11 Congenital Stationary Night Blindness (CSNB): An Inherited Retinal Disorder Where Clear Correlations Can Be Made

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Abstract

Congenital stationary night blindness (CSNB) refers to a group of clinically and genetically heterogeneous retinal disorders. Few of those are associated with fundus abnormalities while the majority show largely normal fundi. Clear genotype-phenotype correlations can be performed for patients with the Riggs-form of CSNB, fundus albipunctatus, Oguchi disease, and the Schubert-Bornschein-form of CSNB. In total 15 different genes were associated with those showing more than 500 different mutations in more than 400 cases. While mutations in genes important for the rod phototransduction lead to the Riggs-form of CSNB, fundus albipunctatus, Oguchi disease, mutations in genes important for the downstream signaling from the photoreceptors to the adjacent bipolar cells lead to the Schubert-Bornschein-form of CSNB. In this book chapter, phenotypic characteristics of the different forms of CSNB are summarized for an accurate diagnosis. Clear genotype-phenotype correlations mentioned herein should lead to an improvement of genetic testing.

Keywords

CSNB · Full field electroretinogram (ffERG) Fundus · Riggs-type ERG · Oguchi disease Fundus albipunctatus · Schubert-Bornschein-type ERG · Incomplete CSNB · Complete CSNB · Major gene defects · Genotype-phenotype correlations · Protein localization correlates with the phenotype · In vitro and in vivo models

11.1 Introduction

Congenital stationary night blindness (CSNB) is a clinically and genetically heterogeneous inherited retinal disorder. This book chapter aims to summarize the main and common features of the disease. As the name implicates the disease is

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present from birth. However, other clinical symptoms are not always reflected by the name: night blindness may not be the chief symptom and is a very subjective sign in the well-lighted environment of big cities. Similarly, not all cases show a stationary disease; progression can be also noted. In many cases diurnal vision is also affected: reduced visual acuity, light sensitivity, high myopia, nystagmus, and strabismus may be also diagnosed. However, using fundus examination and electroretinography, patients can be precisely clinically diagnosed, classified which will direct the genetic strategy. Patients, for whom a genetic analysis does not identify a known gene defect, may harbor mutations in non-coding regions of known genes underlying the same phenotype or in a novel gene. For the latter ones, the respective protein localization can be as well correlated to the phenotype.

11.2 Epidemiology

To our knowledge, the frequency of CSNB in the general population has not been documented. This might be due to undiagnosed cases. Indeed, specific clinical examinations are necessary to correctly diagnose CSNB. In 2015 we summarized genetic data of 300 index patients with CSNB, previously published by us and others [1]. Taking into account our newly collected cases since then, we see that these numbers are continuously growing. To date (February 2019), in total, more than 500 different mutations have been published. Similarly, since 2015 in more than 180 novel index cases with CSNB from our worldwide collaboration, the genetic cause was resolved. In respect to the collection of our large European cohort with inherited retinal disorders, including ~5000 index cases, 2% of those present CSNB.

11.3 Clinical Features

To correctly diagnose CSNB, fundus examination and full-field electroretinogram (ffERG) incorporating the International Society for Clinical Electrophysiology of Vision (ISCEV) standards are essential [2]. Furthermore, documentation of the mode of inheritance is important for the proper classification of CSNB. Table 11.1 summarizes the main clinical features of the different forms of CSNB.

11.3.1 Riggs-Type of Congenital Stationary Night Blindness: A Form of Night Blindness with Largely Normal Fundus

The Riggs-type of CSNB [4] represents a rod-photoreceptor dysfunction. The ffERG shows severely reduced scotopic responses. At low light intensities (dark adaptation (DA) 0.01) the b-wave is severely reduced or absent. At a bright flash in addition to the b-wave reduction also the a-wave is reduced (DA 10.0). This reflects primary rod-dysfunction. Photopic ERGs (LA 3.0 and LA 3.0 30 Hz) are normally consistent with normal cone function. This form of CSNB has been reported as autosomal dominant and autosomal recessive modes of inheritance with specific mutations in genes coding for proteins of the rod phototransduction cascade. The phenotype is relatively mild including night blindness no nystagmus, and normal photopic visual acuity with only a few cases showing myopia [1, 5, 6]. This relatively mild phenotype may be the reason why to date only few cases with this Riggs-type of CSNB were described. Historically, this form of CSNB was detected in the Nougaret family, coming from Southern France, [7–11], and in another family reported by Rambusch [12, 13]. In both,

Table 11.1 Summary of general clinical characteristics and mode of inheritance of most CSNB (modified from [3])

	Riggs-CSNB	Funds albipunctatus	Oguchi	icCSNB	cCSNB	*GNB3*-CSNB
Mode of inheritance	Autosomal dominant autosomal recessive	Autosomal recessive	Autosomal recessive	x-chromosomal autosomal recessive	x-chromosomal autosomal recessive	Autosomal recessive
Fundus abnormalities	No	Variable, dots focal lesions from the retinal pigment epithelium/Bruch's membrane complex to the inner limiting membrane with an additional decrease in outer nuclear layer thickness	Mizuo-Nakamura	Myopia possible	Myopia	No
Night blindness	Yes	Yes	Yes	Possible	Yes	Possible
Photophobia	No	No	No	Often	No	Possible
High myopia	No	No	No	Possible	Often	No
Hyperopia	No	No	No	Often	No	No
Nystagmus	No	No	No	Often	Often	Possible
Strabismus	No	No	No	Often	Often	No
DA 0,01 ERG	⇓	⇓	⇓	↓	⇓	↓
DA 3,0 ERG	a-wave ⇓ b-wave ⇓	a-wave ⇓ b-wave ⇓	a-wave ⇓ b-wave ⇓	a-wave normal b-wave ⇓	a-wave normal b-wave ⇓	a-wave normal b-wave ↓
LA 3,0 ERG	Relative normal	Mildly abnormal	Relative normal	a-wave normal but broader b-wave ⇓	a-wave normal but broader b-wave with a sharply rising peak	a-wave normal but can be broader b-wave can be ↓
LA 3,0 30 Hz ERG	Relative normal	Mildly abnormal	Relative normal	⇓	Normal amplitude, may have a flattened trough, may show mild implicit time shifts	↓ not as icCSNB
Recovery of ERG after long dark adaption	No	Yes	Yes	No	No	

⇓ strongly reduced or absent, ↓reduced

the phenotype was transmitted as an autosomal dominant trait. A few cases with autosomal recessive Riggs-type CSNB have been reported. However, in the latter cases especially the photopic responses are less consistent with the classic Riggs-form of CSNB [14–16].

11.3.2 Fundus Albipunctatus: A Form of Night Blindness with Fundus Abnormalities

Fundus albipunctatus (FA) is characterized indirectly by rod-photoreceptor dysfunction. Albeit that the respective gene defect underlying this disease is expressed in the retinal pigment epithelium, the mutant form leads to the dysfunction of the recycling of rhodopsin, specifically expressed in rod-photoreceptors. Therefore patients are effectively "bleached" most of the time. Thus the diagnosis cannot be made purely by ISCEV standard ERGs as the recovery following extended DA needs to be confirmed [1]. At low light intensities (DA 0.01) the b-wave is severely reduced or absent. At a bright flash in addition to the b-wave reduction also the a-wave is reduced (DA 10.0), which reflects primary rod-dysfunction. Similar scotopic ERGs are found in patients with the Riggs-form of CSNB. However, 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 [17]. Photopic ERGs are mildly abnormal in about half of the cases and often show flicker ERG delay [1]. In addition patients with FA are characterized by night blindness but visual acuity, color vision, and visual fields are usually normal. Strikingly, patients with FA have specific fundus abnormalities. They often show small white dots in the posterior pole and mid-periphery with sparing of the macular region. Fundus appearance may change with time from flecks in childhood to fine dots with age that may fade or increase over the years [1, 18–20]. Albeit FA does not present a progressive rod-cone dystrophy showing optic nerve pallor, nor retinal blood vessel attenuation, nor pigmentary bone spicule migration in the periphery, phenotypic variability leading to more progressive phenotypes have been described [17, 21]. The disease is inherited in an autosomal recessive fashion. Albeit only one gene defect is associated with this disease, founder mutations in the same gene are responsible that this form is a relatively frequent cause of CSNB [1].

11.3.3 Oguchi Disease: A Form of Night Blindness with Fundus Abnormalities

Oguchi disease (OD) is also characterized by rod-photoreceptor dysfunction. Similar scotopic ERGs are found in patients with the Riggs-form of CSNB. At low light intensities (DA 0.01) the b-wave is severely reduced or absent. Also here, in response to a bright flash in addition to the b-wave reduction also the a-wave is reduced (DA 10.0), which reflects primary rod-dysfunction. After prolonged dark adaptation, rod sensitivity recovers, and the ERG response to a single-flash results in nearly normal a- and b-waves [22]. However, unlike FA, the ERG response to a subsequent single bright flash is markedly attenuated and similar to that recorded after short dark adaptation (20 min). The abnormal desensitization 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 [1, 23]. Photopic recordings are usually normal [24]. Patients affected with OD are congenitally night blind, but have normal visual acuity, color vision, and visual fields [1]. Similarly as in patients with FA, patients with OD show specific fundus abnormalities, known as the Mizuko-Nakamura phenomenon: the fundus has a golden-yellow discoloration that disappears after prolonged dark adaptation [25, 26]. Although Oguchi disease is considered to be a stationary and rela-

tively mild disease, some cases show more severe phenotypes and disease progression [27–32]. Historically OD was first described by a Japanese soldier complaining of night blindness. The disease is inherited in an autosomal recessive mode of inheritance, with only a few cases described.

11.3.4 Schubert-Bornschein-Type of Congenital Stationary Night Blindness a Form of "Night Blindness" with Largely Normal Fundus

The Schubert-Bornschein-type of CSNB represents a signaling defect from photoreceptors to bipolar cells. Similarly, as the Riggs-type of CSNB, the ffERG show severely reduced scotopic responses. At low light intensities (dark adaptation (DA) 0.01) the b-wave is reduced or absent. However, unlike in the Riggs-type of CSNB, in the Schubert-Bornschein-type of CSNB, after stimulation with a bright flash, only the b-wave is reduced while the a-wave is normal (DA 10.0), resulting in an electronegative waveform [33]. The Schubert-Bornschein-type of CSNB is the most common form of CSNB with largely normal fundi. It can be further subdivided into an incomplete (ic) and complete (c) form of CSNB. This classification is based on ffERG characteristics [34, 35] but is also in correlation with the localization of the proteins implicated in CSNB [1].

11.3.5 Incomplete Congenital Stationary Night Blindness

The incomplete form of CSNB (icCSNB) is characterized by both ON- and OFF-bipolar cell dysfunction. The ffERG shows reduced but present scotopic responses to a dim flash. Therefore this form was called incomplete CSNB [1]. At low light intensities (DA 0.01) the b-wave is reduced but present. At a bright flash, only the b-wave is reduced, while the a-wave is normal (DA 10.0), confirming normal rod phototransduction. This results in the previously mentioned electronegative ERG waveform [34]. The photopic responses are severely affected: the LA 3.0 30 Hz ERG is severely reduced and delayed with most having a distinct bifid peak. The single-flash cone ERG (LA 3.0) is also markedly subnormal with a profoundly reduced b/a ratio such that the a- and b-wave are usually of similar size [1]. Long-duration stimulation shows abnormalities in both ON- and OFF-responses [36]. Incomplete CSNB gets sometimes misdiagnosed with cone dystrophy due to profound photopic alteration, but the macula is usually normal unlike in cone dystrophies [1, 37]. However, in some cases, disease progression and more severe phenotypes were noted [38–42]. The incomplete form is a common form of CSNB and has been mainly reported in X-linked and in a few autosomal recessive cases with mutations in genes coding for proteins present at the synapse of photoreceptors. The phenotype of icCSNB is more heterogeneous than the one observed of cCSNB (please see below) with patients present with little or no night vision disturbances [35, 43–45]. However, photophobia is more common in icCSNB [44]. In addition, icCSNB patients may have myopia, hyperopia, nystagmus, strabismus, reduced visual acuity, and color vision defects [44].

11.3.6 Complete Congenital Stationary Night Blindness

The complete form of CSNB (cCSNB) is characterized by selective ON-bipolar cell dysfunction. The ffERG show severely reduced or absent scotopic responses to a dim flash. Therefore this form was called complete CSNB [1]. At low light intensities (dark adaptation (DA) 0.01) the b-wave is absent. At a bright flash only the b-wave is reduced, while the a-wave is normal (DA 10.0), confirming normal rod phototransduction. This results in the previously mentioned electronegative ERG waveform [34]. The photopic responses are less altered in cCSNB com-

pared to icCSNB: the LA 3.0 30 Hz ERG is often of normal amplitude but it has a pathognomonic, although it may have a flattened trough and may show mild implicit time shifts. The single-flash cone ERG (LA 3.0) has a normal a-wave amplitude but with a broadened through; the waveform has a sharply arising b-wave with no oscillatory potentials and a mildly reduced b/a ratio [34, 46]. Long-duration stimulation shows selective abnormalities in the ON-responses [36]. Similarly, as the incomplete form of CSNB, the complete form of CSNB is also a common form of CSNB with reported X-linked and autosomal recessive reported cases with mutations in genes coding for proteins mainly present at the dendritic tips of ON-bipolar cells. Patients with cCSNB are indeed congenitally night blind, have decreased visual acuity, and often show myopia, nystagmus and strabismus [1, 44]. Disease progression has not been noted.

11.3.7 GNB3-CSNB

Recently a novel gene defect underlying CSNB was identified [47, 48]. The phenotype cannot be classified in one of the subforms mentioned above [3]. Only a few cases have been described so far and the phenotypes seem to be variable even in those. At low light intensities (DA 0.01) the b-wave is reduced. At a bright flash, only the b-wave is reduced, while the a-wave is normal (DA 10.0), confirming normal rod phototransduction. The photopic responses are very variable: the LA 3.0 30 Hz ERG can be reduced and delayed. In the single-flash cone ERG (LA 3.0) the a-wave is normal but can be delayed and the b-wave is reduced and delayed. Long-duration stimulation shows abnormalities of the ON- but not the OFF-responses. Patients with mutations in *GNB3* may be night blind, showing myopia and nystagmus. But these ocular features were not observed in all patients. More patients with the same gene defect to be identified in the future may help to better classify this novel form of CSNB.

11.4 Molecular Biology

Table 11.2 summarizes the major gene defects underlying CSNB.

11.4.1 Gene Defects Implicated in Congenital Stationary Night Blindness

Inherited retinal disorders are clinically and genetically very heterogeneous. While often it is difficult to deliver clear genotype-phenotype correlations, for CSNB it is possible. Indeed, mutations in genes important for the rod phototransduction cascade can lead to isolated rod-photoreceptor dysfunction as found in the Riggs-form of CSNB, in FA and OD (Fig. 11.1). In contrast, mutations in genes important for the signaling from photoreceptors to bipolar cells or in genes important for the uptake of this signal lead to incomplete and complete CSNB, respectively. In vitro and in vivo models are in most cases helpful models to dissect retinal signaling and the pathogenic mechanisms implicated in CSNB [1]. Table 11.2 summarizes the different gene defects underlying CSNB, their chromosomal localization, the mode of inheritance, and the link to OMIM. Figure 11.1 shows the retinal localization of the molecules implicated in CSNB in a schematic drawing.

11.4.2 Gene Defects Underlying the Riggs-Type of Congenital Stationary Night Blindness, Fundus Albipunctatus, and Oguchi Disease

Specific mutations in genes coding for proteins important for the rod phototransduction cascade, including *RHO* coding for rhodopsin, *GNTA1*, coding for the α-subunit of transducin, *PDE6B*, coding for the β-subunit of the phosphodiesterase and *SLC24A1*, coding for the solute carrier family 24 members 1 have been identified in autosomal

Table 11.2 Gene defects of CSNB

Disease	OMIM	Mode of inheritance	Gene defect	OMIM	Localization
Riggs-CSNB CSNB1D # 613830 Autosmal recessive SLC24A1 #603617 15 q22.31	CSNBAD1 #610445	Autosomal dominant	*RHO*	#180380	3q22.1
	CSNBAD3 #610444	Autosomal dominant	*GNAT1*	#139330	3p21.31
	CSNB1G #616389	Autosomal recessive	*GNAT1*	#139330	3p21.31
	CSNBAD2 #163500	Autosomal dominant	*PDE6B*	#180072	4p16.3
Fundus albipunctatus	Fundus albipunctatus #136880	Autosomal recessive	*RDH5*	#601617	12q13.2
Oguchi	Oguchi disease 1 #258100	Autosomal recessive	*SAG*	#181031	2q37.1
	Oguchi disease 2 # 613411	Autosomal recessive	*GRK1*	#180381	13q34
Schubert-Bornschein icCSNB	CSNB2A # 300071	X-linked	*CACNA1F*	#300110	Xp11.23
Schubert-Bornschein icCSNB	CRSD[a] # 610427	Autosomal recessive	*CABP4*	#608965	11q13.2
Schubert-Bornschein icCSNB[b]	Retinal cone dystrophy 4 #610478	Autosomal recessive	*CACNA2D4*	#608171	12p13.33
Schubert-Bornschein cCSNB	CSNB1A #310500	X-linked	*NYX*	#300278	Xp11.4
Schubert-Bornschein cCSNB	CSNB1B #257270	Autosomal recessive	*GRM6*	#604096	5q35.3
Schubert-Bornschein cCSNB	CSNB1C #613216	Autosomal recessive	*TRPM1*	#603576	15q13.3
Schubert-Bornschein cCSNB	CSNB1E #614565	Autosomal recessive	*GPR179*	#614515	17q12
Schubert-Bornschein cCSNB	CSNB1F #615058	Autosomal recessive	*LRIT3*	#615004	4q25
GNB3-CSNB	CSNB1H #617024	Autosomal recessive	*GNB3*	#139130	12p13.31

[a]CRSD = congenital non progressive cone rod synaptic disorder
[b]Patient with this gene defect were previously diagnosed with icCSNB

dominant and autosomal recessive patients with the Riggs-type of CSNB [1]. The Nougaret family from the South of France had the p.Gly38Asp mutation in *GNAT1* [11]. In the meanwhile, two other *GNAT1* missense mutations were found in two autosomal dominant families [49, 50] and a homozygous *GNAT1* missense mutation in one autosomal recessive family [16], while the Rambusch family had the p.His258Asn mutation in *PDE6B* [51]. To date, only a second autosomal dominant family with a mutation in *PDE6B* was found [52]. Similarly, only a few autosomal dominant families revealed mutations in *RHO* [53–57] and a few autosomal recessive families revealed mutations in *SLC24A1* [14, 15]. The exact pathogenic mechanism of these mutations in genes coding for proteins of the phototransduction cascade, remains to be elucidated. Among others, constitutive activation would indeed explain the desensitization and reduced photo-response leading to night blindness [1].

Specific mutations in genes coding for proteins important for the rod phototransduction cascade, including *RDH5*, coding for the retinol dehydrogenase, *SAG* coding for arrestin and *GRK1* coding for the rhodopsin kinase have been identified

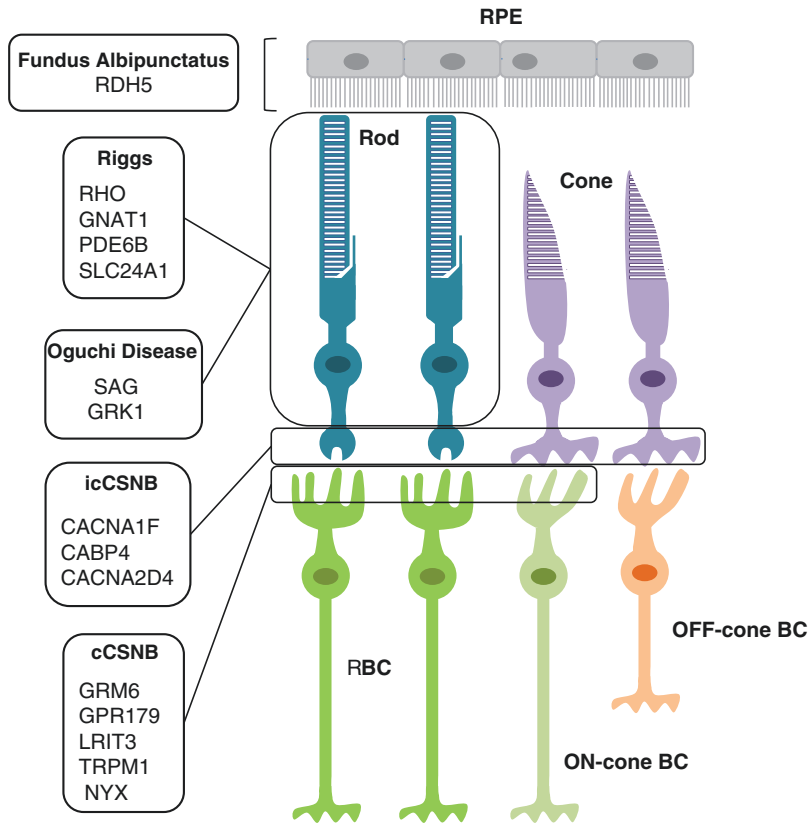

Fig. 11.1 Cellular role of proteins implicated in CSNB. Fundus Albipunctatus is due to mutations in *RDH5* and the respective protein is localized in the retinal pigmented epithelium (RPE, in gray). Mutations in genes coding for proteins localized in rod-photoreceptors (in blue), such as RHO, GNAT1, PDE6B, SLC24A1, SAG, and GRK1 can either cause the Riggs-type of CSNB or Oguchi disease. The icCSNB phenotype is attributable to defects in genes coding for proteins localized at the synapse of both rod- and cone photoreceptors (CACNA1F, CABP4, CACNA2D4) while cCNSB is due to mutations in *GRM6, GPR179, LRIT3, TRPM1, NYX* coding for proteins involved in the ON-BC processing (RBC, strong green and ON-cone BC, light green) while OFF-cone bipolar cells (OFF-cone BC, orange) do not present these proteins

in patients with autosomal recessive FA (*RDH5*) and OD (*SAG* and *GRK1*) showing some similarities with patients with the Riggs-form of CSNB but having additional fundus abnormalities. As mentioned before specific phenotypes can be recovered after extended DA. This correlates with the function of the affected proteins. Indeed, RDH5 is responsible for converting 11-*cis*-retinol into 11-*cis*-retinal in the retinal pigment epithelium (RPE), and is thus involved in the recycling of rhodopsin. Thus rhodopsin regeneration is delayed, FA patients are effectively "bleached" but after long DA rhodopsin levels can be normalized and thus the ERG [1]. OD patients have mutations in *SAG* and *GRK1*, both genes encoding proteins involved in the deactivation process of the phototransduction cascade [58, 59]. The phenotype represents basically no shut-off of the phototransduction cascade. After extended DA the ERG and fundus phenotype can be restored.

Gene defects underlying the Schubert-Bornschein-type of congenital stationary night blindness a form of "night blindness" with largely normal fundus.

11.4.3 Gene Defects Underlying Incomplete Congenital Stationary Night Blindness

Mutations in *CACNA1F*, coding for the α1-subunit (Cav1.4) of an L-type voltage-dependent calcium channel, *CABP4* coding for the calcium-binding protein 4, and *CACNA2D4* coding for the calcium channel, voltage-dependent, α-2/δ subunit 4 lead to icCSNB or related cone rod dystrophies with some overlapping phenotypes [1, 60–63]. The mutation spectrum comprises missense and splice site mutations, large and small deletions, and duplications. More recently we showed that intronic and synonymous variants in *CACNA1F* can also lead to a splice defect causing icCSNB [64]. The respective proteins are important downstream of the phototransduction cascade, by transmitting signals from the photoreceptors to the adjacent bipolar cells. Indeed, they localize at the photoreceptors and more specifically in a horseshoe-shaped manner in rod and cone photoreceptor synapse active zone within the outer plexiform layer (OPL) [1, 65–67]. Together these molecules are important for the correct functioning of the calcium channel. During darkness calcium ions are taken up by this channel, leading to glutamate release at the synaptic cleft [1]. Together, Cav1.4, CABP4, and CACNA2D4 form the pore are important to correctly targeting the channel to the synaptic membrane, to modulate calcium currents, and to bind calcium ions [1, 68–73]. Mutations in *CACNA1F*, *CABP4,* and *CACNA2D4* can be associated with loss or gain of function with insufficiently expressed genes resulting in an altered or non-functional calcium channel activity disturbing the regulation of the glutamate at the synaptic cleft. Different pathogenic mechanisms have been associated with the different mutations in these genes, which may explain the phenotypic variability. Both rod and cones make synaptic contacts with bipolar cells. There are two types of bipolar cells: ON- and OFF-bipolar cells expressing different glutamate receptors and responding differently to light. ON-bipolar cells express the metabotropic glutamate receptor 6 (GRM6/mGluR6) [74–76] and depolarize in response to light [77–79], while OFF-bipolar cells express ionotropic glutamate receptors and hyperpolarize at light offset [80–82]. ON-bipolar cells make synaptic contacts with both rod and cone photoreceptors, while OFF-bipolar cells only contact with cone photoreceptors [83]. Since molecules implicated in icCSNB localize in synaptic terminals of both, rod and cones, as a consequence ON- and OFF-responses in those patients are altered as shown in the ERG by long-duration stimulation.

11.4.4 Gene Defects Underlying Complete Congenital Stationary Night Blindness

Mutations in *GRM6*, coding for metabotropic glutamate receptor 6, *GPR179*, coding for the G-protein coupled receptor 179, *LRIT3* coding for the leucine-rich repeat, Ig-like and transmembrane domains 3 protein, *NYX*, coding for nyctalopin and *TRPM1*, coding for the transient receptor potential cation channel subfamily M member 1 lead to cCSNB [84–91]. The mutation spectrum comprises missense and splice site mutations, large and small deletions, and duplications [1]. The respective proteins play their role in ON-bipolar cells by receiving the signals transmitted from the synaptic cleft. Indeed, they localize at the dendritic tips of ON-bipolar cells within the outer plexiform layer (OPL) and are important for the depolarization of ON-bipolar cells at light stimulation, leading to glutamate decrease and TRPM1 channel opening at the end of this cascade [77, 79, 86, 92–97]. Mutations in these molecules lead to the absence of the b-wave and of ON-responses as shown in the ERG by long-duration stimulation.

11.4.5 *GNB3*-Gene Defect

As mentioned above, the *GNB3* gene defect cannot be strictly classified in the different subforms of CSNB. Thus we did not include the protein localization of GNB3 in Fig. 11.1. GNB3 coding for the β-subunit of the G-protein heterotrimer (Gαβγ) is known to be expressed in cones and ON-bipolar cells and modulates ON-bipolar cell signaling and cone transducin function in mice [98]. Due to its expression in cones as well in ON-bipolar cells the dual phenotype associated with *GNB3* mutations maybe explained [47].

11.4.6 Laboratory

Genetic testing of CSNB patients is important for genetic counseling of patients and their families to distinguish from progressive retinal dystrophies with similar phenotypic features [1]. For example, night blindness is one of the first presenting signs of progressive rod-cone dystrophy also called retinitis pigmentosa. At a young age, patients may initially show normal or near-normal fundus appearance. Therefore in addition to accurate phenotyping, molecular confirmation of CSNB helps to correctly diagnose and counsel patients. CSNB patient with largely normal fundus, a Riggs-ERG, and autosomal dominant or autosomal recessive inheritance should be screened for mutations in *RHO* = *GNAT1* > *PDE6B* and *SLC24A1* > *GNAT1* respectively. For patients with an autosomal recessive mode of inheritance and FA, *RDH5* should be targeted, while patients with autosomal recessive CSNB and a phenotype suggestive of OD should be screened for mutations in *GRK1* and *SAG* [1]. Patients and especially male patients with the Schubert Bornschein-type of CSNB should be first screened in *CACNA1F* and *NYX* [1]. Both genes are located on the X-chromosome and represent the major causes of this form of CSNB. If a clinical discrimination of incomplete versus complete CSNB is made, only *CACNA1F* or *NYX* needs to be investigated. Our experience showed that at least 80% of these cases show mutations in one of those genes. Females and excluded male patients with icCSNB could be screened in *CABP4* and *CACNA2D4*, especially if they present with high hyperopia and photophobia. Cases of cCSNB should be screened for defects in *TRPM1* > *GRM6* > *GPR179* > *LRIT3*. In cases where no difference between icCSNB and cCSNB is made the following mutation detection strategy should be applied *CACNA1F* > *NYX* > *TRPM1* > *GRM6* > *GPR179* > *CABP4* > *LRIT3* > *CACNA2D4*. We developed this strategy, based on the prevalence of the specific gene defects [1]. Our recent experience showed that intronic variants and synonymous variants may be also disease causing and should not be overlooked [64]. In case only preliminary clinical phenotyping data are available unbiased microarray analysis (ASPER, Ophthalmics, Tartu, Estonia) [99, 100] and targeted next-generation sequencing (NGS) could be applied [101]. The prior method is based on allele-specific primer extension analysis, which allows the detection of known mutations. The array is regularly updated with new mutations in known genes and mutations that will be identified in novel gene defects. However, since there are only a few mutation hot spots and founder mutations in CSNB and their implicated genes, targeted NGS approaches seem to be more appropriate. Albeit, initially GC-rich and repetitive regions were less well covered by the latter methods, more recent techniques seem to overcome these challenges. After exclusion of mutations by the abovementioned method, targeted whole genome sequencing, whole exome or whole genome sequencing should be applied to identify the disease-causing mutation.

11.5 Summary

Inherited retinal disorders are very heterogeneous and can be deciphered depending on the congenital or progressive course of the disease or by the type of retinal cell that is involved. Herein we describe the genetic and phenotypic characterization of Congenital Stationary Night Blindness (CSNB). Depending on the mutated gene, CSNB patients can present a rod-photoreceptor defect (Riggs-type of CSNB) with or

without fundus abnormalities (Oguchi Disease, Fundus Albipunctatus) or a transmission defect from the photoreceptor to bipolar cells (Schubert-Bornschein type). The incomplete form of Schubert-Bornschein type of CSNB is due to a defect of proteins localized at the photoreceptor synapse while the complete form results from a ON-bipolar cell defect. Together with other clinical symptoms, clear genotype-phenotype correlations can be made as described herein.

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