave in the scotopic bright flash ERG, confirming normal rod phototransduction, but a reduced b-wave giving an electronegative waveform (Fig. 1) (Miyake et al., 1986). Photopic responses are more severely affected than in the complete form: the LA 30 Hz ERG is markedly subnormal and delayed with most having a distinctive bifid peak. The single-flash cone ERG is also markedly subnormal with a profoundly reduced b/a ratio such that the a- and b-wave are usually of similar size (Fig. 1). Long duration stimulation shows abnormalities in both ON and OFF responses (Fig. 1). Incomplete CSNB should be distinguished from cone dystrophies for which scotopic responses are usually relatively preserved, do not classically display an electronegative bright flash ERG, and usually have different photopic ERG waveforms. This distinction between icCSNB and cone dystrophy is however sometimes difficult. Some reports have shown possible progression of visual dysfunction in this subgroup with icCSNB gene defects associated with retinal degeneration (Aldahmesh et al., 2010; Hauke et al., 2013; Huang et al., 2013; Jalkanen et al., 2006; Nakamura et al., 2003a, 2002).

Incomplete CSNB is usually inherited as an X-linked trait with mutations in *CACNA1F* (Table 1.10) (Bech-Hansen et al., 1998; Strom et al., 1998) but more recently rare autosomal recessive cases have been reported with underlying mutations in *CABP4* (Table 1.11) (Zeitz et al., 2006) and possibly in *CACNA2D4* (Wycisk et al., 2006b) (Table 1.12). The phenotype of icCSNB is somewhat more heterogeneous than cCSNB particularly when associated with mutations in *CACNA1F* (Boycott et al., 2000) and patients may present with little or no night vision disturbances (Miyake, 2002). In a recent study, 54% of icCSNB patients reported night blindness that barely impacted on their daily life, compared to the night vision problems reported in 100% of cCSNB cases (Bijveld et al., 2013a, 2013b). Light sensitivity is more common in icCSNB being reported in 53% of cases versus 21% in cCSNB (Bijveld et al., 2013a). This difference was initially outlined by Miyake advocating for two distinct disorders (Miyake, 2002) and subsequently changes in nomenclature were proposed including CSNB1 and "congenital rod synaptic dysfunction" for cCSNB; CSNB2 and congenital rod-cone synaptic dysfunction" for x-linked icCSNB and "congenital cone synaptic dysfunction" for autosomal recessive icCSNB (Khan, 2014; Littink et al., 2009; Riemslag, 2009). The present authors suggest "post-phototransduction defect" or "transmission defect involving either ON- or ON-/OFF-bipolar pathways", which may better distinguish these disorders e.g. from photoreceptor dystrophies. However, the use of these terms may be difficult in routine clinical practice and is likely to become redundant given the increasing emphasis on genetic diagnosis and gene association. For clarity the terms icCSNB and cCSNB are used in the current article.

Patients with icCSNB have variable degree of refractive error from myopia to hyperopia, reported in 22% of cases; median of refractive error of −4.8 D (Bijveld et al., 2013a). Most of the few cases associated with *CABP4* mutations display high hyperopia whereas *CACNA1F* mutations are associated with more variable refractive errors (Bijveld et al., 2013a; Khan, 2014; Khan et al., 2013; Littink et al., 2009). Patients with icCSNB have various degrees of nystagmus and strabismus that require appropriate management, as in cCSNB. Visual acuity in icCSNB is lower than in cCSNB with a median of 0.52 logMAR (about 20/60) (Bijveld et al., 2013a). Visual fields are normal but colour vision may show variable defects unlike cCSNB (Bijveld et al., 2013a). Thus, patients with icCSNB may have more severe daylight symptoms than those with cCSNB, in keeping with involvement of both the cone ON- and OFF-bipolar systems. Interestingly, there is a clear

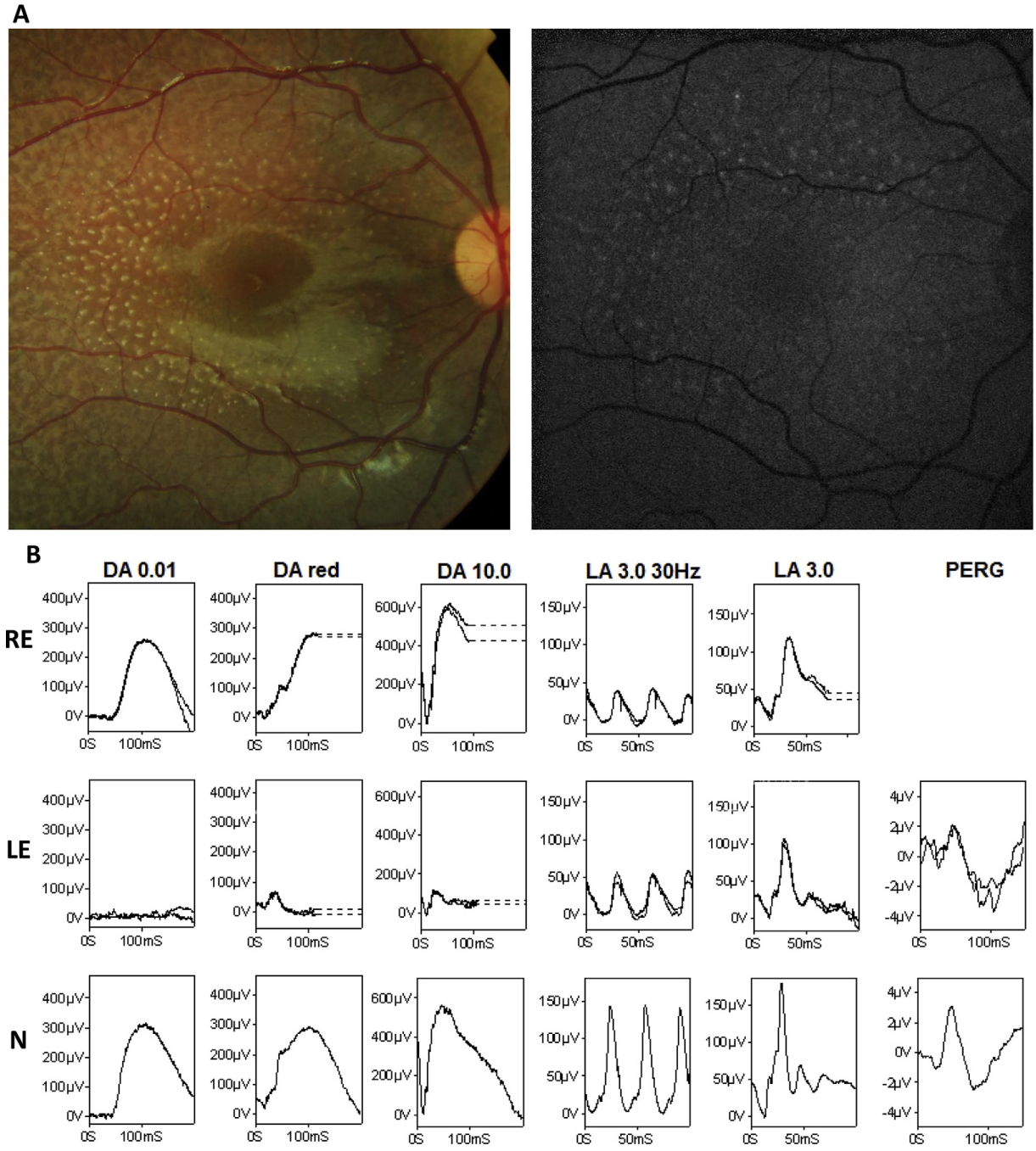

Fig. 2. Colour fundus photography, FAF, and electrophysiological findings in fundus albipunctatus. A) Fundus photograph and FAF image from the right eye of a 10-year-old South Asian patient with FA (homozygous mutation in *RDH5*; p.Gly238Trp). The whole FAF image is enhanced post-acquisition to visualize the low levels of background FAF intensity. B) Full-field ERGs from the right (top row; RE) and left (middle row; LE) eyes of the same patient at the age of 7 years and representative normal traces (bottom row; N). Broken lines replace blink artefacts. Scotopic ERGs are recorded after 25 min dark adaption (LE) or after overnight dark adaptation (RE). The left eye pattern ERG (PERG) was within normal limits. After 25 min DA the dim flash ERG (DA 0.01) was undetectable. Scotopic red flash ERG shows a clear cone component; the rod component was undetectable. The bright flash ERG (DA 10.0) a-wave showed severe reduction and the b-wave was subnormal and of short peak time. Photopic flicker ERGs were mildly reduced and delayed. The scotopic ERGs normalised after overnight dark adaptation of one eye (RE), confirming restoration of rod photoreceptor function and thus establishing the diagnosis. C) Fundus photograph and FAF image from the right eye of 55-year old white European man with myopia and compound heterozygous mutations in *RDH5* (p.Gly116Arg; p.Tyr237Ser). The patient presented with reduced vision in the left eye and had outer retinal abnormalities on OCT bilaterally (not shown). The fundus shows myopic changes; no flecks were detectable at the posterior pole or periphery of either eye. The whole FAF image is enhanced post-acquisition to visualize the abnormally low background intensity and better to reveal the irregular paracentral changes, present bilaterally. D) Full-field ERGs and pattern ERGs from the right (top row; RE) and left (middle row; LE) eyes of the patient and representative normal traces (bottom row; N). Broken lines replace blink artefacts that occur after the ERGs. Scotopic ERGs are recorded after 25 min dark adaption (RE) or after overnight dark adaptation (LE). The PERG is undetectable bilaterally consistent with macular dysfunction. After 25 min DA the right eye dim flash ERG (DA 0.01) was undetectable. Scotopic red flash ERG showed a clear cone component; the rod component was undetectable. The bright flash ERG (DA 10.0) a-wave showed severe reduction and the waveform had a low b/a ratio. Photopic LA 3.0 30 Hz ERGs were mildly reduced, probably consequent upon the eye closure noted during testing in this case. Single flash cone (LA 3.0) ERGs were normal bilaterally. The scotopic ERGs normalised after overnight dark adaptation (LE) in keeping with recovery of rod photoreceptor function. Reproduced with permission from Sergouniotis et al., Phenotypic variability in RDH5 Retinopathy (Fundus Albipunctatus). Ophthalmology. 2011; 118; 1661–1670.

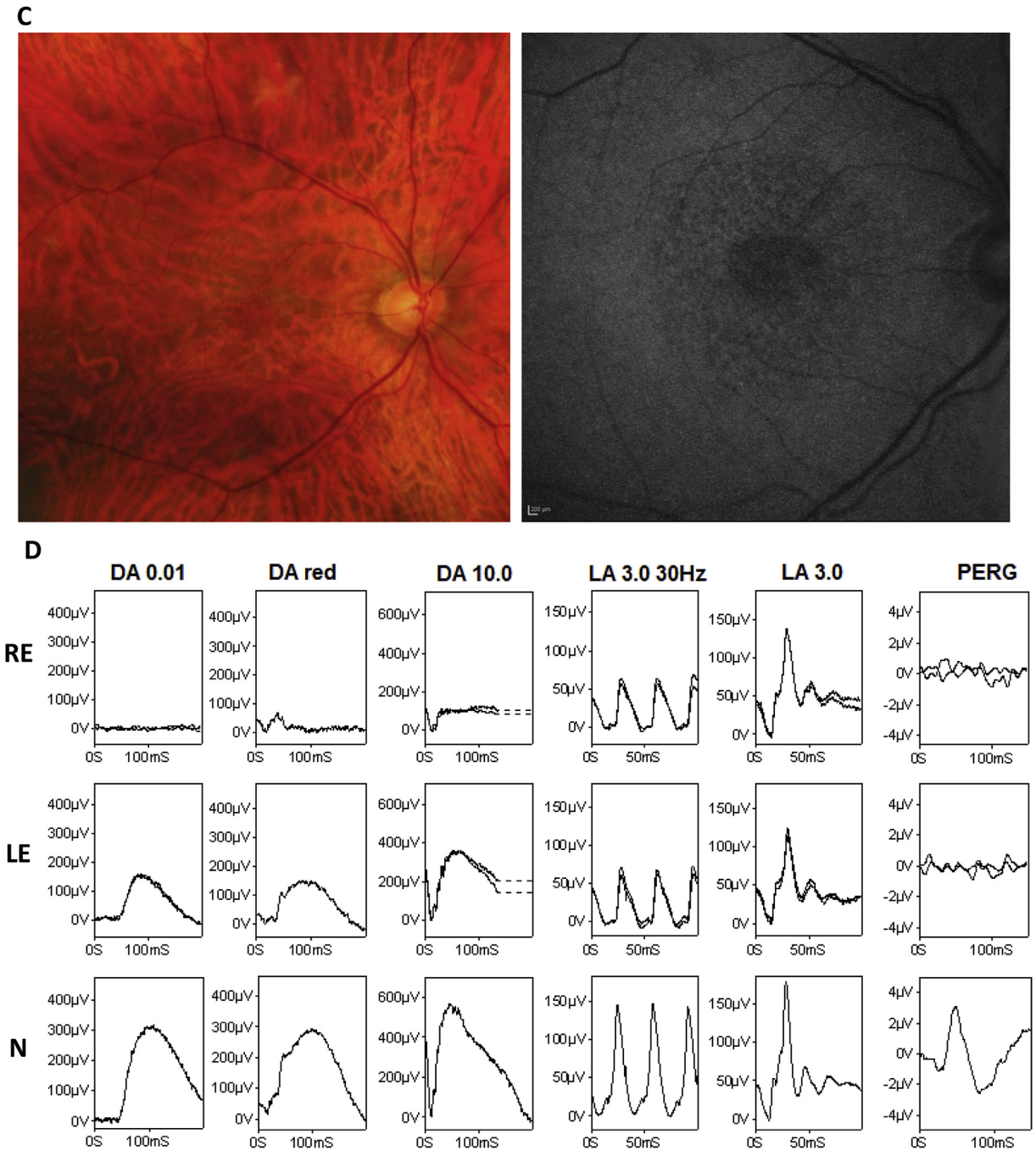

Fig. 2. (*continued*).

genotype–phenotype correlation, since so far genes involved in icCSNB affect proteins at the presynaptic level, impacting both ON- and OFF bipolar signalling, while cCSNB affects post synaptic ON-bipolar function.

Fundus examination is usually normal apart from myopic changes. However, changes in retinal architecture and thin retina have been reported. Chen and co-workers compared five cases of icCSNB including three with a confirmed nonsense mutation in *CACNA1F*, with myopic controls and showed thinning of the retinal ganglion cell layer, inner plexiform layer, inner nuclear layer and retinal pigment epithelium/photoreceptor outer segment complex nasal to the fovea (Chen et al., 2012). Furthermore abnormal synapses were present in the outer nuclear layer in a case of frameshift mutation in *CACNA1F* (Vincent and Heon, 2012). Two histological reports outlined normal photoreceptors and did not find abnormalities in other retinal layers (Vaghefi et al., 1978; Watanabe et al., 1986).

Female carriers of *CACNA1F* mutation are usually asymptomatic. However, a recent report described some functional abnormalities

Table 3
Differential diagnosis for CSNB with abnormal fundus appearance.

For Oguchi disease:
X-linked retinoschisis
Tapetal reflex of carrier of X-linked retinitis pigmentosa
X-linked cone dystrophy (Heckenlively and Weleber, 1986)
For fundus albipunctatus:
Retinitis punctata albescens (including Bothnia dystrophy)
Benign familial fleck retina
Vitamin A deficiency

suggesting that defects in this subgroup may be overlooked (Michalakis et al., 2014).

Tremblay and co-workers reported cortical visual evoked potentials (VEP) evidence of chiasmal misrouting in icCSNB patients, similar to that classically described in albinism (Tremblay et al., 1996). Those data were not supported by a later study, which reported VEP evidence of misrouting in three of twenty CSNB patients including two with *NYX* mutations and one other case with an x-linked pedigree (Ung et al., 2005). Further studies in larger CSNB cohorts are needed to establish the exact prevalence and significance of this type of abnormality.

An allelic variant of icCSNB with *CACNA1F* mutation is represented by Åland Island Eye Disease (AIED) (Table 1.10) also called Forssius-Eriksson Syndrome (Forsius and Eriksson, 1964b). This disorder was first reported in 1964 in a family from Åland Islands in the Bothnia Sea as a rare x-linked form of ocular hypopigmentation associated with iris transillumination, albinoid fundus, foveal hypoplasia, nystagmus, myopia, astigmatism, and dyschromatopsia (Forsius and Eriksson, 1964a,b) but no chiasmal misrouting (van Dorp et al., 1985). Mutations in *CACNA1F* have been reported in cases of AIED and also in a family combining cases of AIED and icCSNB suggesting that both disorders are linked to the same underlying gene defect but also that other genetic or environmental modifiers may influence the phenotypic expression (Jalkanen et al., 2007; Vincent et al., 2011; Wutz et al., 2002).

2.3. Clinical characteristics of CSNB with abnormal fundus appearance

This subgroup includes two autosomal recessive disorders; fundus albipunctatus and Oguchi disease (Table 3).

2.3.1. Fundus albipunctatus

Fundus albipunctatus (FA) is a recessively inherited disorder typically characterized by night blindness, delayed dark adaptation and distinct ocular fundus abnormalities associated with mutations in *RDH5* (Table 1.13) (3. CSNB genes and mutation) (Dryja, 2000; Yamamoto et al., 1999). Visual acuity, colour vision and visual fields are usually normal. Fundus examination usually reveals small white dots in the posterior pole and mid-periphery with sparing of the macular region (Fig. 2A). Fundus appearance may change with time from flecks in childhood to fine dots with age that may fade or increase over the years (Marmor, 1990; Sekiya et al., 2003; Yamamoto et al., 2003). There is no optic nerve pallor, no retinal blood vessel attenuation and no pigmentary bone spicule migration in the periphery. The fundus phenotype may resemble that associated with the early stages of retinitis punctata albescens (RPA; see below), a form of rod-cone dystrophy associated with similar white dots but progressive retinal degeneration with a worse visual prognosis (Table 3). There is phenotypic variability and one 55-year old patient has been described with normal fundus but night blindness and typical ERG abnormalities with genetically confirmed mutations in *RDH5* (Sergouniotis et al., 2011c) (Fig. 2C and D). The term RDH5 retinopathy may be more appropriate than FA in such cases.

FAF abnormalities are variable: isolated dots may appear hyperautofluorescent in young patients (Fig. 2A) and may be associated with normal or focal decrease in autofluorescence (Sergouniotis et al., 2011c; Wang et al., 2012a). In addition, the background level of autofluorescence intensity is severely decreased similar to patients carrying mutations in *RPE65*, (Lorenz et al., 2004; Schatz et al., 2010; Sergouniotis et al., 2011c) and in keeping with disruption of retinoid recycling. The white dots have been presumed to contain 11-*cis*-retinal precursors (Schatz et al., 2010). Additional FAF abnormalities have been reported including a crescent of increased autofluorescence in the inferior part of the retina (Sato et al., 2004) as well as a concentric parafoveal ring of relatively increased autofluorescence as seen in bull's eye maculopathy (Fig. 2C). On SD-OCT, white dots appear as focal lesions from the RPE/Bruch membrane complex to the inner limiting membrane with an additional decrease in outer nuclear layer thickness corresponding to photoreceptor nuclei (Sergouniotis et al., 2011c; Wang et al., 2012a).

The ERG changes in FA patients reflect the underlying pathophysiology (see also 5. CSNB disease mechanisms). RDH5 encodes retinol dehydrogenase, responsible for converting 11-*cis*-retinol into 11-*cis*-retinal in the RPE, and is thus involved in the recycling of rhodopsin. It is known that one feature of the disorder is delayed rhodopsin regeneration, and that patients are effectively "bleached" most of the time, but also that in most patients those rhodopsin levels normalise following extended dark adaptation, which may require an overnight timescale. The diagnosis cannot therefore be made purely by ISCEV standard ERGs as the recovery following extended DA needs to be demonstrated. The ISCEV-standard scotopic ERGs, performed after 20 min dark adaptation, reveal abnormalities that reflect the impaired regeneration of rhodopsin and may resemble those associated with Riggs-type of CSNB or Vitamin A deficiency, being dominated by cone function. The response to a dim flash under scotopic condition is undetectable or shows moderate to severe reduction; scotopic response to a bright flash shows a reduced a-wave with a low b/a ratio or electronegative shape. In most patients, unlike Riggs-type CSNB, prolonged dark adaptation typically results in significant or complete recovery of rod-mediated ERG amplitudes although there is phenotypic variability (Sergouniotis et al., 2011c). Photopic ERGs are mildly abnormal in about half of cases and often show flicker ERG delay (Fig. 2B). Several reports suggest that FA may progress with macular atrophy and cone dystrophy (Hotta et al., 2003; Nakamura et al., 2000; Nakamura et al., 2004a; Nakamura and Miyake, 2002; Nakamura et al., 2003b; Niwa et al., 2005; Sergouniotis et al., 2011c; Wada et al., 2001; Yamamoto et al., 2003). A recent report on adaptive optics also suggests a lower macular cone density with disruption in the regularity of macular cone mosaic spatial arrangement in FA (Makiyama et al., 2014). There is no clear correlation between the progressive cone degeneration and the underlying genetic defect, an important consideration when counselling patients. Dark adaptometry reveals prolonged cone and rod sensitivity recovery (Dryja, 2000).

A similar fundus phenotype has also been described in young patients with Bothnia dystrophy associated with mutations in *RLBP1* (Katsanis et al., 2001; Naz et al., 2011) (Table 1.14). In the early stages the white dots may be indistinguishable from those in FA but there is typical progression characterised by scalloped areas of atrophy that eventually encroach upon the posterior pole and there may be intra-retinal pigment migration. There is some overlap with the FA ERG phenotype but ERGs are usually more severely affected and either show limited recovery following overnight DA or require even longer DA to demonstrate recovery (Burstedt et al., 2008). In the advanced stages there may be a severe rod-cone dystrophy with irreversible ERG reduction. White dots have also been described in association with mutations in *RHO* (Souied et al., 1996) and *LRAT* (Littink et al., 2012) with severe progressive rod-cone disease in these instances that differentiate this phenotype from FA.

Similarly, a case of FA due to compound heterozygous mutations in *RPE65* has been reported (Schatz et al., 2011) (Table 1.15). However, in spite of ERG recovery following extended DA, the rod and cone-mediated ERGs had worsened since childhood. It is noted that

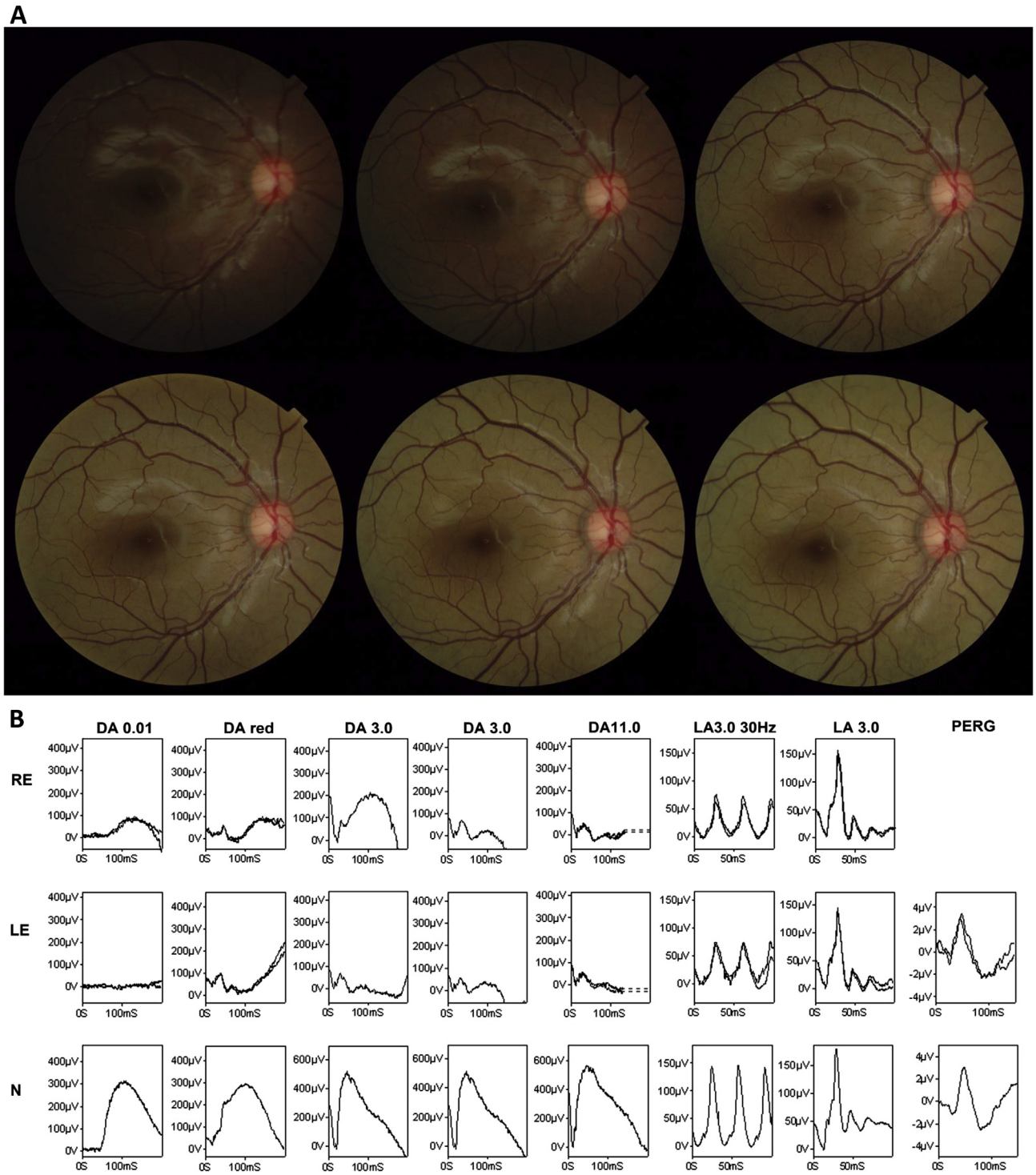

Fig. 3. Colour fundus photography and electrophysiological findings in Oguchi disease. A) Colour fundus photography of the posterior pole of the right eye using a non-mydriatic camera (TRC-NW65, Topcon, Itabashi, Tokyo, Japan) in a 6-year-old girl of South Asian ethnicity. After overnight (12-h) dark adaptation, a series of images were obtained over a 20 min interval. Disappearance of the golden reflex can be seen in the first image taken (top left). The golden colour gradually reappears after 10–15 flashes. Bottom right image is after 20 min and 32 flashes. B) Full-field ERGs from the right (RE) and left (LE) eyes of the patient and normal examples (N) for comparison. After 25 min dark adaptation, left eye rod ERGs (DA 0.01) were undetectable and bright flash ERGs (DA 3.0 and DA 11.0) had a waveform that resembled the early component of the red flash ERG, consistent with a dark-adapted cone system origin (McBain et al., 2007; Sergouniotis et al., 2011a). After overnight dark adaptation of the right eye, ERGs showed partial recovery but a second bright flash (DA 3.0; inter-stimulus interval 60s) resulted in marked ERG reduction. Light adapted ERGs (LA 3.0; 30Hz and 2Hz) revealed no evidence of generalised cone system dysfunction. The pattern ERG (PERG; left eye only) revealed no evidence of macular dysfunction. Reproduced with permission from Sergouniotis et al., Mizuo-Nakamura phenomenon in Oguchi disease due to a homozygous nonsense mutation in the SAG gene. Eye. 2011; 25; 1097–1098.

mutations in *RPE65* are usually associated with a more severe form of early-onset rod-cone dystrophy.

2.3.2. Oguchi disease

Oguchi disease (OD) was first described in a Japanese soldier complaining of night blindness (Oguchi, 1907). It is a rare autosomal recessive disorder characterized by a peculiar fundus characteristic known as the Mizuo-Nakamura phenomenon: the fundus has a golden-yellow discoloration that disappears after prolonged dark adaptation (Mizuo, 1913; Mizuo and Nakamura, 1914) (Fig. 3A). Mutations in *SAG* and *GRK1* (Tables 1.16 and 1.17) have been reported to underlie OD, both genes encoding proteins involved in the deactivation process of the phototransduction cascade (Fuchs et al., 1995; Yamamoto et al., 1997) (see 5. CSNB disease mechanisms). Patients affected with OD classically complain of congenital night blindness, but have normal visual acuity, colour vision and visual fields. The cone dark–adaptation curve is normal but there is delayed rod dark adaptation which eventually fully recovers (Carr and Ripps, 1967; Cideciyan et al., 1998). After 20 min of DA, scotopic FF ERGs reveal abnormalities that resemble the Riggs-type of CSNB, fundus albipunctatus and vitamin A deficiency, characterised by severe and selective rod photoreceptor dysfunction. There is an undetectable scotopic b-wave to a dim flash and there may be an electronegative scotopic response to a bright flash but with significant a-wave reduction (Carr et al., 1965), reflecting rod photoreceptor dysfunction. However, after prolonged dark adaptation, rod sensitivity recovers and the ERG response to a single flash has normal a- and b-waves (Gouras, 1970). The ERG response to a subsequent single bright flash is markedly attenuated (unlike fundus albipunctatus) and similar to that recorded after 20 min of DA. The abnormal desensitisation of the rod system to a repeated bright flash is caused by continued activation of the phototransduction cascade by rhodopsin molecules. This continues until all the chromophore is recycled, requiring a further extended period of DA. Fig. 3B shows typical FF ERGs (Sergounitis et al., 2011a). Photopic recordings usually reveal normal responses for both ON- and OFF-responses (Miyake et al., 1996) but abnormal cone responses have been reported in two siblings with mutations in *SAG* (Hayashi et al., 2011) or in *GRK1* (Hayashi et al., 2007). Although OD is considered as a stationary disorder, these reports and others suggest that it may progress to a photoreceptor degeneration (Azam et al., 2009; Maw et al., 1998; Nakamachi et al., 1998; Nakazawa et al., 1997, 1998).

Histological reports and more recently, high resolution retinal imaging have attempted to identify the defect underlying the Mizuo-Nakamura phenomenon: at least two pathological observations from Japanese groups suggest alterations between photoreceptors and the RPE (Kuwabara et al., 1963; Yamanaka, 1924). Further reports in light of modern imaging techniques gave additional insight to the precise structural abnormalities underlying the Mizuo-Nakamura phenomenon: imaging with a Helium-Neon Scanning Laser Ophthalmoscope revealed diffuse fine white dots under light adapted condition with their disappearance after four hours of dark adaptation suggesting putative abnormal material accumulating in the outer retina and/or the RPE (Usui et al., 2000). Subsequent reports applying SD-OCT did not support the hypothesis of abnormal material accumulation but suggested shortening of rod outer segment structures that may recover after dark adaptation (Hashimoto and Kishi, 2009; Sergouniotis et al., 2011a; Takada et al., 2011; Yamada et al., 2009). This was however not confirmed by Godara et al. (2012) who also reported normal photoreceptor mosaic in OD applying adaptive optics scanning laser ophthalmoscopy. Further studies are needed to better understand how a defect in rhodopsin deactivation leads to the Mizuo-Nakamura phenomenon. Of note, a similar fundus appearance has been reported in rare cases of X-linked retinoschisis and X-linked cone dystrophy (de Jong et al., 1991; Heckenlively and Weleber, 1986; Robson et al., 2009), although these disorders are associated with different ERG phenotypes.

3. CSNB genes and mutations

3.1. Gene identification strategies

CSNB is a group of genetically and clinically heterogeneous retinal disorders caused by mutations in seventeen identified genes (Table 1) with an unknown number yet to be identified. Genes mutated in patients with CSNB have been identified by different methods including classical linkage analysis with a combination of candidate gene and positional cloning approaches, autozygosity mapping, pure candidate gene approaches as well as by whole exome sequencing (WES).

Classical linkage approaches have identified four gene defects underlying CSNB: *PDE6B* (Gal et al., 1994a), *CACNA1F* (Bech-Hansen et al., 1998; Strom et al., 1998), *NYX* (Bech-Hansen et al., 2000; Pusch et al., 2000) and *SLC24A1* (Riazuddin et al., 2010) (Table 1). A limitation of this method is the requirement to examine large families. For example, the "Rambusch family" comprised more than 200 affected individuals across 11 generations (Rosenberg et al., 1991). Linkage analysis using restriction fragment length polymorphism and microsatellite markers in 69 persons (40 affected) identified in the mapped region a mutation in *PDE6B* as the cause of autosomal dominant CSNB (Gal et al., 1994a, 1994b). Similarly, many relatively large families have been used to decipher the genetic causes of x-linked CSNB: using fine mapping and clinical discrimination, based on electrophysiology two different loci, CSNB2 (e.g. Boycott et al., 1998) and CSNB1 (e.g. Berger et al., 1995; Pusch et al., 2001), were identified. Subsequently, two candidate genes (predicted function), present in the linked region, were cloned and confirmed the genetic cause of CSNB2 (*CACNA1F* (Bech-Hansen et al., 1998; Strom et al., 1998)) and CSNB1 (*NYX* (Bech-Hansen et al., 2000; Pusch et al., 2000)). More recently, linkage analysis in a large consanguineous family from the southern part of the Punjab province of Pakistan with 25 individuals participating in the study identified a mutation in the candidate gene *SLC24A1* (predicted function and expression in the retina) as the cause of this autosomal recessive form of CSNB (Riazuddin et al., 2010).

Candidate genes suggested by functional studies or animal models have led to the identification of eleven genes underlying this disorder: *RHO* (Dryja et al., 1993), *GNAT1* (Dryja et al., 1996), *SAG* (Fuchs et al., 1995), *GRK1* (Yamamoto et al., 1997), *RDH5* (Yamamoto et al., 1999), *RLBP1* (Katsanis et al., 2001) and *RPE65* (Schatz et al., 2011) represented good candidates because of their known role in the rod phototransduction cascade or in retinoid recycling in the RPE. For *GRM6* (Dryja et al., 2005; Zeitz et al., 2005b), *CABP4* (Zeitz et al., 2006), *CACNA2D4* (Wycisk et al., 2006b) and *TRPM1* (Audo et al., 2009; Li et al., 2009; van Genderen et al., 2009) animal models existed before the respective genes were associated with CSNB in patients (Fig. 4, as an example for a candidate gene approach leading to the identification of *TRPM1* mutations in patients with cCSNB (see also: 4. Animal models for CSNB). In addition, preliminary data of function and expression of the respective genes reinforced the hypothesis that these genes are implicated in CSNB (see also: 5. CSNB disease mechanisms). In another study a combination of autozygosity mapping in a consanguineous family of South Asian ethnicity using SNP arrays with a candidate approach led to the identification of the *TRPM1* gene defect (Li et al., 2009).

More recently, a WES approach identified two genes, *GPR179* and *LRIT3* underlying cCSNB (Audo et al., 2012a; Zeitz et al., 2013).

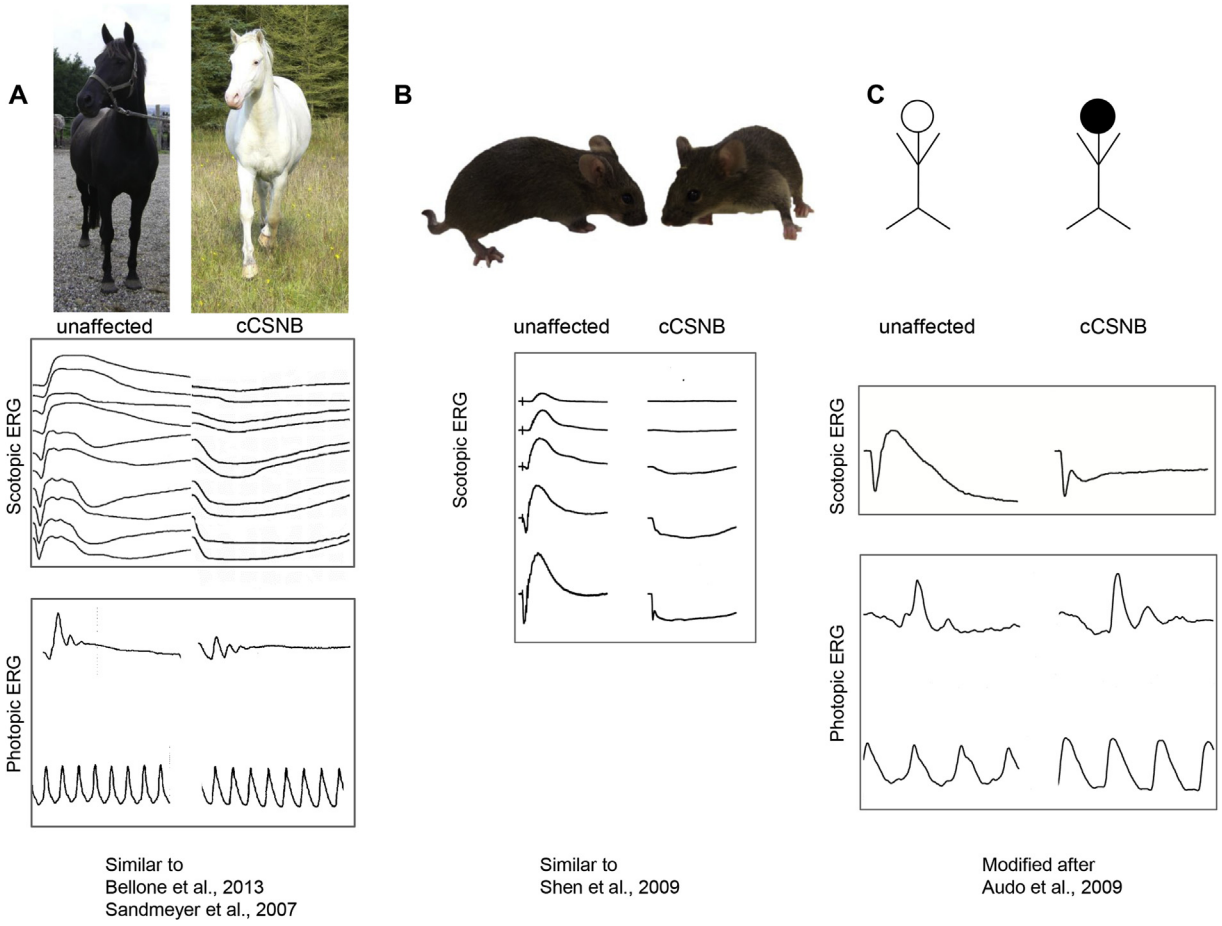

Fig. 4. Candidate gene identification comparing animal and patient phenotypes. This approach is illustrated for the identification of the gene defect *TRPM1* underlying cCSNB by comparing the ERG of an Appaloosa horse with cCSNB (Sandmeyer et al., 2007; Witzel et al., 1977; Witzel et al., 1978) and a mouse model for cCSNB with patients (Shen et al., 2009). A) Affected Appaloosa horses initially showed reduced vision in dim light conditions. The fundi of the affected animals were normal. Electrophysiological studies revealed a "negative ERG" resembling the cCSNB type of ERG response (C). The photopic responses of affected horses seemed to be less affected than the scotopic ERGs, a phenotype reminiscent of cCSNB (C) (Audo et al., 2009). Interestingly, association studies of the coat colouring in these horses revealed that this trait is directly linked with the CSNB phenotype (not the subject of this article, but further explained by Bellone and co-workers (Bellone et al., 2013). Expression analysis of genes linked to this disorder revealed that *TRPM1* was significantly downregulated in the retina and skin of affected horses. Thus, it was proposed that *TRPM1* is responsible for altering bipolar signalling as well as melanocyte function, causing both CSNB and the coat pattern phenotype in Appaloosa horses (Bellone et al., 2008). The horse-pictures were kindly provided by Rebecca Bellone, who obtained permission to publish from the owners of the horses. The ERG -panels are reproduced with permission from Sandmeyer and co-workers. Clinical and electroretinographic characteristics of congenital stationary night blindness in the Appaloosa and the association with the leopard complex. Vet Ophthalmol. 2007; 10:368–375. B) In addition, studies in mice lacking *Trpm1* revealed a severely reduced b-wave in ERG recordings, similar to cCSNB. The ERG-panel was kindly provided by Neil Peachey (C). Figure C was published in part by Audo et al., *TRPM1* is mutated in patients with autosomal-recessive complete congenital stationary night blindness. Am J Hum Genet. 2009:85:720–729 and reproduced here with permission.

The method is unbiased and only a few family members are necessary to identify the gene defect. Since WES detects all exonic and flanking intronic variants the "bottle-neck" of this approach is to identify "the" disease causing variant and data from other family members and filtering procedures are crucial. Other family members are always fundamental to validate the putative disease causing mutation by co-segregation analysis. This becomes even more important in less prevalent gene defects affecting only few families. Our group uses the following filtering program: we retain only variants if they appear with a Minor Allele Frequency (MAF) of $\leq$0.005 for a gene defect inherited as a recessive trait or $\leq$0.001 for a gene defect inherited as a dominant trait in dbSNP 137, HapMap (Altshuler et al., 2010), 1000 Genome (Abecasis et al., 2010), and Exome Variant Server (Tennessen et al., 2012). Priorities are then given to insertion/deletion, frameshift, nonsense and splice site variants. The latter variants are investigated with splice site prediction programs (e.g. http://www.fruitfly.org/seq_tools/splice.html (Reese et al., 1997)). Missense mutations are further analyzed applying pathogenic bioinformatic prediction (e.g. Sift, PolyPhen2) (Adzhubei et al., 2010; Ng and Henikoff, 2001) and conservation across species (http://genome.ucsc.edu/). Data filtering is performed according to disease status (co-segregation of the identified variant(s)) (Fig. 5, example for the identification of the *GPR179* gene defect in one family and a sporadic case). Furthermore we investigate *in house* available transcriptomic databases (collaboration with Dr Léveillard, within the department of genetics with its expression data from the *rd1* mouse model (Fig. 6A)), and publically available transcriptomic databases as such UniGene and a retinal expression database developed by Dr Roska and colleagues (Siegert et al., 2009; Siegert et al., 2012) (Fig. 6B) for putative retinal cell expression of the gene of interest (Fig. 6). For example, most of the genes implicated in cCSNB should reveal increased expression in the *rd1* mouse compared to the wild-type starting from post-natal day 12 (Fig. 6A, example shown for *Nyx*). The *rd1* mouse, carrying *Pde6b* mutations, is a naturally occurring model with progressive rod photoreceptor degeneration, leading to a complete loss of all rods by post-natal day 36, and preserved inner retina (Carter-Dawson et al., 1978). Therefore increased expression in *rd1* compared to wild-type mice suggests that the gene of interest is expressed in the inner retinal layer as expected for most

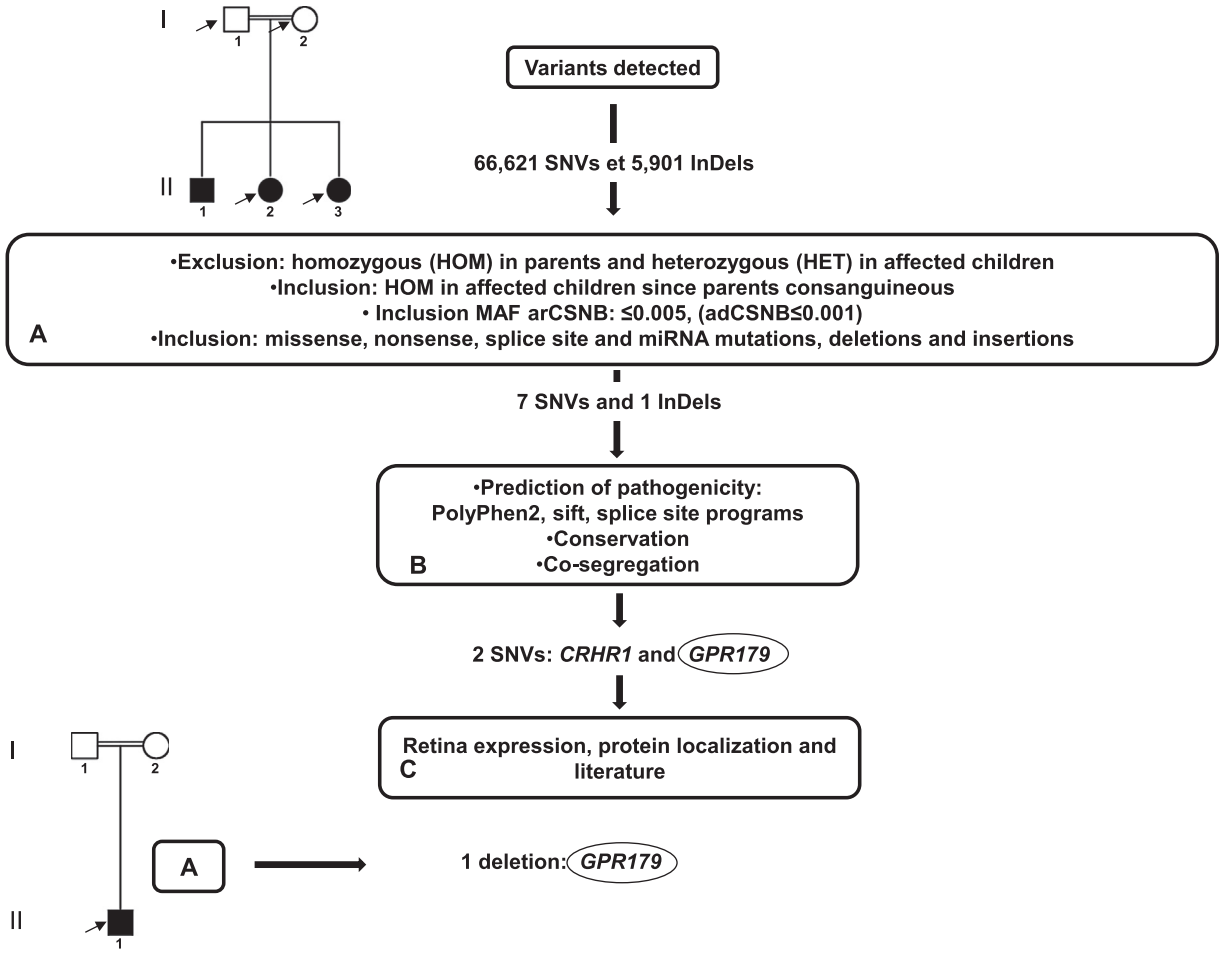

Fig. 5. Filtering defaults to identify the disease causing gene. The WES approach is illustrated for the identification of the gene defect *GPR179* underlying cCSNB in a consanguineous family and in a sporadic case. Four family members of the consanguineous cCSNB were sequenced (marked with an arrow) and on average more than 66,600 SNVs and 5900 InDels were identified. A) After stringent filtering keeping only variants if they had a Minor Allele Frequency (MAF) or less and equal to 0.005 (autosomal recessive cases) (for autosomal dominant cases less or equal to 0.001) in dbSNP 137, HapMap (Altshuler et al., 2010), 1000 Genomes (Abecasis et al., 2010), and Exome Variant Server (EVS) (Tennessen et al., 2012) and keeping only InDels, missense, nonsense and miRNA mutations, 7 SNVs and 1 InDel remained. B) Keeping only variants, which were predicted to be disease causing and co-segregated with the disease in this family only 2 missense mutations remained in *CRHR1* and *GPR179*. Due to the absence of other sequenced family members of the sporadic case, stringent filtering A) did not significantly reduce the possible pathogenic variants for this case with cCSNB. However, the subject revealed a deletion in *GPR179*, which reinforced the idea that *GPR179* is the disease causing gene for all cCSNB patients investigated here (Audo et al., 2012a). C) In addition, available expression data (Uni Gene, *rd1* mouse, Fig. 6) confirmed that *GPR179* was a good candidate underlying cCSNB.

genes underlying cCSNB. Furthermore, genes implicated in cCSNB should show higher expression in bipolar cells marked e.g. with GRM6/mGluR6 in the retinal expression database (Fig. 6B, example shown for *Trpm1*). In addition, we perform literature searches for further convincing evidence on animal models, metabolic pathways or other supporting data for putative pathogenicity (e.g. 3D-modeling (Venselaar et al., 2010)) in collaboration with Dr. Poch, bioinformatician from the "Bioinformatics Platform of Strasbourg" (BIPS).

In cases of very promising candidates the expression of any newly identified gene in the mouse or human retina at the transcript and protein level is also studied by RT-PCR, RNA *in situ* hybridization (Fig. 7A, *Gpr179* as an example for typical expression of genes implicated in cCSNB) and immunolocalization studies (Fig. 7C and D, LRIT3 as an example for typical immunolocalization of protein implicated in cCSNB) (Audo et al., 2014, 2012a; Zeitz et al., 2013). Through a NGS approach in a linked region in mouse, Peachey et al. (2012b) independently identified *GPR179* as the genetic cause of one form of cCSNB (see also: 4. Animal models for CSNB).

3.2. Mode of inheritance and mutations in CSNB

To establish phenotype-genotype correlations, prevalence, and genotyping strategies for CSNB we performed meta-analyses on our cohort and a literature search (together more than 470 cases). To date, more than 360 different mutations have been identified in the seventeen known genes underlying CSNB (Table 1, Fig. 8A). This represents more than 670 affected alleles (Table 1, Fig. 8B). X-linked CSNB account for 57.9% of cases, autosomal recessive and sporadic CSNB accounted for 40% including 23.6% with a fundus abnormality, and the remaining 2.1% of cases had autosomal dominant CSNB (Fig. 8C).

Most of our patients and those of our international cohort (more than 300 index cases) had a Schubert-Bornschein-type ERG, with x-linked or autosomal recessive modes of inheritance with complete or incomplete CSNB phenotypes and with a normal fundus appearance apart from myopic changes. Here we describe novel most likely disease causing mutations of this collected cohort in *NYX* (14) (Table 1.5), *TRPM1* (11) (Table 1.7), *GRM6* (2) (Table 1.6), *GPR179* (2) (Table 1.8) and *LRIT3* (1) (Table 1.9) in patients with

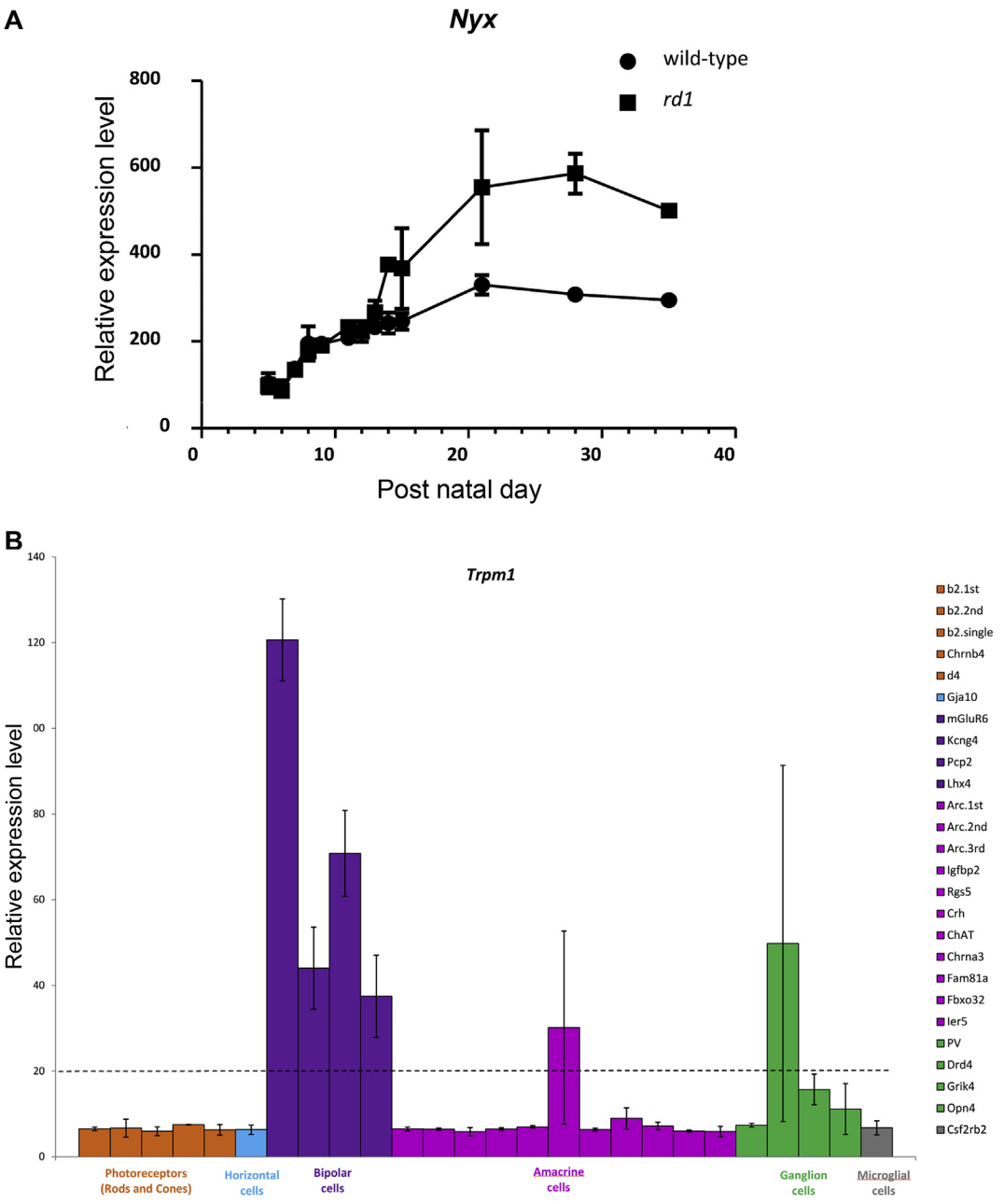

Fig. 6. Expression analysis of candidate gene defects using expression databases. A) Expression of *Nyx* (1446344_at as an example for a known molecule expressed in the inner nuclear layer and implicated in cCSNB) during rod degeneration in the *rd1* mouse. Neural retinas from *rd1* and wild-type mice on identical genetic background (Viczian et al., 1992) were hybridized to the mouse genome 430 2.0 array (Affymetrix, High Wycombe, UK). The expression profiles are similar from post-natal day (PND) PND5 to PND12. Thereafter the relative expression of *Nyx* increases in the *rd1* retina. This phenomenon correlates temporally with the loss of rod photoreceptor cells and is likely due to the unaffected inner retinal cells in the *rd1* specimen at this age. B) Expression of *Trpm1* as an example for a known molecule expressed in bipolar cells using the database generated in Roska's laboratory using retinal cell type specific transgenic mice: http://www.fmi.ch/roska.data/index.php (Siegert et al., 2009; Siegert et al., 2012). Each value on the *x*-axis corresponds to a specific retinal cell type expressing fluorescent proteins. Photoreceptor cell marker: b2: bradykinin receptor, beta 2, Chrnb4: cholinergic receptor, nicotinic, beta polypeptide 4, d4: Rho, GDP dissociation inhibitor (GDI) beta Lhx4: LIM homeobox protein 4; Horizontal cell marker: Gja10: gap junction protein, alpha 10; Bipolar cell marker: mGluR6: glutamate receptor, Kcng4: potassium voltage-gated channel, Pcp2: Purkinje cell protein 2; Amacrine cell marker: Arc: activity regulated cytoskeletal-associated protein, Igfbp2: insulin-like growth factor binding protein 2, Rgs5: regulator of G-protein signalling 5, Crh: corticotrophin releasing hormone, ChAT: choline acetyltransferase, Chrna3: cholinergic receptor, nicotinic, Fam81a: family with sequence similarity 81, Fbxo32: F-box protein 32, Ier5: immediate early response 5; Ganglion cells: PV: parvalbumin, Drd4: dopamine receptor D4, Grik4: glutamate receptor, Opn4: opsin 4 (melanopsin); Microglia marker: Csf2rb2: colony stimulating factor 2 receptor, beta 2, low-affinity (granulocyte-macrophage). Only expression values above 20 are thought to represent significant expression.

cCSNB and in *CACNA1F* (38) (Table 1.10) and *CABP4* (1) (Table 1.11) in icCSNB patients. Few cases of this cohort do not harbour mutations in known genes. Compiling our data with those from the literature, 70 different mutations were associated with gene defects affecting the phototransduction cascade and leading to CSNB with a Riggs-type ERG (*RHO* = 4, *GNAT1* = 3, *PDE6B* = 2, *SLC24A1* = 1), or to CSNB affecting retinoid recycling with fundus abnormalities as in OD (*SAG* = 6 and *GRK1* = 9) and FA (*RDH5* = 40, *RLBP1* = 3 and *RPE65* = 2). Similarly, 294 different mutations have been identified in gene defects affecting the signalling from photoreceptors to

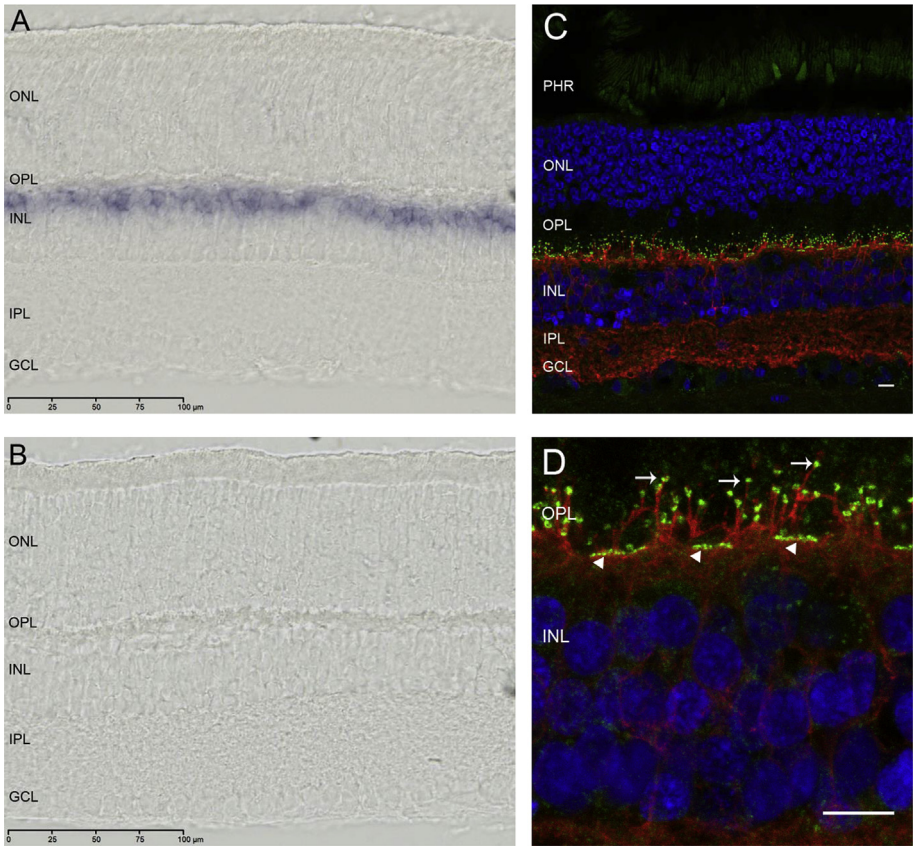

Fig. 7. Expression and immunolocalization studies of candidate gene defects implicated in CSNB. The following abbreviations are used: PHR = photoreceptor layer, ONL, outer nuclear layer; OPL, outer plexiform layer; INL, inner nuclear layer; GCL, ganglion cell layer. A) *Gpr179* is expressed in the somata of the upper part of the inner nuclear in mouse retina. Hybridization was performed with antisense (A) and sense (B) *Gpr179* (exon 9–11) riboprobes. Signal is visualized in purple (A). Scale bar represents 10 µm. C) LRIT3 signal (green) in the OPL double-labelled with an ON-bipolar cell marker against $G\alpha_o$ (red) was detected in human retina by confocal microscopy. A strong signal with the human LRIT3 antibody was detected in a punctate manner at presumed dendritic tips of the ON-bipolar cells. D) 3.5× zoom of Fig. 7C to focus on the staining of LRIT3 at the presumed dendrites of bipolar cells. Scale bar represents 10 µm. Figures were modified after (Orhan et al., 2013; Zeitz et al., 2013).

bipolar cells, of which 133 occurred in cases with icCSNB (*CACNA1F* = 126, *CABP4* = 5 and *CACNA2D4* = 2) and 161 in cases with cCSNB (*NYX* = 69, *GRM6* = 22, *TRPM1* = 51, *GPR179* = 14 and *LRIT3* = 5) (Table 1, Fig. 8A). Taking into account founder and recurrent mutations more than 670 affected alleles were described (Table 1, Fig. 8B) establishing the following prevalence for CSNB: *RHO* ≥ *GNAT1* > *PDE6B* ≥ *SLC24A1* in cases with a Riggs-type ERG (Fig. 9A), *RDH5* > *SAG* > *GRK1* > *RLBP1* > *RPE65* in cases with fundus abnormalities (Fig. 9B), *CACNA1F* > *CABP4* > *CACNA2D4* in cases with icCSNB (Fig. 9C) and *NYX* > *TRPM1* > *GRM6* > *GPR179* > *LRIT3* in cases with cCSNB (Fig. 9D). Founder mutations have been identified especially in cases of FA with *RDH5* mutations and OD with *SAG* mutations. They and recurrent mutations, including cases with homozygous mutations, represent 75.1% and 85.7% respectively of the mutations identified. Of those the c.160C>T p.Arg54* in *RDH5* has been identified in Jewish families of different ethnicity (Pras et al., 2012) and three other mutations in the same gene c.712G>T p.Gly238Trp (Gonzalez-Fernandez et al., 1999; Hajali et al., 2009; Iannaccone et al., 2007; Schatz et al., 2010; Sergouniotis et al., 2011c; Yamamoto et al., 1999), c.839G>A p.Arg280His (Gonzalez-Fernandez et al., 1999; Kuroiwa et al., 2000; Miyazaki et al., 2001; Nakamura et al., 2000, 2004a; Niwa et al., 2005; Sato et al., 2004) and c.928delinsGAAG p.Leu310delinsGluVal (Hayashi et al., 2006; Hirose et al., 2000; Makiyama et al., 2014; Nakamura et al., 2000; Nakamura and Miyake, 2002; Niwa et al., 2005; Sato et al., 2004; Sekiya et al., 2003; Wada et al., 2000; Wang et al., 2008) represent founder mutations in Japanese cases of FA. Some recurrent mutations were also noted in patients with mutations in autosomal recessive and x-linked CSNB associated with the Schubert-Bornschein-type electroretinogram. In *CACNA1F* 28.4% and in *NYX* 32.3% of the mutations are recurrent mutations. In contrast to FA and OD the mutations identified here are distributed all over the gene, with most of them occurring in two or three families. Although founder effect mutations were suggested for some of them, such as the c.3133 p.Leu1045Profs*11 *CACNA1F* mutation identified initially in a subgroup of patients of Mennonite ancestry (Bech-Hansen et al., 1998; Boycott et al., 2001; Strom et al., 1998) and the c.855delG p.Asp286Thrfs*62 *NYX* mutation identified in three independent Flemish families (Leroy et al., 2009), comprehensive haplotyping needs to be done in the future to confirm this hypothesis (Table 1). To date the number of genetically unsolved cases for all CSNB patients is difficult to estimate. Our cohort consists mainly of icCSNB, cCSNB and unclassified CSNB cases. Our recent work concentrated mainly on the identification of genes underlying cCSNB. For this phenotypic group, only a few patients lack mutations in the known genes indicating that most of the gene defects have been already identified. For the icCSNB group of patients, many cases of our cohort still need to be excluded for mutations in known genes. If we consider only patients with a clear complete or incomplete CSNB and excluded for mutations in known genes, we estimate that approximately 20% of them may carry mutations in a novel gene.

The mutation spectrum comprises for most of the gene defects implicated in CSNB, truncating, missense and splice site

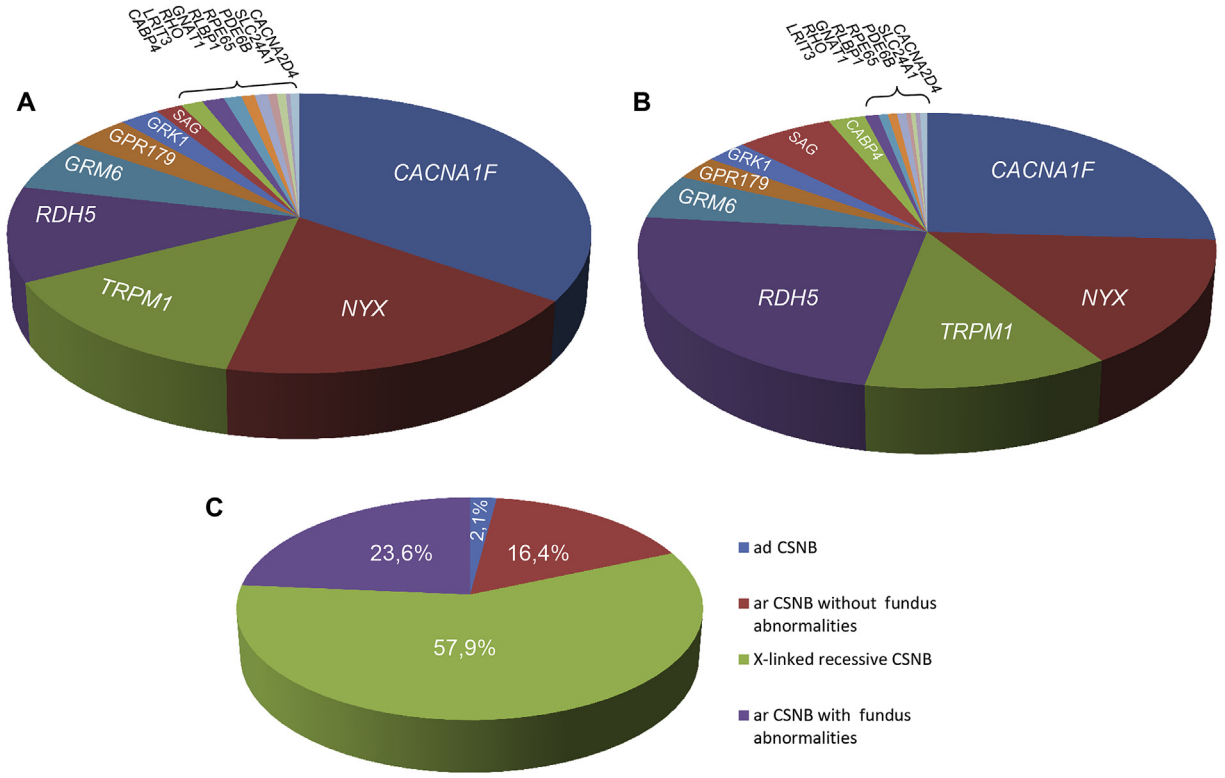

Fig. 8. Prevalence of gene defects, affected alleles and inheritance patterns associated with CSNB. Meta-analysis showing the prevalence of A) different gene mutations B) the relative number of affected alleles for each implicated gene mutation and C) mode of inheritance implicated in CSNB. The differences between (A) (B) is is explained by the inclusion of founder mutations observed for some genes and the inclusion of recessive cases harbouring homozygous mutations (B).

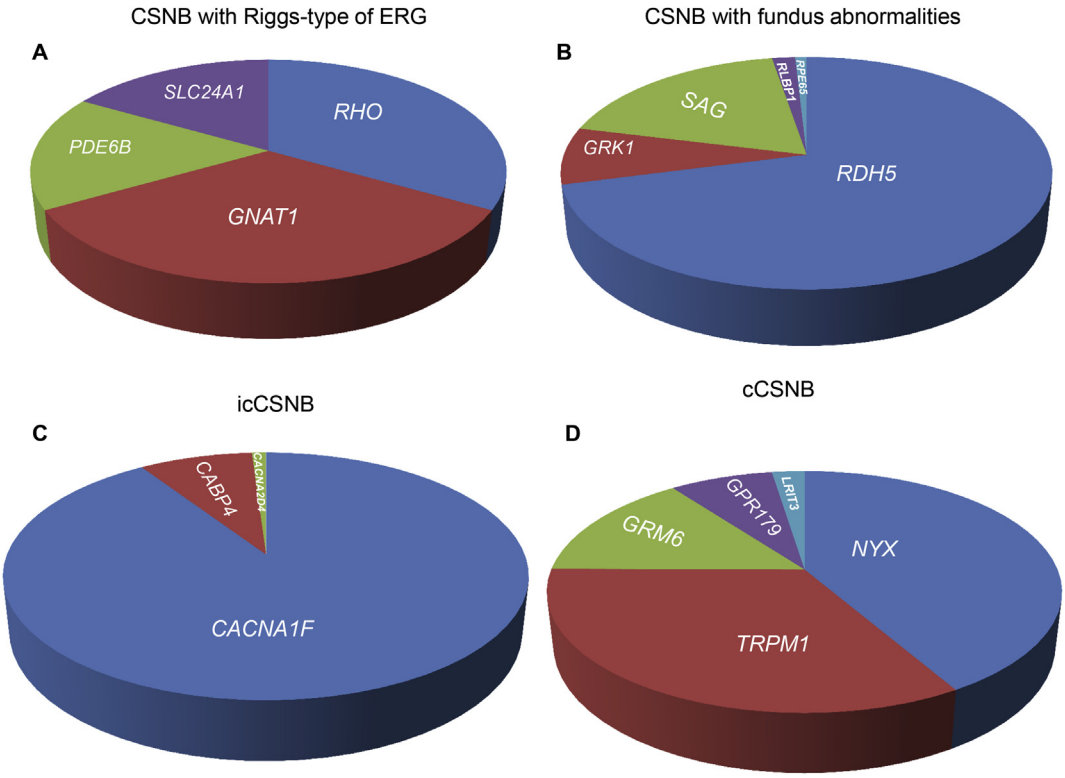

Fig. 9. Prevalence of gene defects with different types of CSNB. A) Mutations in patients with a Riggs-ERG phenotype have be found in *RHO*, *GNAT1*, *PDE6B* and *SLC24A1*.B) Mutations in patients with arCSNB and fundus abnormalities have been found in *RDH5*, *SAG*, *GRK1*, *RLBP1* and *RPE65*. C) Mutations in patients with X-linked and autosomal recessive icCSNB have been found in *CACNA1F*, *CABP4* and *CACNA2D4*. D) Mutations in patients with X-linked andautosomal recessive cCSNB have been found in *NYX*, *TRPM1*, *GRM6*, *GPR179* and *LRIT3*.

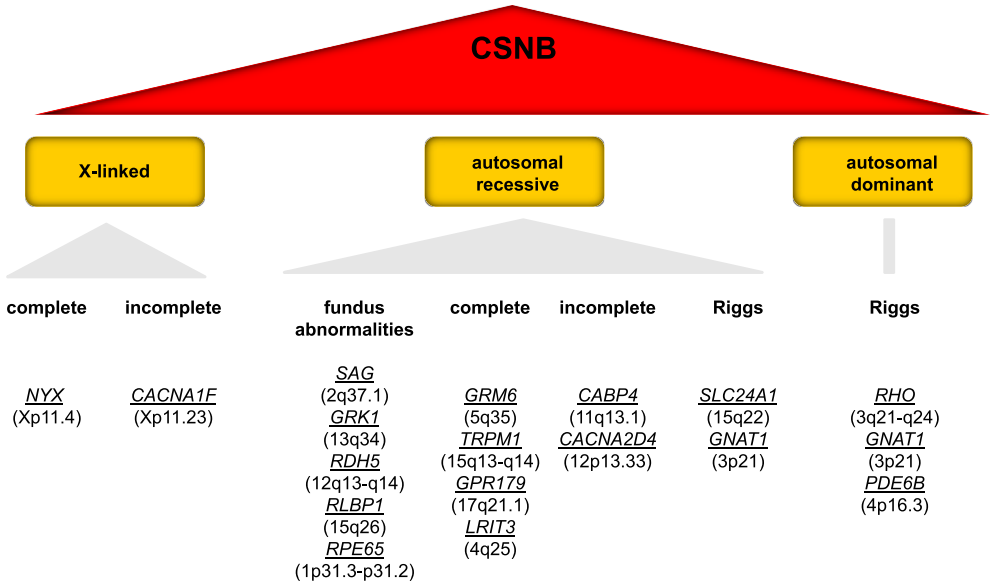

Fig. 10. Phenotype–genotype correlation for CSNB. The mode of inheritance and precise clinical and ERG phenotyping allows direct targeted sequencing to establish the genetic diagnosis.

mutations. However, it is noted that autosomal dominant CSNB is mostly confined to missense mutations. Similarly, cCSNB patients with *NYX* mutations mainly harbour missense mutations (Table 1).

3.3. Molecular diagnosis

Molecular testing of CSNB patients is important for genetic counselling of affected families and to differentiate from progressive retinal dystrophies with similar phenotypic features. For example, night blindness is the commonest presenting symptom of retinitis pigmentosa (progressive rod-cone dystrophy) and may initially manifest with normal or near-normal fundus appearance (Tables 2 and 3), emphasising the importance of accurate ERG diagnosis. Molecular confirmation of CSNB facilitates counselling and management, excludes the possibility of significant disease progression and will be essential to identify candidates amenable to possible future therapeutic interventions. Although CSNB is a heterogeneous group of disorders, thorough clinical examination including determination of the mode of inheritance is a useful first step toward gene-specific sequencing to identify disease causing mutations (Fig. 10). Precise phenotype-genotype correlations can be drawn especially for CSNB cases with fundus abnormalities as in OD and FA (Fig. 10) (see 2. Phenotypic characteristics of CSNB): Patients with autosomal recessive CSNB and a phenotype suggestive of OD should be screened for mutations in *GRK1* and *SAG*, while in patients with FA, *RDH5* should be targeted. After exclusion of the latter gene defects *RLBP1* and *RPE65* could be screened, as there is some phenotypic overlap (Fig. 10; Tables 1.14 and 1.15; see 2. Phenotypic characteristics of CSNB) (Katsanis et al., 2001; Naz et al., 2011; Schatz et al., 2011). To date, most of the mutations leading to the Schubert-Bornschein phenotype have been identified in *CACNA1F* and *NYX* (Tables 1.10 and 1.5, Figs. 8 and 9); this might be partly related to the longer association with CSNB than for other genes, although most of the recently collected CSNB cases reveal x-linked inheritance with mutations in one or the other. An efficient approach would be to screen *CACNA1F* or *NYX* in male patients depending on the phenotype, irrespective of whether there is evidence of x-linked inheritance. Females and excluded male patients with icCSNB could be screened in *CABP4* and *CACNA2D4*, especially if they present with high hyperopia and photophobia (see also 2. Phenotypic characteristics of CSNB) and other cases of cCSNB screened for defects in *TRPM1*, *GRM6*, *GPR179* and *LRIT3*. We developed this strategy, based on the prevalence of the specific gene defects (Fig. 9, Table 1). In a few cases and in a three generation family of our cohort, a single mutation in *TRPM1* was identified, indicating that this gene may also be implicated in autosomal dominant CSNB (Audo et al., 2012b). Future co-segregation and phenotype-genotype studies in additional cases are needed to confirm this hypothesis. For the cases with Schubert-Bornschein phenotype but in the absence of precise clinical data, the gene size and the prevalence could be considered. This would suggest the following mutation detection strategy: *NYX* > *CACNA1F* > *TRPM1* > *GRM6* > *GPR179* > *CABP4* > *LRIT3* > *CACNA2D4*. Since some female carriers with *CACNA1F* mutations develop a phenotype, presumably due to random X-inactivation (Table 1.10), it may be necessary to screen *NYX* or *CACNA1F* in those without a recessive gene defect. Thereafter excluded cases could be investigated by WES or whole genome sequencing (WGS) to identify novel putative gene defects underlying CSNB. When autosomal dominant or autosomal recessive inheritances are established the most prevalent gene defects should be screened: *RHO* > *GNAT1* > *PDE6B* and *GNAT1* ≥ *SLC24A1* respectively. For these screening strategies Sanger sequencing seems to be the gold standard. In case only preliminary clinical phenotyping data are available unbiased microarray analysis (ASPER, Ophthalmics, Tartu, Estonia) (Vaidla et al., 2013; Zeitz et al., 2009) and targeted NGS could be applied (Audo et al., 2012b). The prior method is based on allele-specific primer extension analysis, which allows the detection of known mutations. The array is continuously updated with new mutations in known genes and mutations that will be identified in novel gene defects. Considering our comprehensive study and meta-analysis on all published mutations in CSNB and in the presence of basic clinical description, we estimate to identify the causative mutation by an updated genotyping microarray in probably most of the cases with fundus abnormalities. However, many founder mutations have been described in CSNB with fundus abnormalities and thus targeted mutation specific Sanger sequencing seems to be more cost-effective. A more comprehensive alternative to microarray

analysis could be targeted NGS developed for all known and candidate genes underlying inherited retinal disorders (Audo et al., 2012b) or WES or WGS. However, at this time we recognized that GC-rich and repetitive regions as found in many CSNB genes are poorly covered or targeted by these approaches (Audo et al., 2012b) and thus mutations may be missed. Another cost- and time-efficient alternative for cases for which only preliminary phenotyping data are available would be to screen all candidate genes by a molecular inversion probe (MIP) strategy, which allows multiplexing of samples while sequencing (O'Roak et al., 2012). The bottleneck of this method is again the high GC-rich content of candidate genes, which require considerable rebalancing to improve capture uniformity (O'Roak et al., 2012). Further studies are needed to investigate possible solutions.

In summary, although CSNB is heterogeneous, precise clinical examination and detailed electrophysiology are useful first steps toward gene-specific sequencing to identify disease causing mutations. In this context, Sanger sequencing seems to be the gold standard. WES or WGS is likely to detect unidentified gene defects.

4. Animal models for CSNB

Animal models have been shown to be an excellent tool to identify and to elucidate the pathogenic mechanism of gene defects underlying CSNB. In addition, well characterized animal models are crucial to develop pharmaceutical or genetic treatments. In Table 4 we summarize more than 30 animal models of CSNB. Most are mouse models, but for some gene defects other species including zebrafish, rat, dog and horse have been described. We provide the gene defect with the respective accession number if known, the type of the mutation and the method used to generate the model in addition to the observed phenotype. For the different forms of CSNB, specific types of models exist in which the mutations are either naturally occurring (Baehr and Frederick, 2009), chemically-induced (N-ethyl-N-nitrosourea, ENU) (Justice et al., 1999), knockout alleles created by replacing genomic sequences with specific selection cassettes, transgenes (Bernstein and Breitman, 1989) or morpholinos against the translation start sites developed (Nasevicius and Ekker, 2000). We recognize that although these models show phenotypes resembling those of humans, there are many limitations e.g. species differences, less controllable copy-numbers of the wild-type versus mutant alleles in transgenic models. In addition, models for CSNB associated with mutations in proteins of the phototransduction cascade seem to diverge from the human phenotype more than models of mutations affecting signalling proteins from the photoreceptor to bipolar cells. The advantage of animal models, besides the possibility of *in vivo* functional and structural assessment similar to humans (e.g. ERG recording as well as retinal imaging including FAF and SD-OCT), is to allow *post mortem* studies for a more precise analysis of retinal structure in comparison with unaffected controls. ERGs are particularly informative but there is, as yet no international standard for animal ERGs, precluding strict comparison between different laboratories. ERG standards for animal models would likely be especially important for mutants with phototransduction cascade defects, where the ERG phenotype in animal models seems to be more variable (e.g. variability in a-wave reduction).

4.1. Mouse models affecting the phototransduction cascade

4.1.1. Mouse models for autosomal dominant CSNB or autosomal recessive CSNB

Five transgenic mouse models have been created, carrying amino acid exchanges previously found in autosomal dominant and autosomal recessive CSNB patients (Dryja et al., 1996; Gal et al., 1994a; Sieving et al., 1992): two models of RHO (p.Gly90Asp (Naash et al., 2004; Sieving et al., 2001)), two models of GNAT1 (p.Gly38Asp (Moussaif et al., 2006) and p.Gln200Leu (Kerov et al., 2005)) and one of PDE6B (p.His258Asn (Tsang et al., 2007)) (Table 4) (see 5. CSNB disease mechanisms). Many other mutations in *RHO* (Dryja et al., 1990) as well as in *PDE6B* (McLaughlin et al., 1993) including mouse models (e.g. Chang et al., 2002; Hobson et al., 2000) lead to progressive rod-cone dystrophy and not to CSNB. Transgenic CSNB mice harbouring the p.Gly90Asp mutation have normal numbers of photoreceptors, but a considerable loss of rod sensitivity as measured by ERG. The desensitization effect increased with the copy number of mutant alleles, while it did not cause significant rod degeneration (Sieving et al., 2001). Similar observations have been also reported by Naash et al. (2004) characterizing another transgenic line carrying the same amino acid exchange. However, they also recognized that although retinas with transgenic opsin levels equivalent to one endogenous allele appeared normal for a period of about 3–4 months, retinal degeneration was observed in the late stages. Similarly, higher levels of p.Gly90Asp opsin expression produced earlier signs of retinal degeneration and more severe disruption of photoreceptor morphology (Naash et al., 2004).

The biochemical, electrophysiological, and vision-dependent behavioural analyses of the transgenic mouse model harbouring the p.Gly38Asp exchange in GNAT1 initially found to be disease causing in heterozygous “Nougaret” patients, revealed reduced rod sensitivity, impaired activation, and slowed recovery of the phototransduction cascade in homozygous mice (Moussaif et al., 2006) (Table 4). However, rod-mediated sensitivity in heterozygous mice was not decreased to the extent seen in heterozygous patients. The cause of the phenotypic differences between humans and mice is not clear but may relate to interspecies differences in rod signalling (Field and Rieke, 2002; Field et al., 2005). Alternatively, it may reflect limitations of the transgenic technique since there are difficulties generating the same amount of normal and mutant allele expression as in patients, which would also explain the phenotypic variability observed in the other transgenic mouse described above. Interestingly, before the mutation p.Gln200Glu was associated with autosomal dominant CSNB (Szabo et al., 2007), a transgenic mouse model with a different amino acid substitution (p.Gln200Leu) was created to better understand the role of transducin (Kerov et al., 2005). Animals producing high levels of this mutation showed decreased rod-sensitivity in the absence of retinal degeneration, but the amount of wild-type alleles is not clear and thus needs to be validated to establish whether the phenotype is in accordance with autosomal dominant inheritance. For mice lacking homozygously *Gnat1* an ERG phenotype resembling stationary night blindness but with mild age-dependent retinal degeneration has been described (Calvert et al., 2000) (Table 4) and may prove to be a useful model for autosomal recessive CSNB, as recently described in some patients with a Riggs-type of ERG (Naeem et al., 2012).

Transgenic mice harbouring the p.His258Asn exchange in PDE6B, found initially in the “Rambusch family” with autosomal dominant CSNB (Gal et al., 1994a; Muradov et al., 2003), showed a background-dependent phenotype: in the albino (B6CBA × FVB) F2 hybrid background, ERGs from p.His258Asn mice showed selective loss of the b-wave with relatively normal a-waves. Surprisingly, when the p.His258Asn allele was crossed into the DBA (pigmented) genetic background, no evidence of selective reduction in b-wave was seen, rather a- and b-wave amplitudes were reduced (Tsang et al., 2007). These observations suggest differences with the genetic background (see 5. CSNB disease mechanisms). In addition, variability in the ERG a-wave reduction has been shown in other

patients with the Riggs phenotype (Zeitz et al., 2008), probably reflecting different degrees of dark-adapted cone function in the absence of rods. In addition, modifiers may influence the phenotype. Quantification of the mutant versus wild-type allele should be performed for these mouse lines to determine whether the phenotype is consistent with the human form of autosomal dominant CSNB.

4.1.2. Mouse model for fundus albipunctatus

Mice lacking *Rdh5* manifest a phenotype that only partly resembles human disease (Driessen et al., 2000) (Table 4). Under normal environmental conditions, *Rdh5* knockout mice do not display white dots similar to those observed in FA patients. It is likely that the typical retinal appearance in FA patients results from a developmental defect caused by a role of 11-*cis*-retinol dehydrogenase in 9-*cis*-retinoic acid biosynthesis, which differs in rodents compared to primates (Driessen et al., 2000). Furthermore, only at high bleaching conditions do $Rdh5^{-/-}$ mice show delayed dark adaptation. Since $Rdh5^{-/-}$ mice are still capable of regenerating their rod visual pigment, there may be other enzyme(s) to catalyze 11-*cis*-retinol oxidation in the retina (Driessen et al., 2000).

4.1.3. Animal models for Oguchi disease

Researchers have generated *Sag* and *Grk1* knockout mice to study the function of the associated proteins (Chen et al., 1999a, 1999b; Xu et al., 1997). To our knowledge the specific fundus appearance (Mizuo-Nakamura phenomenon in OD patients) has never been reported in mice but distinct observations mentioned below, correspond to clinical features observed in patients (Table 4). Mice lacking functional SAG or GRK1, as in humans, show evidence of continued activation of the phototransduction cascade, resulting in prolonged photoreceptor hyperpolarisation (see 5. CSNB disease mechanisms). This is in keeping with arrestin (SAG) and rhodopsin kinase (GRK1) being necessary for deactivation of rhodopsin (Chen et al., 1999a, 1999b; Xu et al., 1997). However, the mice are also more susceptible to light damage leading to retinal degeneration. More recently a dog with a late onset progressive retinal atrophy with a naturally occurring no-stop change (c.1216T>C p.*405Rext*25) in *SAG* was described (Goldstein et al., 2013). Although some dogs showed an altered tapetal reflexion on fundus examination, characterized by a golden-brown or bronze discoloration, there was no clear correlation with the *SAG* genotype (Goldstein et al., 2013). It is noted that *SAG* and *GRK1* mutations may also be associated with progressive disease in patients (Azam et al., 2009; Fujinami et al., 2011; Hayashi et al., 2007, 2011; Isashiki et al., 1999; Maw et al., 1998; Nakamachi et al., 1998; Nakazawa et al., 1998; Sippel et al., 1998; Sonoyama et al., 2011; Zhang et al., 2005).

4.2. Animal models for the Schubert-Bornschein type of CSNB affecting molecules important for the signalling from photoreceptors to bipolar cells

Several animal models for the Schubert-Bornschein type of CSNB have been created or occured naturally (Table 4), characterised by molecular abnormalities that impair bipolar cell transmission.

4.2.1. Animal models for icCSNB

There are nine animal models with similar phenotypes and three different gene defects affecting *CACNA1F*, *CABP4* or *CACNA2D4* (Table 4). All show defective retinal neurotransmission, manifest as reduced b-waves under scotopic and photopic conditions (similar to patients) but show additional structural abnormalities. The phenotype is therefore more severe than in humans with some features more in keeping with cone-rod dystrophy than icCSNB. Recently, for one icCSNB patient with a known *CACNA1F* mutation (p.Leu1045Profs*11 or p.Leu1056Profs*11, depending on the reference AJ006216 or NM_005183.2; also found in two different patients from our cohort) (Bech-Hansen et al., 1998; Strom et al., 1998) OCT revealed abnormal synapses in the ONL (Vincent and Heon, 2012) (see 2. Phenotypic characteristics of CSNB). However this is not a universal finding, OCT may be normal in cases with other *CACNA1F* mutations (p.Gly603Arg, NM_005183.2 and p.Arg614*, AJ006216 (Chen et al., 2012; Vincent et al., 2011). Since the p.Leu1045Profs*11 mutation is a relatively common cause of icCSNB detailed examination may determine whether phenotypic differences in animals and humans are mutation-specific or relate to modifiers or other factors. In general, this indicates that animal models are useful but that the data need to be interpreted with caution. However, detailed immunhistological and phenotypic studies in animals are likely to prove crucial for the development of new therapies aimed at functional rescue.

4.2.1.1. Mouse models for CACNA1F gene defect. Four mouse models have been described for *CACNA1F*: two laboratory-generated knockout mutants with inserted neo-cassettes in exon 7 (*Cacna1fΔEx7*) (Mansergh et al., 2005) and exon 14–17 (*Cacna1fΔEx14-17*) (Michalakis et al., 2014; Regus-Leidig et al., 2014; Specht et al., 2009; Zabouri and Haverkamp, 2013); one laboratory-generated knockin mouse carrying a missense mutation (p.Ile756Thr) for a human mutation (p.Ile745Thr) (Hemara-Wahanui et al., 2005; Knoflach et al., 2013; Regus-Leidig et al., 2014; Specht et al., 2009) and a naturally occurring mouse (*nob2*) carrying an inserted transposon in exon 2, which leads to alternative splicing resulting in two transcripts (Table 4). The major transcript gives rise to a truncated protein (90%), while the minor transcript (10%) leads to full length protein with some different amino acids at the N-terminus, abolishing an important filamin binding-site (Chang et al., 2006; Doering et al., 2008) (Table 4). Therefore the latter model does not represent a total knockout model. However, it may be especially useful as not all *CACNA1F* mutations identified in patients are predicted to lead to complete loss of function. In some respects this model is more closely related to human disease than the complete knockout mouse models, which are associated with a more progressive phenotype. All four hemizygous models show similarities: the Cav1.4 subunit normally localizing in the OPL is mislocalized, the OPL is thinner than in unaffected mice and ectopic neurites from depolarizing bipolar and some horizontal cells are documented (Chang et al., 2006; Knoflach et al., 2013; Mansergh et al., 2005; Michalakis et al., 2014; Regus-Leidig et al., 2014). Sprouting of cones has been observed in some cases (Knoflach et al., 2013; Zabouri and Haverkamp, 2013). The main phenotypic differences between these models are revealed by the ERG. In the total knockout models the scotopic ERG b-waves and oscillatory potentials are absent and the a-wave amplitudes are normal to marginally reduced, resembling cCSNB rather than icCSNB (Table 4, Fig. 1). In the knockin model, under the same conditions, the authors claimed that the ERG b-waves are severely reduced but still present, similar to patients with icCSNB. However, the a-wave amplitudes seemed reduced (Table 4). Although, this is in contrast to typical icCSNB, the reduction of a-wave is similar to that seen in patients with the same mutation (Hemara-Wahanui et al., 2005). Interestingly, in the *nob2* mice the b-wave and oscillatory potentials are reduced and the a-wave does not show any alterations. The partial preservation of the b-wave under dark adapted conditions in these mice is similar to that seen in icCSNB patients with *CACNA1F* mutations. Similarly, knockout mice do not show any recordable photopic ERG activity, modelling a more progressive phenotype,

Table 4
Animal models for genes underlying congenital stationary night blindness.

Gene defect and Accession number	Animal model	Type of mutation	Method or disvovered	ERG phenotype	Other phenotypic features	Models human phenotype	Reference
Rho NM_145383.1	Mouse	Exon 1 c.269G>A and c.270A>C (Sieving et al., 2001) c.269G>A and c.270A>T (Naash et al., 2004) p.Gly90Asp	Two transgenes to model adCSNB family with p.Gly90Asp (Sieving et al., 1992; Sieving et al., 1995)	Loss of rod sensitivity	Depending on the amount of endogenous rhodopsin and p.Gly90Asp allele retinal degeneration	adCSNB yes, with limitations due to variability in phenotype	(Naash et al., 2004; Sieving et al., 2001)
Gnat1 NM_008140.2	Mouse	Exon 2 probably c.113G>A p.Gly38Asp	Transgene to model Nougaret-pedigree (Dryja et al., 1996)	Reduced rod photoreceptor responses		Most likely CSNB but not adCSNB since only homozygous mice show phenotype	(Moussaif et al., 2006)
	Mouse	Exon 6 not clear p.Gln200Leu	Transgene GtαEEGln200Leu to understand physiology; later p.Gln200Glu exchange identified in adCSNB patients (Szabo et al., 2007)	Not clear if in *Gnat1*$^{+/-}$ background. But in high levels of transgene reduced rod photoreceptor responses	No retinal degeneration, reduced levels of proteins involved on cGMP metabolism in rods e.g. PDE catalytic subunits	Most likely CSNB, phenotyping of transgenes with *Gnat1*$^{+/-}$ needs to be done to confirm adCSNB	(Kerov et al., 2005)
	Mouse	In exon 4–5 neomycin selection cassette inserted	Transgene	*Gnat1*$^{+/-}$ not mentioned. *Gnat1*$^{-/-}$ no rod b-wave, no a-wave (from rods) but normal cone b-wave	*Gnat1*$^{+/-}$ morphology normal; *Gnat1*$^{-/-}$ mild age dependent retinal degeneration	Most likely arCSNB	(Calvert et al., 2000)
Pde6b NM_008806.2	Mouse	Exon 4 c.772C>A p.His258Asn	Transgene, to model Rambusch-pedigree (Gal et al., 1994)	Selective loss of b-wave or a- and b-wave reduction	ERG findings dependent on genetic background	adCSNB yes with limitations due to variability in phenotype	(Tsang et al., 2007)
Rdh5 NM_134006.4	Mouse	In exon 1, 2 and 3 neomycin selection cassette inserted	KO	Delayed dark adaptation	Delayed 11-cis-retinal regeneration, delayed dark adaption kinetics no other ERG abnormalities in dark adapted KO mice in fully dark-adapted mice	No fundus abnormalities, only kinetics similar as in patients	(Driessen et al., 2000)
Sag NM_009118.2	Mouse	In 5′promoter elements and in the first two exons neo selection cassette inserted	KO	Prolonged photoresponses = defective rhodopsin shut-off	Increased susceptibility to light damage, fundus abnormalities not investigated	More severe phenotype than in patients with Oguchi disease, fundus not studies	(Chen et al., 1999b; Xu et al., 1997)
Sag NM_001003230.1	Dog	Exon 16 c.1216T>C p.*405Rext*25	Spontaneous in Basenji dogs	Data not shown, but late onset of initial visual loss in dim light (night blindness), which gradually progress in some cases to total blindness	Thin retinal blood vessels, pallid optic nerve head, irregular pattern of tapetal reflectivity	Progressive retinal atrophy, typical Oguchi fundus not present	(Goldstein et al., 2013)
Grk1 AF085240	Mouse	In exon 1 neomycin selection cassette inserted	KO	Prolonged photoresponses = defective rhodopsin shut-off	Increased susceptibility to light damage, fundus abnormalities not investigated	More severe phenotype than in patients with Oguchi disease, fundus not studies	(Chen et al., 1999a)
Cacna1f NM_019582.2	Mouse	In exon 7 self-excising Cre-lox-neo cassette inserted p.Gly305*	*Cacna1f*Δ*Ex7* Total KO	Dark adapted: a-wave reduced, b-wave missing, light adapted: cone absent	No CACNA1F in the OPL, thinner than normal OPL, develop ectopic neurites from DBCs and horizontal cells, absence of optokinetic responses	Severe icCSNB or cone-rod dystrophy, yes	(Mansergh et al., 2005)

	Mouse	In exon 2 transposon insertion leading to 2 transcripts: 90%:* in exon 2, 10%: coding for full length protein but some different amino acids at the N-terminus, which abolish protein binding to filamin	Spontaneous (*nob2*) in *AXB-6/PgnJ* strain, incomplete KO	Dark adapted: reduced b-waves? light adapted: b-wave, cone responses are reduced	No CACNA1F in the OPL, thinner than normal OPL, develop ectopic neurites from DBCs and horizontal cells, but normal optokinetic responses	icCSNB yes	(Chang et al., 2006; Doering et al., 2008)
	Mouse	In exon 14–17 neo cassette inserted, probably truncated protein	*Cacna1fΔEx14-17*	Dark adapted: a-wave normal, b-wave absent, light adapted: b-wave absent cone function reduced by behavioural tests; heterozygous mice reduction of b-wave and cone function in between wt and hemizygous mice consistent with X-inactivation	No CACNA1F in the OPL, and the IPL, develop ectopic neuritis from DBCs and horizontal cells; heterozygous mice patchy pattern probably due to mosaic defects	Severe icCSNB or cone-rod dystrophy, yes	(Michalakis et al., 2014; Specht et al., 2009)
	Mouse	Exon 17 c.2267T>C p.Ile756Thr	Knockin mimicking gain of function human mutation Exon 17 c.2234T>C p.Ile745Thr	Dark adapted: reduced b-waves, light adapted: b-wave, cone responses are reduced, in accordance with icCSNB on patients, a-wave reduced also found in patient with p.Ile745Thr	Disperse staining of CACNA1F, extending into ONL. Most synapses immature but some mature, explained why still b-wave present, thinner OPL, ONL, cones were shorter and few cones sprout, develop ectopic neurites from DBCs, reduction in expression of *Cacna1f*, β_2 and $\alpha_2\delta$-4	icCSNB to cone-rod dystrophy ERG similar as patient with the same mutation	(Hemara-Wahanui et al., 2005; Knoflach et al., 2013; Liu et al., 2013; Specht et al., 2009)
Cacna1f DQ393415	Rat	Exon 23 c.2941C>T p.Arg981*	Spontaneous in Sprague–Dawley strain	a-wave reduced, b-wave missing, cone responses reduced	Rod bipolar and horizontal cells reduced, but neither rod bipolar nor horizontal cells dendrites were observed to extend beyond the OPL in the rat, behavioral differences	icCSNB	(An et al., 2012; Gu et al., 2008; Zhang et al., 2003; Zheng et al., 2012)
Cacnafa XM_001333478.5	Zebrafish	Exon 5 c.626T>A p.Leu209* c.3430C>T p.Gln1144*	ENU induced	Reduced a-wave, delayed and reduced b-wave	Thinner OPL	Complete blindness on behavior test, but ERG and morphology in accordance with icCSNB	(Jia et al., 2014; Muto et al., 2005)
Cabp4 NM_144532.2	Mouse	In exon 1 and part of exon 2 neo cassette inserted, protein is not detectable	*Cabp4*ΔEx1-2 KO	Dark adapted: a-wave reduced, b-wave missing, light adapted, a- slightly reduced, b-wave severely reduced	Thinner OPL, reduction in the number of synaptic ribbons and photoreceptor terminals and deflation of rod spherules and cone pedicles. Formation of ectopic synapses between rods and rod bipolar or horizontal cells in the outer nuclear layer.	Severe iCSNB, or cone-rod dystrophy	(Haeseleer et al., 2004)
Cacna2d4 NM_001033382.2	Mouse	In exon 25 c.2451dup p.Gly818Argfs*15 reduced RNA	Spontaneous in C57BL/10 strain	a-wave reduced, b-wave missing, cone ERG absent	Thinner opl, loss of ribbon synpases, degeneration of rods	Severe icCSNB, cone-rod dystrophy	(Ruether et al., 2000; Wycisk et al., 2006a)

(*continued on next page*)

Table 4 (*continued*)

Gene defect and Accession number	Animal model	Type of mutation	Method or disvovered	ERG phenotype	Other phenotypic features	Models human phenotype	Reference
Nyx AY114303.1	Mouse	Exon 4 c.567_651del p.Ile189Metfs171*	Spontaneous (*nob*) in *BALB/cGr-nr/nr* strain	Dark and light adapted: b-wave missing heterozygous mice reduction of b-wave consistent with X-inactivation	–	cCSNB, yes	(Pardue et al., 1998) (Gregg et al., 2003; Peachey et al., 2012a)
Nyx NM_001077617	Zebrafish	Morpholino against the translation site	KO	b-wave missing	–	cCSNB, yes	(Bahadori et al., 2006)
Grm6 NM_173372.2	Mouse	In Exon 8, neo selection cassette inserted	KO ($Grm6^{tm1Nak}$)	Dark and light adapted: b-wave missing	–	cCSNB, yes	(Koyasu et al., 2008; Masu et al., 1995)
Grm6 NM_173372.2	Mouse	Mutation in intron 2 leads to splice site with larger transcript: c.486+648C>T, r.486_487+486ins582_6446, p.Ile163Glyfs*103	Spontaneous (*nob3*) in (B10.D2-Tg (*Igh2k3 −83*)1Nemz/J) strain	Dark and light adapted: b-wave missing	–	cCSNB, yes	(Maddox et al., 2008)
Grm6 NM_173372.2	Mouse	Exon 3 c.553T>C, p.Ser185Pro	N-ethyl-N-nitrosourea (ENU) induced (*nob4*)	Dark and light adapted: b-wave missing	–	cCSNB, yes	(Pinto et al., 2007) (Maddox et al., 2008)
Grm6b NM_001080020.1	Zebrafish	Morpholino against the translation site	KO	b-wave missing	–	cCSNB, yes	(Huang et al., 2012)
Trpm1 XM_001492235.2 predicted	Horse	Downregulation of *Trpm1*, 1378 bp long terminal repeat (LTR) insertion in intron 1 of TRPM1	Spontaneous in horses with leopard complex spotting	Dark and light adapted: b-wave missing, some a-wave abnormalities probably due to artifacts	Specific coat pattern	cCSNB yes	(Bellone et al., 2010a; Bellone et al., 2008; Bellone et al., 2010b; Bellone et al., 2013; Sandmeyer et al., 2007)
Trpm1 NM_001039104.2	Mouse	In exons 4–6 neo selection cassette inserted	*Trpm1*ΔEx4-6 ($Trpm1^{tm1Lex}$) KO	Dark and light adapted: b-wave missing	–	cCSNB, yes	(Morgans et al., 2009; Shen et al., 2009) (Koike et al., 2009)
	Mouse	Exon 23 c.3202G>A, p.Ala1068Thr	ENU induced ($Trpm1^{tvrm27/tvrm27}$)	Dark and light adapted: b-wave missing	Heterozygous mice show reduction of b-wave	cCSNB, yes	(Peachey et al., 2012a)
Gpr179 NM_001081220.1	Mouse	Transposon insertion (~6.5 kb) in intron 1	Spontaneous (*nob5*) in C3H strain	Dark adapted: b-wave missing, light adapted: severely reduced till missing	–	cCSNB yes	(Peachey et al., 2012b)
Gpr179	Zebrafish	Morpholino against the translation site	KO	b-wave missing	–	cCSNB yes	(Peachey et al., 2012b)
Lrit3 KF954709.1	Mouse	In Exons 3–4 selection cassette inserted *Lrit3ΔEx3-4* c.611_2046delinsGGCCATAG p.Phe204Trpfs*3	KO	Dark adapted: b-wave missing, light adapted: severely reduced till missing	INL slightly reduced (OCT)	cCSNB yes	(Neuille et al., 2014)

while the knockin and *nob2* mice reveal detectable but reduced photopic responses, in keeping with typical icCSNB (Audo et al., 2008; Chang et al., 2006; Doering et al., 2008; Knoflach et al., 2013; Mansergh et al., 2005; Michalakis et al., 2014). Cross-sectional analysis across different ages documented age-dependent photoreceptor degeneration for the *Cacna1fΔEx14-17* and for the knockin mouse model, which was more severe in the knockin model (Regus-Leidig et al., 2014). In addition, behavioural tests of the targeted knockout and knockin mice suggested a more severe phenotype than icCSNB. Although this is different in patients with typical icCSNB, a similar but more severe phenotype has been reported in a large family in association with p.Ile745Thr exchange in *CACNA1F*; there was severe non-progressive visual impairment with intellectual disability in some (Hope et al., 2005).

Both *Cacna1f* knockout mouse models show functional blindness and could be better described as models for cone-rod dystrophy (Knoflach et al., 2013; Mansergh et al., 2005; Michalakis et al., 2014) and it is noted that patients with X-linked cone–rod dystrophy type 3 show mutations in *CACNA1F* (Boycott et al., 2000; Hauke et al., 2013; Huang et al., 2013; Jalkanen et al., 2006). Further studies are needed to clarify differences between mouse and humans in terms of genetic background, genetic modifiers, or the type of *CACNA1F* mutation that may influence the phenotype (Bech-Hansen et al., 1998; Boycott et al., 2000; Hope et al., 2005; Jalkanen et al., 2007, 2006; Strom et al., 1998; Vincent et al., 2011). Interestingly, heterozygous *Cacna1fΔEx14-17* knockout mice (females) have a retinal mosaic consistent with differential x-chromosomal inactivation, characterized by adjacent vertical columns of affected and wild type-like retinal network. Vertical columns in heterozygous mice are comparable to either the wild type retinal network of normal mice or to the retina of hemizygous mice. Affected retinal columns display pronounced rod and cone photoreceptor synaptopathy and cone degeneration. These changes lead to vastly impaired vision-guided navigation under dark and normal light conditions and reduced retinal ERG. Similar observations have yet not been described for the other *Cacna1f* mouse models, but some female patient carriers for *CACNA1F* mutations in the same study showed similar intermediate phenotypes.

4.2.1.2. Rat model for CACNA1F gene defect. A naturally occurring rat model harbouring a nonsense mutation in exon 23 (c.2941C>T, p.Arg981*) was identified by ERG recordings obtained from an outbred Sprague Dawley rat (Gu et al., 2008; Zhang et al., 2003) (Table 4). Labelling for both rod bipolar cells and horizontal cells in affected retinas were reduced, especially for horizontal cells but neither rod bipolar nor horizontal cell dendrites were observed to extend beyond the OPL in the rat (Gu et al., 2008; Zheng et al., 2012). Under dark-adapted conditions, ERG b-waves and oscillatory potentials were severely reduced. This resembles the phenotype in the two total knockout mouse models (Mansergh et al., 2005; Michalakis et al., 2014). Under light-adapted conditions, the affected rats have detectable but reduced cone ERGs. This phenotypic feature resembles the findings in humans more than mouse models. Rats lacking functional CACNA1F show additional behavioural changes not directly related to visual deficit (not discussed in detail here), suggesting a diverse role in multiple non-retinal systems (An et al., 2012).

4.2.1.3. Zebrafish models for CACNA1F gene defect. Recently two zebrafish models with *Cacna1f* mutations have been described by Jia and colleagues (Jia et al., 2014). The so -called “wait until dark (wud)” mutants were identified in a large-scale mutagenesis screen for defects in visual behaviour (Muto et al., 2005). Genetic mapping localized the gene defects in both to a region harbouring a gene, later named *Cacna1fa*, which shows strong homology to human *CACNA1F* (Jia et al., 2014). Subsequent sequencing revealed c.626T>A and c.3430C>T *Cacna1f* mutations leading to premature stop codons p.Leu209* and p.Gln1144* respectively. Both mutants result in the absence of specific OPL localization of CACNA1F, which might be due to nonsense mutations or the antibody, which may not allow the detection of truncated protein. The *wud* mutants show no other morphological abnormalities than thinner OPLs. The ERG had a small a-wave followed by a delayed and reduced b-wave component (Jia et al., 2014). There is normal visual background adaptation and spontaneous swimming activity, but optokinetic response and optomotor response are absent, indicating that *wud* mutants are blind. Behaviourally, adult *wud* mutants are blind in bright and dim light, indicating that both cone and rod pathway functions are defective. Thus these models represent a potentially useful method to study the function and phenotype of CACNA1F in a cone-dominated system. Further studies are needed to better understand why in some aspects these fish resemble the retinal phenotypes in icCSNB (ERG, morphology) but in other ways are more comparable with a more general cone and rod dystrophy (day and night vision blindness). As for the mouse models, species-specific differences, modifiers and mutation differences may contribute to the different phenotypes.

4.2.1.4. Mouse model for CABP4 gene defect. While animal models for *Cacna1f* were specifically designed or naturally occurring mutants used to investigate the subcellular basis of this retinal disorder, the *Cabp4* mouse model had been created before the gene defect was found in patients with autosomal recessive icCSNB (Haeseleer et al., 2004). Due to the similar phenotype compared to the *Cacna1f* models, it served us as a helpful tool for a candidate gene approach (Zeitz et al., 2006). It represents a laboratory generated model, in which in exon 1 and part of exon 2 a neo cassette was inserted (*Cabp4*ΔEx1-2), which leads to a total knockout model with no detectable CABP4 protein. Initially this model was created to better understand the role of calcium binding proteins and more specifically CABP4 (Table 4) (Haeseleer et al., 2004). Haeseleer and co-workers showed that the OPL was thinner in *Cabp4*$^{-/-}$ mice, with a reduction in the number of synaptic ribbons and photoreceptor terminals, dilated rod spherules and cone pedicles as well as the presence of ectopic synapses originating from rod bipolar and horizontal cells extending into the ONL. Dark adapted *Cabp4*$^{-/-}$ mice showed significantly lower ERG a- and b-waves compared to controls. This is also true for light adapted *Cabp4*$^{-/-}$ mice, with smaller differences in the a-wave amplitudes than in the b-wave amplitudes. The phenotypic features closely resemble *Cacna1f* animals and thus provide a good model to study the disease and underlying pathogenic mechanism.

4.2.1.5. Mouse model for CACNA2D4 gene defect. As for the *Cabp4* mouse model, the phenotype and the mutation in a mouse model lacking functional CACNA2D4 was described before mutations were identified in the human ortholog and prompted a candidate gene approach in our laboratory (Ruether et al., 2000; Wycisk et al., 2006a, 2006b). The naturally occurring mouse model carries a duplication (c.2451dup) leading to a truncated protein (p.Gly818Argfs*15) (Table 4). Homozygous affected animals displayed an electronegative response with significant reduction of the scotopic a-wave and profound loss of the b-wave. Under photopic conditions, cone-specific ERG is undetectable. With age, the dark-adapted a-wave amplitude further decreases, but the rate of reduction is comparable to unaffected mice. The number of photoreceptor nuclei is reduced by one third. Electron microscopy revealed a profound loss of ribbon-shaped synapses between rod and rod-bipolar cells and severely abnormal ribbons for cones

(Ruether et al., 2000). Due to the functional failure of cones and early onset degeneration of rods, the *Cacna2d4* mutated mice were classified as a model for cone-rod dystrophy and it was argued that, as for the *Cacna1f*-mutants with cone-rod dystrophy mentioned above, these mice are probably also congenitally blind (Wycisk et al., 2006a). Interestingly, in one patient initially diagnosed with icCSNB and later reclassified with a mild form of cone dystrophy (b-wave under scotopic conditions preserved), and also in his affected sister a homozygous mutation in the human ortholog, *CACNA2D4* (c.2406C>A; p.Tyr802*) was identified (Wycisk et al., 2006b). The phenotype in the mouse model, as well as in that observed in patients is not identical to typical icCSNB, but there is some overlap with the phenotype associated with *CACNA1F* and *CABP4*; some patients and mice with these genotypes develop a cone or cone-rod dystrophy similar to that associated with *CACNA2D4* mutants.

4.2.2. Animal models for cCSNB

Clinical findings for twelve cCSNB animal models involving five different genes have been published including *GPR179*, *GRM6*, *LRIT3*, *NYX*, and *TRPM1,* (Table 4). The phenotype is “non progressive”, “stationary” and characterised by “night blindness” in the animal models as well as in patients. Striking phenotypic variability in cCSNB has not been documented (Chang et al., 2006). All animals show absent scotopic ERG b-waves and exhibit no obvious morphological abnormalities. With the exception of one mouse model (missense mutation in *Trpm1*) all have null alleles. The ERGs in most models differ from humans under photopic conditions; in almost all mice the photopic b-wave amplitude is undetectable but in patients with cCSNB photopic b-waves are clearly present although of abnormal waveform (see earlier). This may reflect inter-species differences in cone populations and properties (Pardue et al., 1998).

4.2.2.1. Mouse model for NYX gene defect. For the *NYX* gene defect one naturally occurring mouse model carrying a deletion in exon 4 (c.567_651del; p.Ile189Metfs171*) has been described (Table 4). The phenotype in these mice was reported before the human gene defect was discovered (Pardue et al., 1998). Here, the gene defect identification in patients (Bech-Hansen et al., 2000; Pusch et al., 2000) helped to identify the mutation in the mouse model (Gregg et al., 2003). Since the most obvious phenotype in the mice is the missing b-wave in the dark and light adapted ERG, representing a post-phototransduction or post-receptoral neuronal defect, this model was called *nob* mouse (for “no b-wave”; see *nob2* mouse and *nob3*, *nob4*, *nob5* and *nob6* mice as mice with post-receptoral defects discovered thereafter) affecting the rod and cone mediated pathways (Table 4). At the light microscopic level, the *nob* retina appears to have a normal cellular structure (as expected from the human phenotype) but decreased sensitivity to light (Gregg et al., 2003; Miyake et al., 1986). The phenotype was observed at six-weeks (congenital) and showed no progression after four months (Pardue et al., 1998) consistent with a stationary disorder.

4.2.2.2. Zebrafish model for NYX-gene defect. In order to investigate whether the absent b-wave was not only rod-mediated but also cone-mediated, we studied the function of NYX in zebrafish, which represents a cone-dominated vision model (Bahadori et al., 2006). Loss of function induced by morpholino antisense injection directed against the translation start site revealed a defect in synaptic transmission of the ON-pathway (no b-wave) and impaired contrast sensitivity in visual performance assays, indicating that *NYX* mutations lead to rod (mouse model) and cone-postsynaptic (zebrafish model) transmission defect. Similar to effects on the human and mouse visual system, all observed effects of nyctalopin depletion in the zebrafish retina are functional and not structural in nature (Bahadori et al., 2006). Although morpholino models are not good models to document potential disease progression, they are still useful to study the phenotype from morpholino treated larvae at 4 dpf (days postfertilization). Since the phenotype was already present at this early time, it is most likely consistent with the congenital nature of CSNB.

4.2.2.3. Mouse models for GRM6 gene defect. Three mouse models have been described for *GRM6*: One laboratory-generated complete knockout (*Grm6*^{tm1Nak}) (Masu et al., 1995), a naturally occurring mouse (*nob3*) carrying a mutation in intron 2, which leads to a novel splice site with a larger transcript: c.486+648C>T, r.486_487+486ins582_6446, which is predicted to truncate the protein (p.Ile163Glyfs*103) (Maddox et al., 2008) and a chemically induced mouse model (*nob4*) harbouring a missense mutation in exon 3 (c.553T>C; p.Ser185Pro) (Maddox et al., 2008; Pinto et al., 2007) (Table 4). Clinically, the three mouse lines resemble each other in that they all lack the scotopic and photopic b-wave, while the a-waves are well preserved. Furthermore, the retinal cell organization is not affected. The total knockout model rendered *GRM6* as a good candidate to be mutated in patients with cCSNB, which was confirmed by us and others (Dryja et al., 2005; Zeitz et al., 2005b), whereas the other models were identified thereafter. In addition, compound heterozygous mice harbouring the *nob3* and *nob4* mutations showed similar vision impairments, as homozygous *nob3* and *nob4* mice, indicating that *nob3* is allelic to *nob4*. The overall phenotype is in accordance with the phenotype of the *nob* mice and patients with cCSNB described above indicating a dysfunction of ON-bipolar cell signalling. Furthermore, significant visual dysfunction occur in all *Grm6* mutant mice (Iwakabe et al., 1997; Maddox et al., 2008; Takao et al., 2000), similar to the human cCSNB phenotype (Dryja et al., 2005; O'Connor et al., 2006; Zeitz et al., 2005b). However, neither the mutant mice nor the patients are completely blind under scotopic or photopic conditions, indicating that there are compensating mechanisms that underlie the differences in retinal output and visual behaviour (Maddox et al., 2008). Phenotypic differences were observed when the responses of retinal ganglion cells (RGC) of *nob3* were compared to *nob4* mice, which were explained by the different type of mutations (Maddox et al., 2008). Although there was severe ON-GC dysfunction, as in other *Grm6* mutant mice, OFF-centre RGC respondes to full-field stimulation differed to those in *nob4* mice, with fewer altering their receptor field centre sign response to become OFF/ON (Maddox et al., 2008). The authors suggested a different input to the inner retina between *nob3* and *nob4* ON-bipolar cells due to distinct mutations. RGC response recording in other *Grm6* mouse models (to be developed) and in patients could be used to test this hypothesis.

4.2.2.4. Zebrafish model for GRM6 gene defect. Phylogenetic and gene structure analysis indicated that the zebrafish genome harbours two *Grm6* paralogs, namely *Grm6a* and *Grm6b*. Studies on expression and on function using morpholinos revealed a concentration-dependent reduction of the ERG b-wave (cone ON-response), and suggested that *Grm6b* represents the ortholog of *GRM6* (Huang et al., 2012) (Table 4). In addition to expression and localization in bipolar cells it was also found in ganglion cells, suggesting a more widespread role for GRM6-mediated signalling in the central nervous system. These studies show that morpholino models are not only important to study specific functions of a protein but can also help to identify the real ortholog of genes with high sequence homology as found for the class III metabotropic glutamate receptors (GRM4, GRM6, GRM7 and GRM8).

4.2.2.5. Horse model for TRPM1 gene defect. Horses homozygous for a specific coat pattern, termed leopard complex spotting or appaloosa spotting, were described with an undetectable ERG b-wave under scotopic conditions and a reduced b-wave under photopic conditions (Table 4) (Sandmeyer et al., 2007) suggesting a phenotype similar to cCSNB. Association studies of the coat pattern in these horses revealed that this trait is directly linked to the CSNB phenotype. Transcript analysis of genes linked to this disorder revealed that *TRPM1*, also known as melastatin (*MLSN1*), was significantly down-regulated in the retina and skin of affected animals (Bellone et al., 2008). DNA sequencing of annotated *Trpm1* exons in horse did not identify a causative mutation, however fine mapping detected a single haplotype associated with the specific coat pattern and CSNB (Bellone et al., 2010b). Targeted DNA re-sequencing of a 300 kb region surrounding this haplotype identified three associated SNPs: in intron 2: g.108281765T>C and g.108288853C>T and g.108337089T>G in the potential regulatory region 5′upstream of *Trpm1* (SNP exchange on reverse strand given) (Bellone et al., 2010a, 2010b; Sandmeyer et al., 2012). RNA-Seq data pinpointed a 1378 bp insertion in intron 1 of *TRPM1* as the potential cause. The insertion has been characterized as a long terminal repeat (LTR) of an endogenous retrovirus, which was strongly associated with the coat pattern and the CSNB phenotype (Bellone et al., 2013). This insertion is thought to disrupt normal gene expression by premature polyadenylation (Bellone et al., 2013).

4.2.2.6. Mouse models for TRPM1 gene defect. In addition to the naturally occurring *Trpm1* horse mutant, knockout *Trpm1*ΔEx4-6 (*Trpm1*^{tm1Lex}) with inserted neo-cassette in exons 4–6 were generated and initial scotopic ERGs revealed a complete lack of the b-wave but normal a-wave (Shen et al., 2009), confirming that TRPM1 plays an important role in ON-bipolar cell function (Table 4). Together, the studies of *Trpm1* in horse and mouse rendered this gene a good candidate to be mutated in patients with cCSNB, which was later confirmed (Audo et al., 2009; Li et al., 2009; van Genderen et al., 2009). In the same year two independent studies used these mice to substantiate the hypothesis that TRPM1 is required for the depolarizing light response in retinal ON-bipolar cells (Koike et al., 2010; Morgans et al., 2009), by showing that under scotopic and photopic conditions homozygous mutants lack the b-wave, whereas the a-wave amplitudes are preserved (Morgans et al., 2009). While the ON-bipolar cell responses are completely abolished, the OFF-responses are not affected. Together these studies clearly show that the mouse model resembles the human phenotype. In addition to the *Trpm1* knockout mouse model described above, an ENU induced mouse model with a missense mutation in exon 23 (c.3202G>A, p. Ala1068Thr) of *Trpm1* (*Trpm1*$^{tvrm27/tvrm27}$) (Table 4) has been described. Homozygous *Trpm1*$^{tvrm27/tvrm27}$mice shows the same ERG phenotype with normal anatomy as homozygous *Trpm1*^{tm1Lex} mice. This holds also true for compound heterozygous F1 offspring from crossed homozygous *Trpm1*$^{tvrm27/tvrm27}$ and *Trpm1*^{tm1Lex} mice, indicating that the *tvrm27* is an allele of *Trpm1* (Peachey et al., 2012a). Interestingly, although the phenotype of heterozygous *Trpm1*^{tm1Lex} mice is comparable to wild-type mice, heterozygous *Trpm1*$^{+/tvrm27}$ showed reduced ERG b-wave amplitudes in dark-adapted conditions (32% decrease). This phenomenon has not been observed in other autosomal recessive mouse lines tested (*Grm6*, *Gpr179*) (Peachey et al., 2012a). A similar reduction in the response of *Trpm1*$^{+/t\ tvrm27}$ depolarizing bipolar cells on GRM6 agonist LY341495 or the TRP agonist capsaicin (Caterina et al., 1997) was evident in patch-clamp whole cell recordings, indicating that the p.Ala1068Thr mutation has dominant negative effect with respect to TRPM1 channel function. These findings are important for diagnosis in patients. Indeed in some of our patients with cCSNB only one heterozygous mutation has been detected. However due to the absence of other family members, we were only able to show probable autosomal dominant CSNB due to *TRPM1* mutation for one family (Table 1.7) (Audo et al., 2012b).

4.2.2.7. Mouse model for GPR179 gene defect. The *nob5* mouse lacking functional GPR179 represents a spontaneous mutation in a colony of C3H mice and was identified via ERG when this line was crossed to a line of C3H mice lacking the *rd1* mutation (C3H-f$^{+/+}$) (Peachey et al., 2012b). Mapping, genome capture, high throughput sequencing and direct sequencing revealed a ~6.5 kb transposable element inserted in intron 1 of *Gpr179*, which led to a dramatic reduction of *Gpr179* expression and likely represents a null allele (Peachey et al., 2012b). Similarly, as observed for the other mice with cCSNB, *nob5* mice did not show any recordable b-wave under dark adapted conditions, while the a-wave amplitudes were preserved. Under light-adapted conditions the b-wave amplitudes were severely reduced or absent (Peachey et al., 2012b). The retinal anatomy was not affected. These findings are in accordance with a dysfunction of the depolarizing bipolar cell pathway as found in the other models of cCSNB.

4.2.2.8. Zebrafish model for GPR179 gene defect. To test directly whether reduced *Gpr179* expression was responsible for the *nob5* ERG phenotype, Peachey et al. (2012b) generated a zebrafish morpholino against the translation start of *Gpr179* (Table 4). These morpholinos resulted in significantly reduced ERG b-wave amplitudes, similar to those obtained from embryos injected with morpholinos against *Nyx* (Bahadori et al., 2006; Peachey et al., 2012b). Together, the findings in zebrafish, mouse and patients confirmed the role of GPR179 in cCSNB on depolarizing ON-bipolar cell function (Audo et al., 2012a; Peachey et al., 2012b).

4.2.2.9. Mouse model for LRIT3 gene defect. To obtain an *in vivo* tool to study the pathogenic mechanism of cCSNB due to mutations in *LRIT3*, we characterized a commercially available mouse model lacking functional LRIT3 (LEXKO-2034, Lexicon Pharmaceuticals, The Woodlands, TX, USA and Taconic, Hudson, NY, USA) (Neuillé et al., 2014). For this line no obvious phenotype has been noted by the company (Lexicon Pharmaceuticals: i.e. normal behaviour, haematology, endocrinology, immunology, cardiology, radiology, fertility, ophthalmology). The knockout allele for *Lrit3* produces a transcript including 21 bp of exon 3 and the first 8 bp of the selection cassette (c.611_2046delinsGGCCATAG), which leads to a premature stop codon (p.Phe204Trpfs*3) (Table 4). If a protein is produced, it would code for a shorter protein lacking the Immunoglobulin-like (Ig-like), Serine-rich, fibronectin III, transmembrane and PDZ-binding domains. Similar to other cCSNB mouse models, *Lrit3* mutant mice, exhibited a *nob* phenotype (*nob6*) with severely reduced or undetectable b-waves in the scotopic and photopic ERGs (Neuillé et al., 2014). Optomotor tests revealed strongly decreased responses under scotopic conditions. While no obvious FAF or histological retinal structure abnormalities were observed, SD-OCT showed thinning of the inner nuclear layer, inner plexiform layer, ganglion cell layer and nerve fiber layer but with sparing of the outer nuclear layer (Neuille et al., 2014). Similar findings have been observed in cCSNB patients with *GRM6* mutations (Godara et al., 2012). Future studies are needed to investigate whether selective thinning of these layers is associated with other cCSNB gene defects. The phenotype of the *nob6* mice was noted at 6 weeks and at 6 months and thus confirmed the stationary nature of the phenotype. This novel mouse model is likely to prove useful for investigating the pathogenic mechanism associated with *LRIT3*

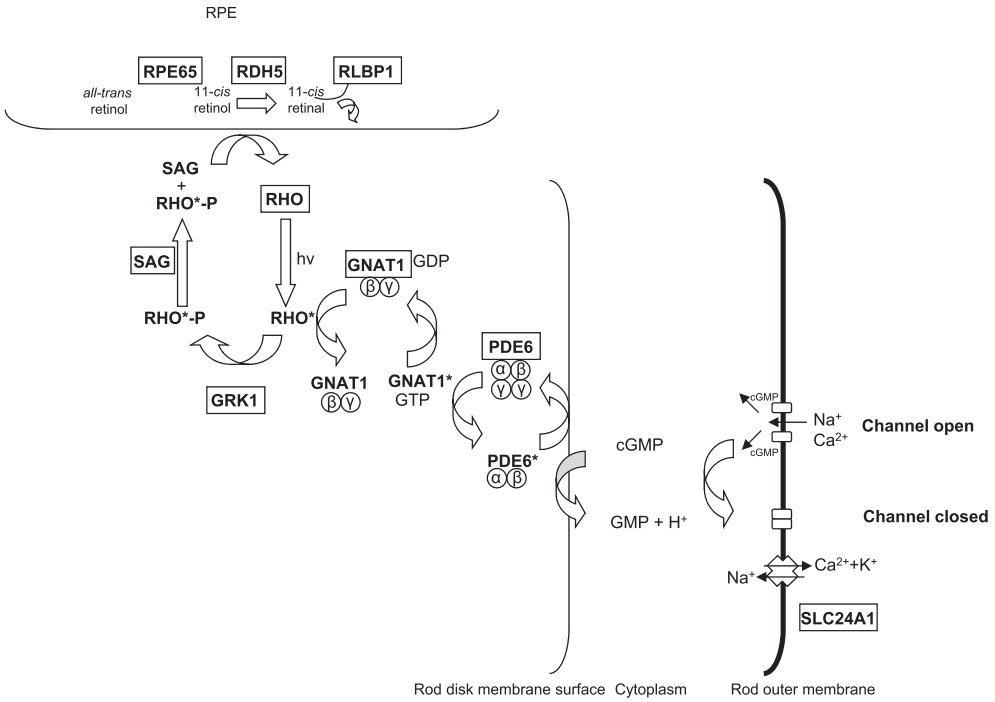

Fig. 11. Schematic drawing of the molecules of the phototransduction cascade highlighting only those implicated in CSNB (boxed).

mutations and for clarifying the role of LRIT3 in the ON-bipolar cell signalling cascade (Neuillé et al., 2014).

5. CSNB disease mechanisms

5.1. Molecules important in the phototransduction cascade and retinoid recycling (RHO, GNAT1, PDE6B, SLC24A1, RDH5, RPE65, RLBP1, GRK1 and SAG)

Several forms of CSNB are caused by mutations that affect molecules of the phototransduction cascade or retinoid recycling and these are highlighted in Fig. 11. Rhodopsin (RHO), a seven transmembrane G-protein coupled receptor represents the light-sensitive pigment of rod photoreceptors, which consists of the 11-*cis*-aldehyde of vitamin A (11-*cis*-retinal) bound covalently to opsin. Upon absorption of a photon by the rods, the chromophore is converted to its *all-trans* isomer and subsequently RHO becomes activated (RHO*). The activated RHO binds the α-subunit of the G-protein transducin (GNAT1), which in turn binds the phosphodiesterase-6 (PDE6) γ subunit. Due to the binding of the PDE6γ subunit by the activated form of transducin, the αβ catalytic subunit of the PDE6 becomes activated. The activated PDE6 then lowers cytoplasmic cyclic guanosine 3′, 5′-monophosphate (cGMP) concentrations; thereby closing cGMP gated cationic channels in the rod plasma membrane. In the dark, sodium (Na^+) and calcium (Ca^{2+}) ions enter the rod and cone outer segments through the open cGMP channel and are extruded by the rod and cone Na^+/Ca^{2+}-Potassium (K^+) exchangers (NCKXs). The extrusion is coupled with an inward Na^+ gradient and an outward K^+ gradient. In response to light, cGMP gated cation channels close, resulting in a reduction in the calcium concentration within the photoreceptor cell because of closure of the channel and the continued function of the exchanger (Sharon et al., 2002). In the rod photoreceptors, SLC24A1 is thought to be the NCKX (Kimura et al., 1999; Reid et al., 1990; Sharon et al., 2002) .

During recovery from the photoresponse, GNAT1 is deactivated by hydrolysis of bound GTP, permitting PDE6 γ subunit to rapidly re-inhibit the PDE6 αβ catalytic subunit (reviewed in (Tsang et al., 2007) (Zeitz, 2007)). The shut-off of the phototransduction cascade occurs via phosphorylation of RHO by rhodopsin kinase (GRK1) and subsequent binding to arrestin (SAG), which further prevents binding of GNAT1 by RHO. The binding of SAG to phosphorylated RHO enables RHO to exchange bleached *all-trans* retinal to 11-*cis*-retinal so that RHO can be activated again by absorption of another photon. Furthermore, 11-*cis*-retinol dehydrogenase, RDH5, which is expressed specifically in the RPE, has been proposed to catalyse the conversion of 11-*cis*-retinol to 11-*cis*-retinal (Simon et al., 1995). RPE65 represents the isomerase, catalyzing the reaction just upstream, converting all-*trans*-retinol to 11-*cis*-retinol (Moiseyev et al., 2005). The hydrophobic 11-*cis*-retinal is chaperoned to the RPE plasma membrane by cellular retinaldehyde-binding protein RLBP1 (Fig. 11) (Lamb and Pugh, 2006).

RHO represents a gene with 5 exons and codes for a protein with 348 amino acids. Computer modelling and *in vitro* studies of the four *RHO* mutations associated with CSNB (p.Gly90Asp, p.Thr94Ile, p.Ala292Glu and p.Ala295Val) (Fig. 12A, Table 1.3) revealed that naturally occurring salt bridges are lacking in the altered rhodopsin proteins, and thus the mutant proteins remain in their active state. Consequently, rod photoreceptors are activated without light, which results in desensitization and reduced photo-response leading to night blindness (al-Jandal et al., 1999; Dryja et al., 1993; Gross et al., 2003a, 2003b; Rao et al., 1994; Rim and Oprian, 1995; Zeitz, 2007; Zeitz et al., 2008). In contrast, mutations in *RHO* leading to RP have been associated with progressive degeneration of rod photoreceptors due to apoptosis. Early symptoms include night blindness but classically patients develop tunnel vision and progressive centripetal visual field loss with eventual central macular cone involvement (reviewed in (Garriga and Manyosa, 2002; Zeitz, 2007)). Constitutive activation of RHO as the pathogenic mechanism for CSNB was in accordance with *in vivo* studies: Sieving and co-workers showed that transgenic mice harbouring the p.Gly90Asp exchange have normal numbers of photoreceptors, but a considerable loss of rod sensitivity as measured by ERG. The desensitization effect increased with the

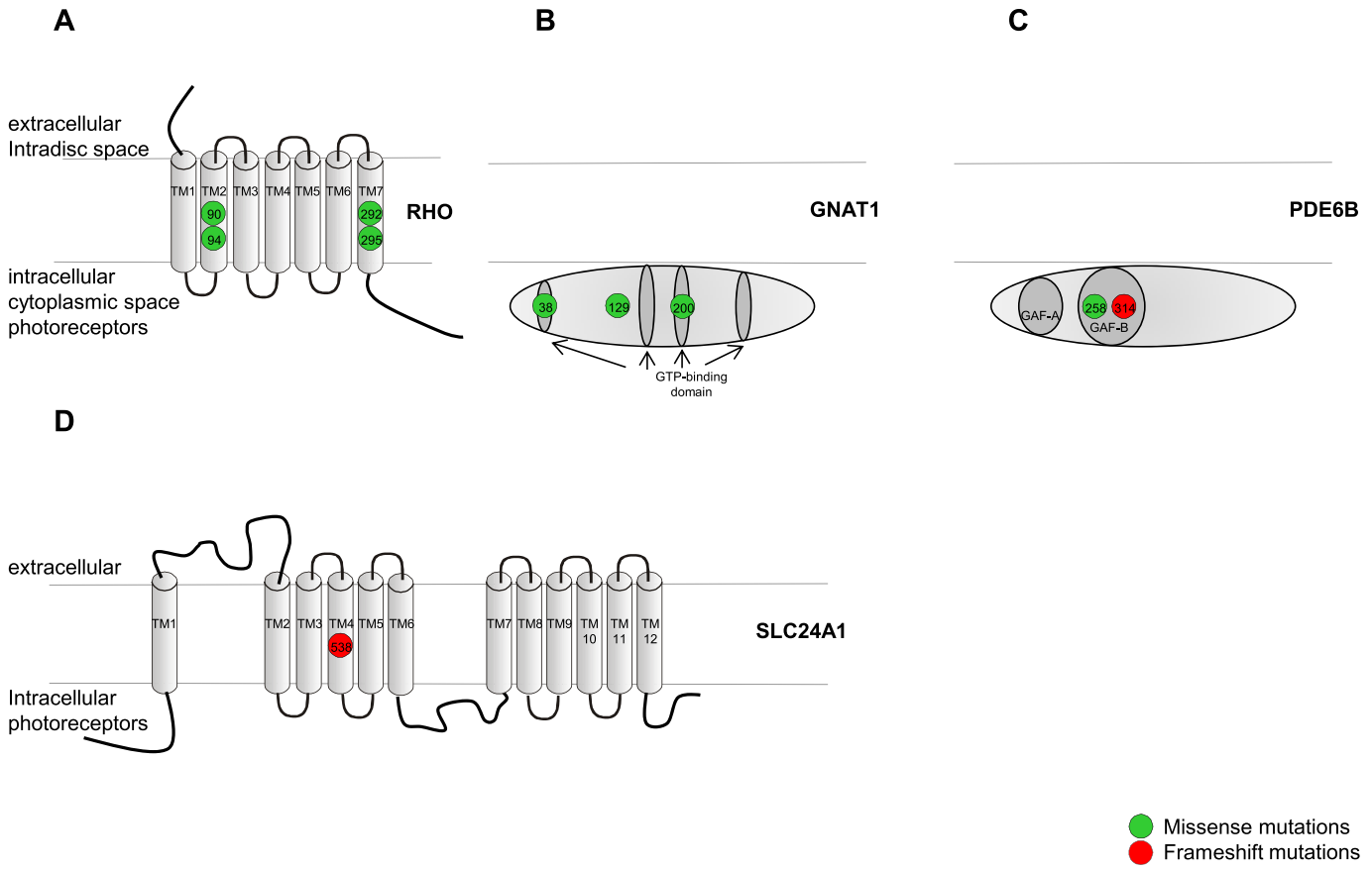

Fig. 12. Schematic drawing of A) RHO (Ref: NM_000539), B) GNAT1 (Ref: NM_144499.2, C) PDE6B (Ref: NM_000283) and D) SLC24A1 (Ref: NM_004727.2) with known frameshift (red) and missense (green) mutations. Topological models were drawn with the most prominent domains (if known) in accordance to prediction programs (http://www.uniprot.org/) or previous publications (Riazuddin et al., 2010).

copy number of mutant alleles (Sieving et al., 2001). Naash and co-workers argued that the ERG sensitivity loss in another transgenic line carrying the same amino acid exchange derives from the reduced quantal absorption that results from a failure of p.Gly90Asp opsin to bind to its chromophore and form a normal complement of light-sensitive visual pigment (Naash et al., 2004). In addition to reduced rod sensitivity older mice and mice expressing higher levels of p.Gly90Asp opsin showed signs of retinal degeneration and some disruption of photoreceptor morphology (Naash et al., 2004). Modifiers and the amount of mutant allele may influence the phenotype. Constitutive activation was also shown in *Xenopus laevis* with transgenes expressing the mutated coding sequence (p.Gly90Asp, p.Thr94Ile and p.Ala292Glu of bovine rhodopsin.

GNAT1 represents a gene with 9 exons and codes for a protein with 350 amino acids containing four GTP-binding sites (Fig. 12B). Initially, constitutive activation was also the suggested mechanism for the p.Gly38Asp substitution in *GNAT1* (Dryja et al., 1996) (Fig. 12B, Table 1.1). However, *in vitro* studies have shown that this variant did not affect the affinity of the activated form of transducin (α) (GNAT1) (Fig. 11) to the $\beta\gamma$ subunit of transducin, nor the ability of the heterotrimer to be activated by the photo-excited RHO. The most striking impairment was a defect in the mutant effector function. Activated GNAT1 failed to bind the γ subunit of PDE6 to activate PDE6. Thus in contrast to CSNB caused by constitutive activation of the visual cascade by rhodopsin mutants, this *GNAT1* mutation results in decreased visual signalling due to loss of transducin effector function (Muradov and Artemyev, 2000; Zeitz, 2007). These findings were confirmed by biochemical studies in transgenic mouse lines carrying the p.Gly38Asp (Moussaif et al., 2006). This is in contrast with "true" constitutively active GTPase-deficient transgenic mutant mice carrying a p.Gln200Leu in GNAT1 (Kerov et al., 2005) (Table 4). More recently a second GNAT1 exchange, p.Gln200Glu, underlying autosomal dominant CSNB in patients has been identified (Fig. 12B) (Szabo et al., 2007). Comparison to the existing mouse model with amino acid Gln200 being affected, computer modelling and biochemical data suggested that this p.Gln200Glu mutant exhibits impaired GTPase activity, and thereby leads to constitutive activation of the phototransduction cascade (Szabo et al., 2007). A third GNAT1 variant, p.Asp129Gly was recently associated with autosomal recessive CSNB having a predicted impact of the structure of the protein (Naeem et al., 2012) (Fig. 12B, Table 1.1). However, the exact pathogenic mechanism remains unclear and it is not known why this mutation leads to autosomal recessive and the other mutations to autosomal dominant CSNB. Due to structural abnormalities the p.Asp129Gly GNAT1 mutant may be degraded, but in contrast to the dominant mutations, one normal GNAT1 allele may be sufficient to maintain function. Thus, the underlying pathogenic mechanism and mode of inheritance of *GNAT1* mutations in autosomal dominant CSNB and autosomal recessive CSNB may be mutation dependant.

PDE6B is a gene with 22 exons, codes for a protein with 854 amino acids and contains two cGMP-specific phosphodiesterase, adenylyl cyclase and FhlA (GAF-A and GAF-B) domains (Fig. 12C). To investigate the pathogenic mechanism of CSNB due to the p.His258Asn substitution in *PDE6B* similar *in vitro* studies have been performed (Muradov et al., 2003) (Fig. 12C, Table 1.2). The authors showed that, although this mutant protein can still directly bind cGMP, re-binding of the

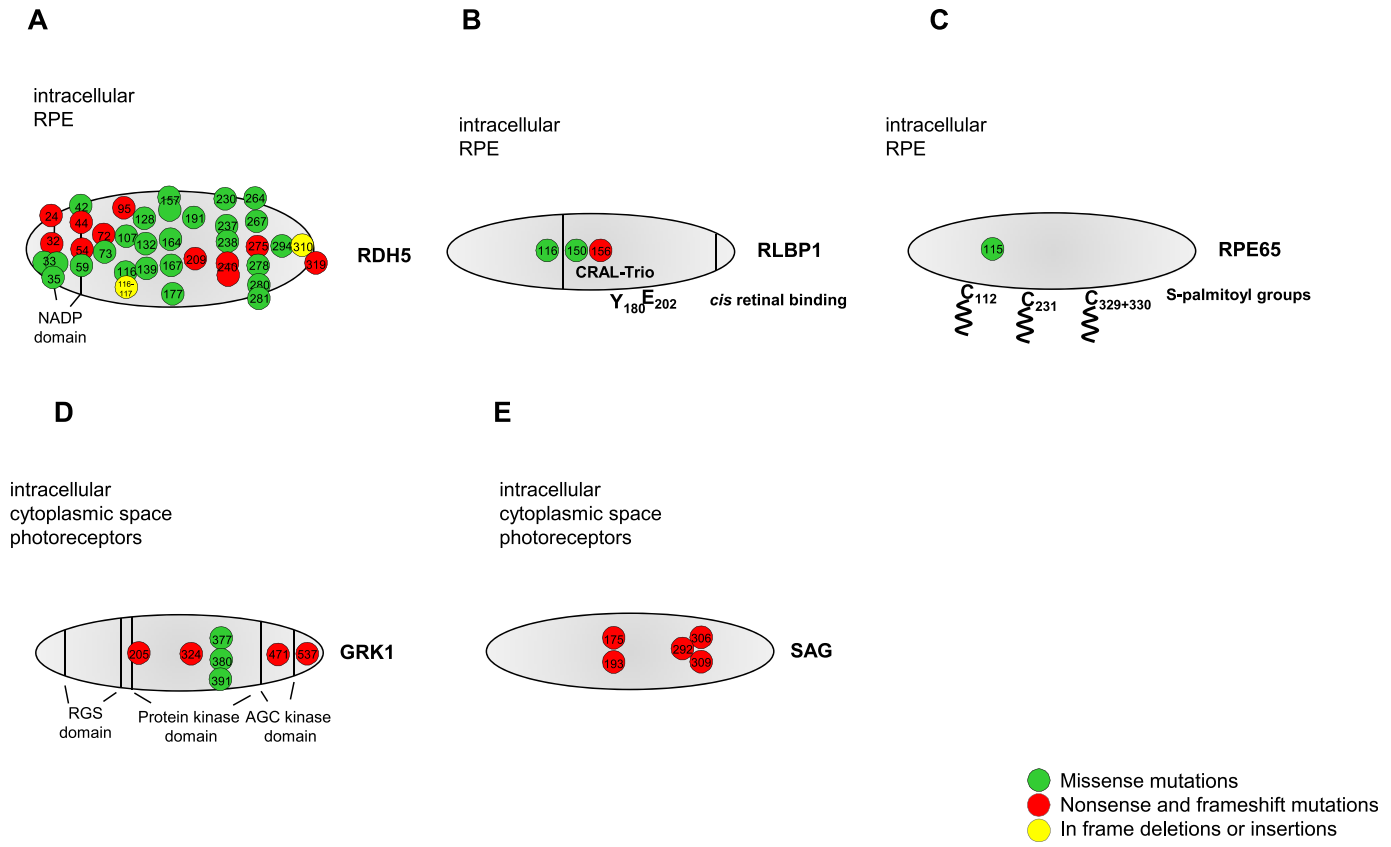

Fig. 13. Schematic drawing of A) RDH5 (Ref: NM_001199771.1), B) RLBP1 (NM_000326.4), C) RPE65 (Ref: NM_000329.2), D) GRK1 (Ref: NM_002929.2), E) SAG (Ref: NM_000541), with known different nonsense, frameshift (red), missense (green) mutations and in frame insertions and deletions (yellow). Topological models were drawn with the most prominent domains (if known) in accordance to prediction programs (http://www.uniprot.org/).

inhibitory γ-subunits is decreased (Fig. 11). Thus reduced affinity for the γ-subunits should constitutively stimulate PDE6 and desensitize rods, similar to the pathogenic mechanism observed in CSNB patients with *RHO* mutations. More recently a novel mutation (c.940_941insGCTTCTCAGGAAATTGTCTTCT) in an autosomal dominant CSNB patient has been described leading to a p.Tyr314Cysfs*50 (Manes et al., 2014) (Fig. 12C). Studies in rod-photoreceptors of transgenic frogs expressing truncated PDE6B show that the mutant can still traffic to the rod outer segments. However, the truncated mutant maintains the ability to bind non-catalytic cGMP and the inhibitory γ subunit, and thus interferes with the inhibition of normal PDE6αβ catalytic subunit by the γ subunit (Manes et al., 2014). Constitutive activation of the phototransduction cascade was suggested as the pathogenic mechanism leading to the absence of rod adaptation and CSNB. This is in contrast with RP patients carrying *PDE6B* or *PDE6A* mutations. These mutations are likely to produce folding defects of the protein, which lead to the absence of PDE6 activity associated with elevation of cGMP levels. This elevation is thought to be a general cause of retinal degeneration in RP patients (Muradov et al., 2003). These results were validated in transgenic mice carrying the same exchange in the respective mouse protein (Tsang et al., 2007). The cGMP-phosphodiesterase activity of dark adapted p.His258Asn mice showed an approximately three-fold increase in the rate of cGMP hydrolysis, consistent with the hypothesis that inhibition of the PDE6 activity by the regulator γ subunit is blocked in the mutant. Phenotypic differences were noted (see also 4. Animal models for CSNB), which are most likely caused by differences in the genetic background.

SLC24A1 represents a large gene with 10 exons and codes for a protein with 1099 amino acids. To date only one homozygous *SLCA24A1* (c.1613_1614del, p.Phe538Cysfs*23) mutation has been implicated in autosomal recessive CSNB and was found in the fourth transmembrane region, in the first of two ion exchanger domains (Riazuddin et al., 2010) (Fig. 12D, Table 1.4). In the absence of *in vitro* and *in vivo* studies it was suggested that the mutation leads either to nonsense-mediated mRNA decay or to a modified NCKX lacking important cation-binding and transporter domains. The complete or even partial loss of SLC24A1 would result in abnormal levels of intracellular Ca^{2+} concentrations that could potentially interfere with the proper functioning of the rod photoreceptors (Riazuddin et al., 2010). Depending on the site of mutation this gene may be implicated in CSNB or RP (Sharon et al., 2002).

RDH5 contains 5 exons, encoding a protein with 318 amino acids. It is implicated in FA (Fig. 13a, Table 1.13) and is expressed in the RPE, where it is involved in the recycling of rhodopsin by catalyzing the conversion of 11-*cis*-retinol to 11-*cis*-retinal (Fig. 11). *In vitro* studies of recombinant mutant RDH5 showed reduced activity compared with recombinant wild type enzyme (Yamamoto et al., 1999). However, RDH5 seems not to be the only enzyme important for the conversion of 11-*cis* retinol to 11-*cis* retinal. Studies using RPE membranes indicated the existence of an alternative oxidizing system for the production of 11-*cis* retinal (Cideciyan et al., 2000) and *Rdh5*$^{-/-}$ mice were still capable of regenerating their rod visual pigment (Driessen et al., 2000). Other enzymes such as RDH11 (Kim et al., 2005), are also important for this conversion, but are not discussed here since they have not been implicated in CSNB.

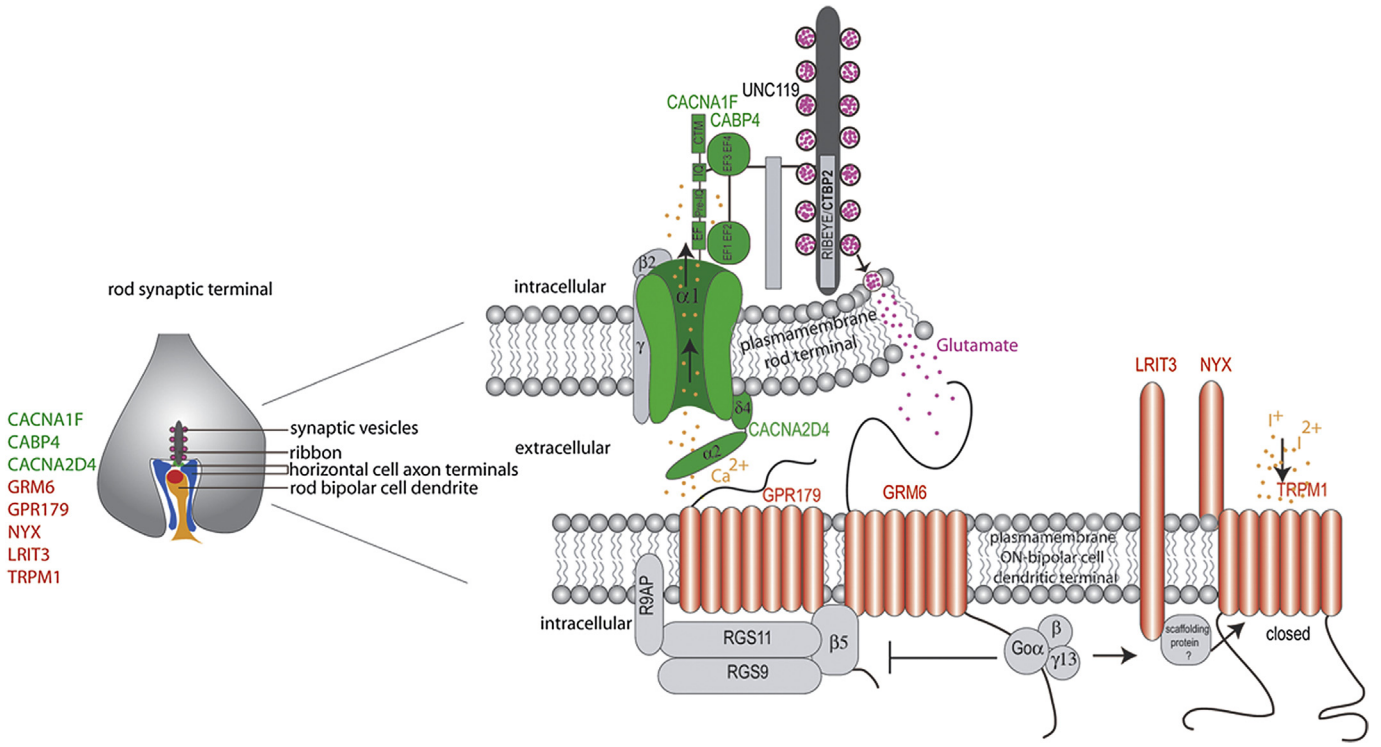

Fig. 14. Schematic drawing of major molecules important for the glutamate release at photoreceptor synapse (shown for a rod cell) and the downstream ON-bipolar cell signalling. Molecules associated with icCSNB/cone or cone-rod dystrophy are shown in green. Molecules associated with cCSNB are shown in red.

RLBP1 (Fig. 13B) represents a gene with 9 exons and codes for a protein with 317 amino acids and *RPE65* represents a gene with 14 exons and code for a protein with 533 amino acids (Fig. 13C). In rare cases these genes have been implicated with RPA showing phenotypic similarties to FA (please see above, Tables 1.14 and 1.15). It was suggested that RPE65, RDH5 and RLBP1 interact physically in the retinoid cycle in the RPE (Schatz et al., 2011), which may explain the similar phenotype found in these cases.

The two genes, *GRK1* with 7 exons coding for 563 amino acids (Fig. 13D) and *SAG*, with 16 exons coding for 405 amino acids (Fig. 13E), mutated in patients with OD encode photoreceptor proteins involved in recovery after photoactivation (Fuchs et al., 1995; Hayashi et al., 2006; Maw et al., 1998; Nakamura et al., 2004b; Yamamoto et al., 1997) (Fig. 11) (Tables 1.17 and 1.16). *In vitro* experiments demonstrated that a deletion in exon 5 of *GRK1* abolishes its enzymatic activity. Thus it was suggested that the lack of phosphorylation and SAG binding to the activated form of RHO leads to a reduction of the recovery of the inactivated form of RHO. This could explain the reduced rod sensitivity, observed in patients with OD (Cideciyan et al., 1998). *In vivo* studies confirmed those findings: single photon response in $Sag^{-/-}$ or $Grk1^{-/-}$ mice revealed basically no shut-off of the phototransduction cascade (Fig. 11), indicating that the photoreceptors remain in the hyperpolarized state. Each photoactivated RHO molecule stays active until its binding to photoisomerized *all-trans*-retinal is lost. Thus GRK1 and SAG are both necessary for normal deactivation of RHO (Chen et al., 1999a, 1999b; Xu et al., 1997).

5.2. Molecules important for glutamate release (*CACNA1F, CABP4* and *CACNA2D4*)

CACNA1F, CABP4 and *CACNA2D4* mutated in icCSNB or cone/cone-rod dystrophies encode proteins, which play a role downstream of the phototransduction cascade, by transmitting signals from the photoreceptors to the adjacent bipolar cells. *CACNA1F* encodes the α_1-subunit (CACNA1F, Cav1.4) of an L-type voltage-dependent Ca^{2+} channel (VDCCs), which mainly localizes to photoreceptors and more specifically in a horse-shoe-shaped manner to rod and cone photoreceptor synapse active zone within the outer plexiform layer (OPL) (Liu et al., 2013; Michalakis et al., 2014; Morgans, 2001; Specht et al., 2009) (Fig. 14). This subunit is part of a heteromultimeric protein complex, consisting of the α_1-subunit, which forms the pore that carries the calcium influx across the synaptic membrane, and the subunits β, γ and α2δ are auxiliary molecules (Catterall, 2000). The α1-subunit imparts most of the conductive properties of the channel, whereas the auxiliary subunits modulate calcium currents and channel activation/inactivation kinetics (Arikkath and Campbell, 2003; Gurnett et al., 1996; Song et al., 2003). The latter subunits are also involved in proper assembly and membrane localization of the calcium channel complexes (Arikkath and Campbell, 2003). Experiments have suggested that the corresponding β subunit of this channel in photoreceptors is β2, which is encoded by *Cacna2b*. Deletion of this β2-subunit in mice causes a similar phenotype as in patients and mice with *CACNA1F* mutations, and the normal distribution of the α_1-subunit of the channel in the OPL is indeed dependent on the expression of this β2-subunit (Ball et al., 2002) (Fig. 14). Similarly, the α2δ4 (CACNA2D4) protein is most likely the α2δ-subunit in photoreceptors (Fig. 14), as animals and patients have a similar icCSNB and cone/cone-rod/rod-cone dystrophy phenotype (Wycisk et al., 2006a, 2006b) and the protein localizes in photoreceptor synapses in the OPL (Mercer et al., 2011). The Ca^{2+} influx through Cav1.4 channels triggers the continuous release of glutamate from the photoreceptor synapse in the dark to the ON-bipolar dendrites which express mainly the high-affinity, sixth subtype metabotropic glutamate receptor (GRM6 also called mGluR6) (see 5.3 Molecules important for glutamate-induced signalling from the photoreceptors to ON-bipolar cells (GRM6,

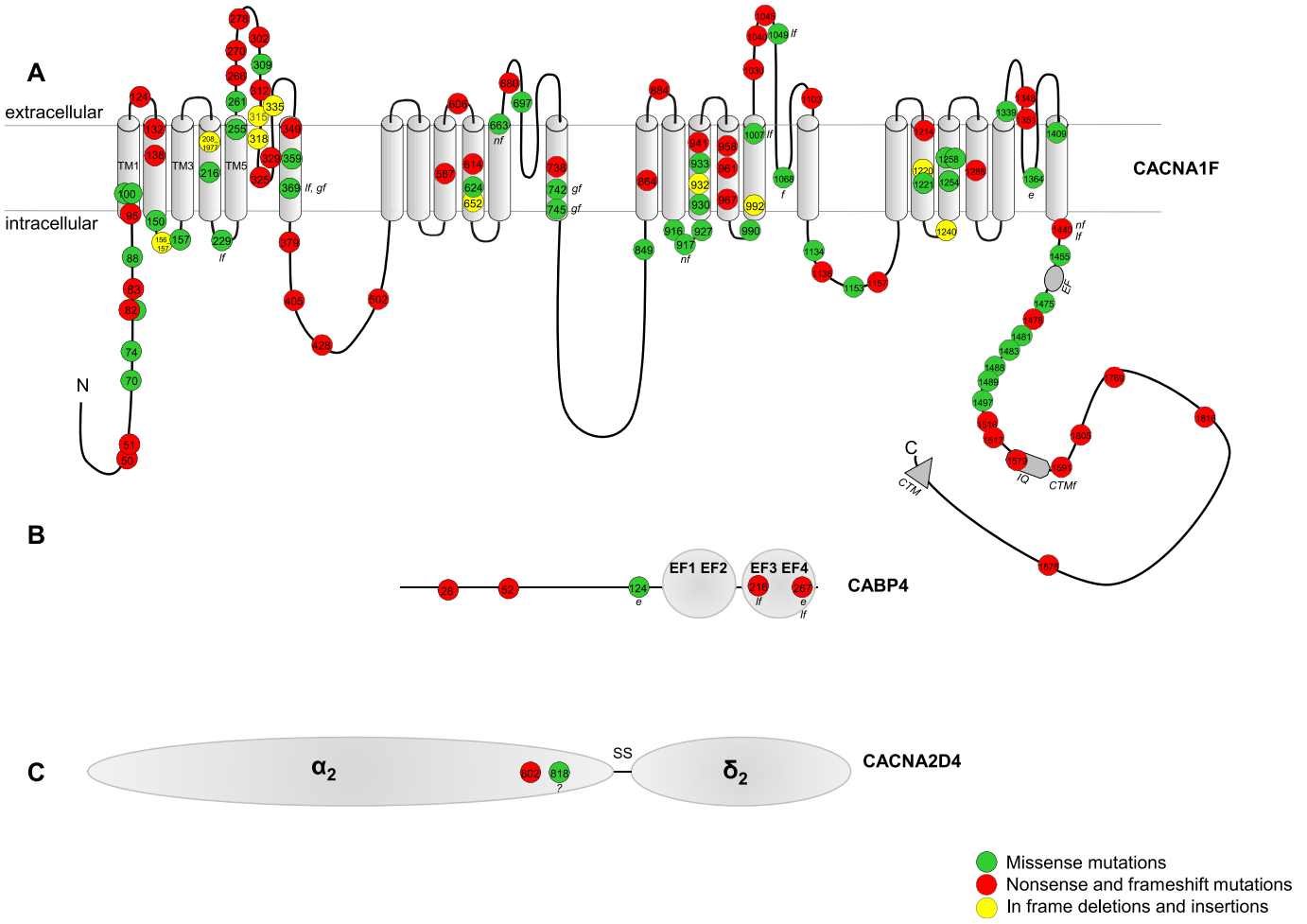

Fig. 15. Schematic drawing of A) CACNA1F (Ref: AJ006216), B) CABP4 (Ref: NM_145200.3) and C) CACNA2D4 (Ref: NM_172364.4) with known and novel different nonsense, frameshift (red), missense (green) mutations and in frame insertions and deletions (yellow). The presumedsplice site mutations (Table 1) are not depicted. EF = putative EF-hand motif; IQ = IQ-motif, CTM = C-terminal modulator; TM = transmembrane domain; *lf* = loss of functional defect; *gf* = defect causing gain of function; CTM*f* = CTM functional defect; *nf* = no functional defect identified; e = *expression* defect; ? Unclear if mutation since only found heterozygously in a patient. Topological models were drawn with the most prominent domains (if known) in accordance to prediction programs (http://www.uniprot.org/).

GPR179, NYX, TRPM1, LRIT3); horizontal cells as well as OFF-bipolar cells employ ionotropic glutamate receptors (for review (Wassle, 2004)). Ionotropic glutamate receptors will not be discussed in this article, since to date none have been implicated in CSNB or in retinal disease in general. The Cav1.4 C-terminus possesses regulatory functions and contains a Ca^{2+}-binding EF-hand domain, a pre-IQ and IQ-domain as well as an inhibitor of Ca^{2+}-dependent inactivation (ICDI) domain (Shaltiel et al., 2012; Singh et al., 2006; Wahl-Schott et al., 2006). Because this domain further modulates Cav1.4 channel activation it is also termed C-terminal modulator (CTM) (Striessnig et al., 2010) (Fig. 14). This domain performs functionally important intramolecular interactions with the other domains of the Cav1.4 C-terminus. In other calcium channels these other C-terminal domains mediate Ca^{2+}-dependent inactivation (CDI) (Singh et al., 2008; Striessnig et al., 2010). CABPs are neuronal Ca^{2+}-binding proteins with similarity to calmodulin (CAM), which modulate VDCCs (Arikkath and Campbell, 2003; Lee et al., 2002). CABP4 is one member of this family, and like Cav1.4, is specifically located in photoreceptor synaptic terminals (Fig. 14). Like CAM, CABP4 has N-and C-terminal globular domains containing each a pair of EF-hand motifs connected by a central helix, which are important for Ca^{2+} binding (for review: (Haeseleer et al., 2002)). The second EF-hand in the N-lobe is non-functional (Shaltiel et al., 2012) (Fig. 14). It has been shown that CABP4 interacts with the Cav1.4 C-terminus, more specifically with the IQ motif (Haeseleer et al., 2004; Shaltiel et al., 2012) (Fig. 14). Furthermore, *in vitro* studies revealed that CABP4 dramatically increase Cav1.4 channel availability. This effect depends on the presence of the C-terminal CTM region and is absent in mutants lacking the CTM domain (Shaltiel et al., 2012). With respect to its inhibitory effect on CDI, CABP4 and CTM seem functionally equivalent. Other proteins such as UNC119 and RIBEYE/CTBP2, for which protein–protein interactions have been individually shown may link Cav1.4 channels to the synaptic ribbon as suggested by Schmitz and co-workers (Alpadi et al., 2008; Haeseleer, 2008; Schmitz et al., 2012) (Fig. 14), but are not implicated in CSNB.

CACNA1F represents a large gene with 48 exons coding for a protein with 1966 or more amino acids, depending on the isoform. Most of the 126 different mutations currently identified throughout the gene are nonsense, frameshift or missense mutations, but splice site mutations and in frame deletions or insertions have also been described (Table 1.10) (Fig. 15A). The predicted pathogenic mechanism for the nonsense and frameshift mutations is that they truncate the α1-subunit of the channel or lead to nonsense-mediated decay. Several missense mutations have been inserted into

wild-type *CACNA1F* constructs and examined functionally in mammalian and oocyte expression systems by different groups. These i*n vitro* studies showed that the different types of mutations can lead to changes in channel function by different transcript/protein amount, by altered voltage dependence or both (Doering et al., 2007; Hemara-Wahanui et al., 2005; Hoda et al., 2005, 2006; McRory et al., 2004; Stockner and Koschak, 2013). Reduced channel stability that might promote misfolding of Cav.1 channels has been recently indicated as a possible pathogenic mechanism (Burtscher et al., 2014). The p.Gly369Asp resulted in statistically significant changes in the biophysical properties of the channel, while p.Gly663Asp, p.Ala917Asp and p.Trp1440* (position of amino acid according to AJ006216) had little effect on channel function (McRory et al., 2004) (Fig. 15A). However, other studies showed that the p.Trp1440* mutation completely prevented channel function, p.Leu1068Pro and p.Ser229Pro mutations decreased and p.Gly369Asp even increased the channel activity, while the p.Arg508Gln and p.Leu1364His did not affect the gating activity, but reduced the protein expression of the channel (Hoda et al., 2005, 2006) (Fig. 15A). Other studies suggest that p.Arg508Gln represents a common polymorphism or modifier and thus this variant is not depicted (Zeitz et al., 2009). The different observations for the p.Gly369Asp and p.Trp1440* mutations might be due to differences in the expression constructs or different splice variants that have been investigated (Hoda et al., 2005). *In vitro* functional analysis for the p.Phe742Cys revealed gain of function and for the p.Gly1007Arg and Arg1049Trp loss of function as the underlying disease causing mechanism (Peloquin et al., 2007). Similarly, the p.Ile745Thr amino acid exchange leading to a very peculiar and severe phenotype in a New Zealand family was associated with a gain of function (Hemara-Wahanui et al., 2005) (Fig. 15A). The more severe phenotype due to the p.Ile745Thr exchange was also observed in a mouse model, when compared to the *Cacna1f*Δ*Ex14-17* mouse model (>2 month old animals) (Regus-Leidig et al., 2014). However, we are not aware that patients with the p.Phe742Cys mutation, affecting the same functional domain of Cav1.4, show a similar severe phenotype as observed in the New Zealand patients with the p.Ile745Thr exchange. It is not clear if other gain of function mutations in general or at this specific region may lead to more severe phenotypes in patients. Another icCSNB mutation, p.Lys1591* truncates the CTM domain leading to fast Ca^{2+} dependent inhibition and resulting gating differences are suggested to disrupt photoreceptor glutamate release (Singh et al., 2006; Wahl-Schott et al., 2006). Furthermore, it is predicted that mutations located at the C-terminus of the protein may not only influence the channel function, but also affect the binding of CABP4 to Cav1.4 C-terminus. Splice site mutation may affect the fine tuning of the channel as has been shown for alternative splicing of this channel in general (Tan et al., 2012). Mutations that do not show altered function in expression systems may involve sites needed for trafficking or for interaction with the ribbon synapse proteins.

In summary many different *CACNA1F* mutations tested *in vitro* lead to different pathogenic mechanisms, while others do not reveal a significant alteration in channel function or expression. The different type of pathogenic mechanism may explain the variability of the phenotype observed in patients. *In vivo* modelling of the investigated mutants, which did not reveal altered Cav1.4 function, and other mutants to be investigated, may help to establish stronger genotype–phenotype correlations.

CABP4 represents a gene with 6 exons coding for a protein with 275 amino acids. To date, 5 disease causing mutations have been identified (Table 1.11). Blood transcript analysis of two patients carrying either compound heterozygous (c.370C>T; p.Arg124Cys and c.800_801delAG; p.Glu267Valfs*92) or a homozygous mutation (c.800_801delAG; p.Glu267Valfs*92) revealed reduced transcript level, which may lead to lowered channel density (Zeitz et al., 2006), while the CABP4 transcript level of patients with the c.646C>T; p.Arg216* mutation remained the same. Shaltiel and co-workers investigated the p.Arg216* and the p.Glu267Valfs*92 functionally by co-overexpression experiments in the presence of CACNA1F. Although they showed that both mutants interact with CACNA1F, the functional effects of CABP4 mutants are only partially preserved, leading to a reduction of CACNA1F availability and loss of function, which is most likely due to conformational changes of the mutated proteins (Shaltiel et al., 2012) (Fig. 15B).

CACNA2D4 represents a large gene with 38 exons coding for a protein with 1137 amino acids. The nonsense mutation (c.2406C>A; p.Tyr802*) identified in *CACNA2D4* (Fig. 15C) (Table 1.12) is predicted to lead to nonsense-mediated decay (Wycisk et al., 2006b) and indeed, transcript analysis of a mouse with a frameshift mutation in the ortholog gene (c.2451dup; p.Gly818Argfs*15) leads to severely reduced *Cacna2d4* transcript levels (Wycisk et al., 2006a).

Existing total knockout mouse models for *Cacna1f*, *Cabp4* and *Cacna2d4* reveal in general a more severe phenotype than observed in icCSNB patients and thus this species might not represent the best model to understand genotype–phenotype correlations and the pathogenic mechanism for this disease but perhaps for more progressive retinal disorders (see Table 4, and 4.2.1 Animal models for icCSNB).

In summary, mutations in *CACNA1F*, *CABP4* and *CACNA2D4* can be associated with loss or gain of function with insufficiently expressed genes resulting in altered or non-functional Cav1.4 channel activity, which is controlled by the auxiliary subunits (β, γ and α2δ) (Catterall et al., 2005), alternative splicing and associated regulatory proteins (Tan et al., 2012). Together, this disturbs the continuous release of glutamate from the photoreceptor synapse to the bipolar cells resulting in icCSNB, cone or cone-rod dystrophy phenotypes.

5.3. Molecules important for glutamate-induced signalling from the photoreceptors to ON-bipolar cells (GRM6, GPR179, NYX, TRPM1, LRIT3)

The molecules important for further glutamate-induced signalling discussed here are mainly expressed in ON-bipolar cells where they localize in the dendritic tips (reviewed in (Orhan et al., 2013)). During darkness, the photoreceptors continuously release glutamate that binds to GRM6, the metabotropic seven transmembrane G-protein coupled receptor 6 (mGluR6) which activates the alpha subunit of a heterotrimeric G-protein, $G\alpha_o$. This leads to the closure of a non-selective ion channel, TRPM1 (Dhingra et al., 2002, 2000; Koike et al., 2010; Masu et al., 1995; Morgans et al., 2009; Shen et al., 2009) (Fig. 14). $G\alpha_o$ is inactivated by the β subunit of this G protein, β5 and by a GTPase activating (GAP) complex formed by the G-protein signalling regulators RGS7 and RGS11, their membrane anchor R9AP, officially named RGS9BP, and possibly by GPR179. *GPR179* codes for an orphan seven transmembrane G protein-coupled receptor so it is yet not clear if GPR179 has only a regulator function or serves as a co-receptor (for example with GRM6) in this cascade. After light stimulation, the TRPM1 channel opens, leading to depolarization of the ON-bipolar cells, which are largely responsible for generating the ERG b-wave. Specific intracellular motifs present in LRIT3 and *in vitro* and *in vivo* studies of NYX and TRPM1 suggest that LRIT3 and NYX are important for the correct localization of TRPM1 to the dendritic tips of ON-bipolar cells (Pearring et al., 2011; Zeitz et al., 2013). The GAP complex, and also TRPM1, NYX and LRIT3 have been shown in the dendritic tips of ON-bipolar cells (Cao et al., 2012; Gregg et al., 2007; Jeffrey et al., 2010; Koike et al., 2010; Masuho et al., 2010; Morgans et al., 2006, 2007, 2009; Orhan et al., 2013; Orlandi

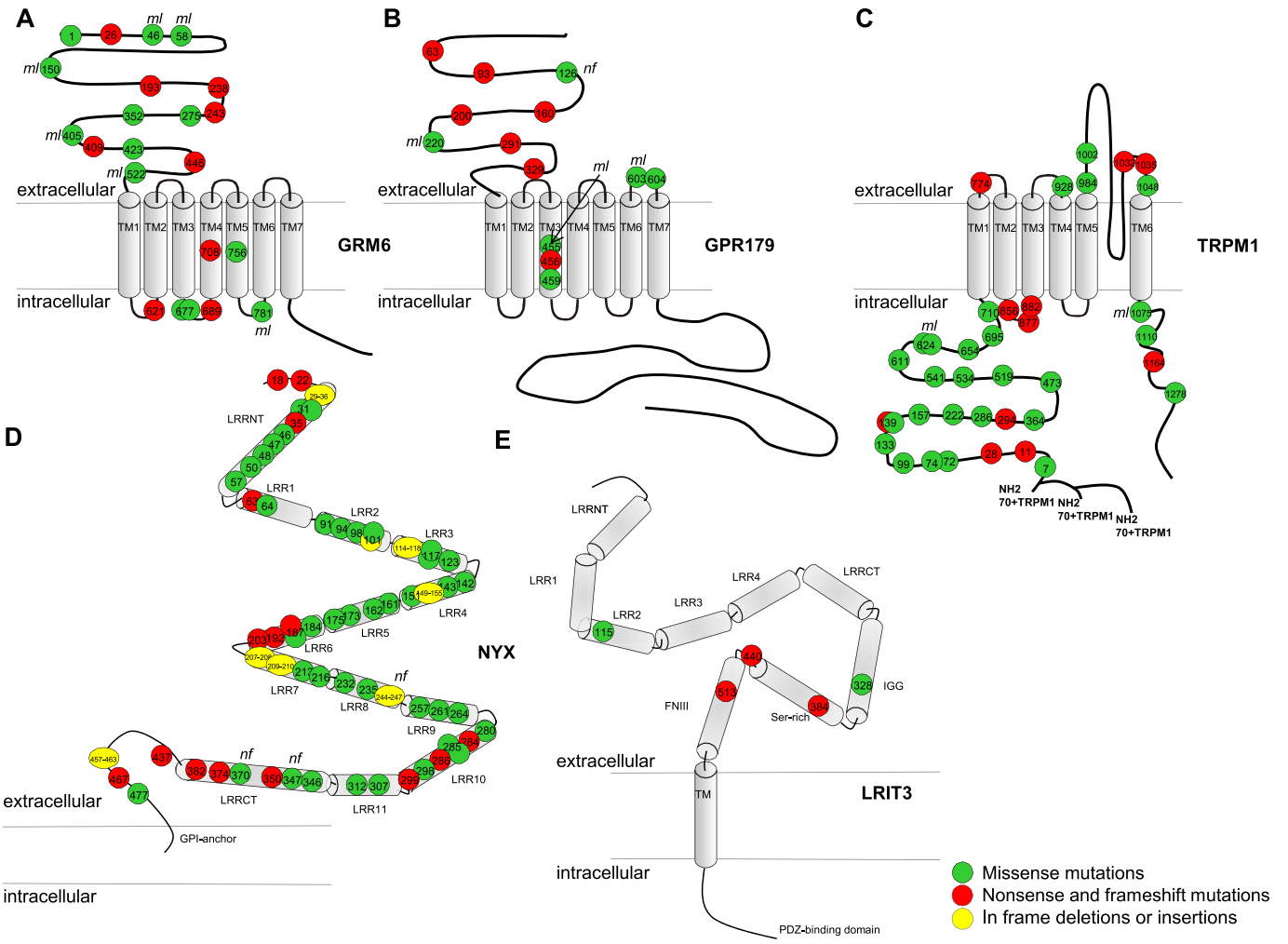

Fig. 16. Schematic drawing of A) GRM6 (Ref: NM_000843), B) GPR179 (Ref: NM_001004334.2), C) TRPM1 (Ref: NM_002420.4), D) NYX 5Ref: AJ278865) and E) LRIT3 (NM_198506.3) with known and novel different nonsense, frameshift (red), missense (green) mutations and in frame insertions and deletions (yellow). The presumed splice site mutations (Table 1) are not depicted. LRRNT = N-terminal leucine-rich repeat (LRR); LRRCT = C-terminal LRR; TM = transmembrane domain; GPI = ; *ml* = mislocalization; *nf* = no functional defect identified. Topological models were drawn with the most prominent domains (if known) in accordance to prediction programs (http://www.uniprot.org/).

et al., 2012; Peachey et al., 2012b; Rao et al., 2007; Shim et al., 2012; Zeitz et al., 2013). Recent immunolocalization studies added a novel molecule, CACNA1S, to this cascade, the exact role of which is yet to be determined (Specht et al., 2009; Tummala et al., 2014). CSNB gene defect identification, as well as *in vitro* and *in vivo* studies have provided important insights into the poorly understood ON-bipolar cell signalling cascade. While all studies are essential to explain the pathogenic mechanism, *in vivo* approaches are particularly useful to localise the respective proteins within the bipolar signalling cascade. Here we concentrate on molecules of this cascade previously implicated in cCSNB.

GRM6 represents a gene with 10 exons coding for the metabotropic glutamate receptor 6 protein with 877 amino acids. So far 22 nonsense, frameshift, and missense mutations in *GRM6* have been identified (Dryja et al., 2005; Malaichamy et al., 2014; O'Connor et al., 2006; Sergouniotis et al., 2011b; Wang et al., 2012b; Zeitz et al., 2007, 2005b) (Table 1.6) (Fig. 16A). For the nonsense and frameshift mutations the underlying pathogenic mechanism is most likely a loss of function of the receptor due to nonsense-mediated mRNA decay or non-functional receptor. Recently, we investigated the pathogenic mechanism of the missense mutations *in vitro*. Some of these mutations are located in the ligand-binding domain, in the cysteine-rich domain and others in the transmembrane domain of the metabotropic glutamate receptor (Zeitz, 2007). Mutations in the ligand-binding domain could lead to a reduced binding affinity for the glutamate by possible conformational changes of the receptor, while the p.Cys522Tyr in the cysteine-rich domain may influence receptor dimerization. Mutations in the transmembrane regions of the glutamate receptor would most likely affect the correct folding and thus the receptor may not reach the cell surface. However our study showed that all investigated missense mutations in *GRM6* lead to a trafficking defect of the GRM6 proteins to the membrane. Although the mutant protein is synthesized in the endoplasmic reticulum (ER), the mutated variants show only reduced Golgi localization and no surface localization at all, while the capability to form dimers is not affected (Zeitz et al., 2007). These data suggest that the complete autosomal recessive CSNB phenotype is due to the lack of the glutamate receptor at the cell surface. The glutamate released from the photoreceptors cannot be bind correctly to GRM6 at the ON-bipolar cell surface, resulting in the blocking of the signal transmission via this receptor. Absence of protein or mislocalization of GRM6 mutant protein was also demonstrated for different mice lacking GRM6 or harbouring mutations in the same gene (Table 4,

Table 5
Animal models for genes underlying congenital stationary night blindness and expression (mis)localizations of the respective or other proteins of the same cascade.

Mouse model	GRM6	GPR179	NYX	TRPM1	LRIT3	GBETA5	RGS7	RGS11	R9AP (RGS9BP)
Grm6$^{-/-}$ (*Grm6*^{tm1Nak})	No RNA DTB no	Reduced protein amount DTB yes	n.d.	Protein yes greatly reduced DTB	n.d.	Reduced DTB	n.d.	Reduced DTB	n.d.
nob3 (*Grm6* c.486+648C>T, r.486_487+486ins582_6446, p.Ile163Glyfs*103)	RNA larger DTB no	Reduced protein amount DTB no	n.d.	Reduced protein amount DTB no	n.d.	Protein yes n.d.	Protein yes n.d.	Reduced protein amount n.d.	Proteins yes n.d.
nob4 (*Grm6* p.Se185Pro)	RNA yes DTB no	n.d.	n.d.	Reduced protein amount DTB no	n.d.	Protein yes Severely reduced DTB	Protein yes Severely reduced DTB	RNA yes Reduced protein amount DTB no	Protein yes Severely reduced DTB
Nob (*Nyx* c.567_651del p.Ile189Metfs*171)	DTB[a] yes	DTB yes	reduced RNA	Reduced protein amount DTB no	n.d.	n.d.	n.d.	n.d.	n.d.
Trpm1 (*Trpm1*ΔEx4-6, *Trpm1*^{tm1Lex})	Protein yes DTB yes	Reduced protein amount DTB yes	DTB yes	no RNA DTB no	n.d.	n.d.	n.d.	n.d.	n.d.
Trpm1 (c.3202G>A, p.Ala1068Thr *Trpm1*$^{tvrm27/tvrm2}$)	DTB yes	n.d.	n.d.	DTB yes	n.d.	n.d.	n.d.	n.d.	n.d.
nob5 (*Gpr179* transposon insertion)	DTB yes	RNA severely reduced DTB no	DTB yes	Reduced protein amount DTB yes	n.d.	n.d.	Protein yes no DTB	Protein yes no DTB	n.d.
nob6 (*Lrit3* c.611_2046delinsGGCCATAG p.Phe204Trpfs*3	n.d.	n.d.	n.d.	n.d.	Altered transcript	n.d.	n.d.	n.d.	n.d.

[a] Dendritic tip staining of bipolar cells = DTB, n.d. = not done.

see also 4.2.2.3 Mouse models mimicking *GRM6* gene defect). All three known mouse models, lacking functional GRM6 (*Grm6*^{tm1Nak}, *nob3* and *nob4*) do not show the typical dendritic tip staining of GRM6 at the ON-bipolar cell surface. In the KO mice, the mRNA is degraded, while the naturally occurring insertion identified in *nob3* mice reveals a larger transcript, and studies in oocytes indicate that the missense mutation identified in *nob4* mice still produce GRM6 protein. However, in both *nob3* and *nob4* mice, GRM6 is mislocalized and not present in the dendritic tips of ON-bipolar cells (Maddox et al., 2008; Masu et al., 1995; Pinto et al., 2007). Other molecules of this cascade showed severe reduction or absence of their dendritic tip ON-bipolar cell staining in the different mouse models lacking GRM6 (Table 5). In contrast, most of the mouse models lacking components of this cascade do not alter the dendritic GRM6 staining to the ON-bipolar cells. Together, these findings may indicate that GRM6 plays a role at the beginning of the cascade and is important for regulation and correct localization of the different molecules (Table 5).

GPR179 represents a large gene with 11 exons coding for an orphan G-protein coupled receptor 179 protein with 2367 amino acids. Until now, 14 different nonsense, frameshift, missense and splice site mutations have been identified (Audo et al., 2012a; Malaichamy et al., 2014; Peachey et al., 2012a) (Table 1.8) (Fig. 16B). Similarly as for GRM6, the nonsense and frameshift mutations are predicted to lead to loss of function of the orphan receptor due to nonsense mediated mRNA decay or non functional receptor. Recently, by performing *in vitro* studies we showed that at least three of the disease causing missense mutations, p.Tyr220Cys, p.Gly455Asp and p.His603Tyr lead to severely reduced cell surface localization of the receptor (Fig. 16B). The splice site mutation leads to missplicing (Orhan et al., 2013). Thus, for most of the mutations identified so far, loss of GPR179 protein at the membrane seems to be the underlying pathogenic mechanism leading to cCSNB. In contrast, the p.Asp126His amino acid exchange seems not to influence the plasma membrane localization (Orhan et al., 2013). The Asp126 residue is localized in the predicted extracellular N-terminal region of the protein (Audo et al., 2012a). Although, the three-dimensional structure of the amino acid residues <300 of GPR179 is currently uncertain, we know from other receptors that the N-terminus of such proteins is important for ligand-binding, and we could therefore hypothesize that the p.Asp126His mutation is also associated with the loss of GPR179 ligand-binding (Audo et al., 2012a) and not with a trafficking defect. However, to verify this hypothesis, the relevant ligand first needs to be identified. The typical dendritic tip staining is abolished in a naturally occurring mouse model carrying a transposable mutation in *Gpr179* (Peachey et al., 2012b). Since *Gpr179* mRNA in these mice is dramatically reduced (Peachey et al., 2012b), nonsense-mediated mRNA decay leading to a null allele is the predicted pathogenic mechanism. Other molecules of this cascade (RGS11, RGS7) showed severe reduction of their dendritic tip staining in the mouse models lacking GPR179 (Table 5). However, GRM6 and TRPM1 immunolocalization was not affected (Orlandi et al., 2012). Mice lacking functional GRM6 have severely reduced dendritic tip staining for GPR179 (Orlandi et al., 2013), but not mice lacking functional TRPM1 (Orlandi et al., 2013) (Table 5) indicating that GPR179 is perhaps important for the regulation/correct localization of regulator proteins but not directly for the correct protein localization of the channel at the end of the cascade.

TRPM1 represents a large gene with 27 exons coding for a transient receptor potential channel, subfamily M, member 1 protein with up to 1642 amino acids depending on the isoforms. Until now, 51 different nonsense, frameshift, missense, splice site mutations and microdeletions have been identified (Audo et al., 2009; Bijveld et al., 2013a; Li et al., 2009; Malaichamy et al., 2014;

Nakamura et al., 2010; van Genderen et al., 2009) (Table 1.7) (Fig. 16C). *In vitro* studies showed that two splice site mutations, c.18-3C>T and c.1023 + 3_6delAAGT, alter normal splicing and lead to abnormal protein production, suggesting that these TRPM1 mutant alleles lead to loss of function (Nakamura et al., 2010). Furthermore, two missense mutations (p.Arg624Cys and p.Phe1075Ser), located in the N- and C-terminal intracellular regions of the six-transmembrane TRPM1 channel inserted in fusion constructs under the control of the GRM6 promoter, reduced typical dendritic tip staining when electroporated in mice retinas (Nakamura et al., 2010). Again, this argues for the underlying pathogenic mechanism of this form of cCSNB being mislocalization of the respective proteins. Our experience for this molecule has shown that pure *in vitro* studies transfecting only normal and mutated TRPM1, in mammalian cells overexpressing this protein, are not sufficient to elucidate the pathogenic mechanism. Even normal TRPM1 alone does not localize to the membrane. Obviously, other components of this cascade need to be present to target TRPM1 to the cell surface. This is in accordance with *in vivo* findings: proteins such as GRM6 and NYX (see below) are important for the correct localization of TRPM1 in the dendritic tips of ON-bipolar cells (Cao et al., 2011; Orlandi et al., 2013; Xu et al., 2012) (Table 5). However, mice lacking TRPM1 protein do not alter GRM6 or NYX dendritic tip ON-bipolar cell localization, which again suggests a role for GRM6 and NYX before TRPM1 in this signalling cascade. Interestingly, a mouse model carrying a missense mutation in *Trpm1* (p.Ala 1068Thr) does not show mislocalization of TRPM1 itself, indicating a dominant negative effect, which would lead to loss of channel function (Peachey et al., 2012a) (Table 4, Table 5). Of note, heterozygous mice also manifest a phenotype (see also 4.2.2.6 Mouse models mimicking *TRPM1* gene defect, Table 4) and some of our cCSNB patients were found to carry only one heterozygous *TRPM1* mutation (Audo et al., 2012b).

NYX represents a small gene with 2 exons coding for nytalopin, a protein containing 11-leucine rich repeat (LRR), flanked by a C-and N-terminal LRR and a GPI anchor with 481 amino acids. To date 69 different missense, nonsense and frameshift mutations, in frame deletions or in frame insertions and microdeletions in *NYX* have been associated with the complete form of CSNB (Bech-Hansen et al., 2000; Bijveld et al., 2013a; Pusch et al., 2000; Simonsz et al., 2009; Wang et al., 2012b; Xiao et al., 2006; Zeitz et al., 2009, 2005a; Zito et al., 2003) (Table 1.5) (Fig. 16D). It is noted that 75% represent missense mutations, which affect amino acids in the LRR core (Fig. 16D). We previously investigated three of these mutations, p.Glu244_Ala247del, p.Leu347Pro and p.Gly370Val, with respect to their impact on subcellular localization (Zeitz et al., 2003). These preliminary results suggest that the location of nyctalopin at the cell surface is necessary for correct function but is not influenced by the mutations. This implies that trafficking defects are not the pathogenic cause of this form of cCSNB, although to test this further, more mutations must be investigated with respect to subcellular localization. Functionally, LRRs have been shown to mediate protein–-protein interactions (Kobe and Deisenhofer, 1994). Recently *in vitro* studies have shown that NYX and TRPM1 (Cao et al., 2011; Pearring et al., 2011) are binding partners and that NYX additionally interacts with GRM6 (Cao et al., 2011). It was suggested that NYX holds TRPM1 at the plasma membrane location (Pearring et al., 2011). Furthermore, *in vivo* studies suggested that GRM6 and NYX are indispensable for correct localization of TRPM1: in mice lacking GRM6 (Cao et al., 2011) or NYX (Pearring et al., 2011), TRPM1 no longer localizes at the dendritic tip of ON-bipolar cells, leading to cCSNB. *In vitro* binding or co-immunolocalization studies with mutated NYX constructs and TRPM1 or GRM6 constructs need to be performed to elucidate if these interaction are abolished, which would explain the pathogenic mechanism related to NYX mutations in cCSNB.

LRIT3 represents another small gene with 4 exons coding for a leucine-rich repeat, immunoglobulin-like domain and transmembrane domain containing protein 3 precursor with 679 amino acids. To date 5 nonsense, frameshift and missense mutations have been described (Zeitz et al., 2013) (Table 1.9) (Fig. 16E). It was suggested that LRIT3, harbouring a PDZ-binding motif, might be a molecule which interacts with intracellular scaffolding complexes to bring the TRPM1 channel to the dendritic tips of bipolar cells and thereafter, NYX and LRIT3 may hold the channel in this form. Confirming this hypothesis will require *in vitro* (binding assays, with normal and mutated constructs) and *in vivo* studies. A recently described mouse model lacking *Lrit3* (Neuillé et al., 2014) (Table 4) may help elucidate this mechanism.

6. Summary and future perspectives

An important first step in the genetic investigation of CSNB is comprehensive phenotyping. Phenotypic characterisation may suggest genes that encode pre- or postsynaptic proteins to be good candidates (Figs. 11 and 14). A “Riggs-type” ERG (marked scotopic ERG a-wave reduction; see Section 2.2.1) may prompt investigation of molecules and novel mutations that affect phototransduction or retinoid recycling whereas an electronegative (“Schubert-Bornshein-type”) ERG (scotopic ERG a-wave normal and b-wave reduced; Section 2.2.2) suggests dysfunction that is postphototransduction. Other ERG and clinical characteristics can refine the phenotype and direct the molecular screening (section 2.2.2).

Certain genotype–phenotype correlations are well established and Sanger sequencing and targeted parallel sequencing may offer the most efficient means of determining a molecular diagnosis. Genetic mapping and candidate-gene approaches, for example those comparing human phenotypes to animal models, have also been widely used (Audo et al., 2009; Pusch et al., 2000; Wycisk et al., 2006b; Zeitz et al., 2006, 2005b). More recently the emergence of massively parallel sequencing techniques has provided a rapid and unbiased mutation detection technology, and has for example, allowed us to identify mutations in two novel genes underlying CSNB (Audo et al., 2012a; Zeitz et al., 2013). There remain patients with no mutation in any of the 17 genes currently associated with CSNB and such cases may be further scrutinized using WES providing other family members are available. Furthermore, expression and protein immunolocalization data, published or acquired *in house*, may help determine which of the variants in a given gene underlie CSNB.

Mutations causing cCSNB may localise to the dendritic tips of ON-bipolar cells, encoding other proteins with a role in postsynaptic signal transmission. It may be speculated that mutations causing icCSNB (associated with preserved ERG a-wave and electronegative waveform with marked cone ERG abnormalities) may occur in genes which play a role in the assembly of a functional calcium channel e.g. like the β2-or γ-subunits on the pre-synaptic photoreceptor terminals (Zeitz, 2007). The phenotypic variability caused by mutations in genes influencing Ca^{2+} current (like human and mouse models for icCSNB) may depend on the location of the mutation within the genes. The channel may be impaired by a reduced quantity of proteins, by its altered binding capacity with other pore-forming or calcium-binding proteins or by its perturbed regulatory activity. In addition, other unknown mutations or polymorphic variants not yet associated with the disease may influence the phenotype. These variants can be located in intronic regions of already known CSNB associated genes or in other genes at sites important for the regulation or expression of the channel. Such a polymorphic variant may act as a modifier of the pathogenic variant affecting the calcium channel. Such modifiers may not

segregate in affected family members and may contribute to phenotypic variability (Zeitz, 2007).

Phenotypic differences between animals and humans have been noted. It is a particular challenge to develop an autosomal dominant CSNB model by a transgene approach with equal distribution of wild-type and mutant allele. The development of uniform standards for animal models and clinical measurement techniques, which are currently largely laboratory-dependent, is likely to prove an important step for collaborative purposes and for pooling of data e.g. the ISCEV standard (Marmor et al., 2009) has enabled more meaningful inter-laboratory comparisons of human ERG data. Although for different gene defects the pathogenic mechanism has been already identified *in vitro* or *in vivo* (e.g. Orhan et al., 2013; Pearring et al., 2011; Zeitz et al., 2007), for others e.g. *LRIT3*, further studies are needed to elucidate the cause of the disease.

Accurate phenotyping and genotyping establish the diagnosis of CSNB and aids genetic counselling and patient management. Such information will be pivotal to develop therapeutic interventions aimed at functional rescue and to identify candidates amenable to potential future treatments. Studies in naturally occurring or generated mouse models for the different types of CSNB indicate that cCSNB results from a functional deficit with no major structural abnormalities (Gregg et al., 2007, 2003; Koike et al., 2010; Masu et al., 1995; Peachey et al., 2012b). This renders the disorder a good target for therapeutic development. Gene therapy can be envisioned to restore function in patients with predicted loss of protein mutations. Proof-of-principle for gene replacement for ON-bipolar dysfunction has been successfully established using transgenic mice expressing EYFP-NYX fusion protein in *nob* mice, leading to restoration of the ERG (Gregg et al., 2007). However, to date gene therapy approaches for CSNB have not been undertaken. Current gene therapy trials (e.g. *RPE65* in LCA, *ABCA4* in Stargardt disease, *MYO7A* in Usher type 1 or CHM in choroideremia) are targeting photoreceptor expression. Most CSNB gene therapy will require bipolar cell targeting, which is technically challenging. Due to the prevalence data and size of the different genes, such a gene delivery approach could be established using mouse models lacking functional NYX or GRM6. If ON-bipolar cells indeed efficiently express the respective proteins, this approach can then be applied to other forms of cCSNB and some other inner retinal disorders. Successful targeting of bipolar cells may also facilitate other therapeutic strategies aimed at restoring vision such as optogenetics for more progressive retinal disorders.

CSNB consortium

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