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Congenital stationary night blindness in a patient with mild learning disability due to a compound heterozygous microdeletion of 15q13 and a missense mutation in *TRPM1*

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ABSTRACT

The complete form of congenital stationary night blindness (cCSNB) represents a non-progressive retinal disorder characterized by night vision problems and often congenital nystagmus, reduced vision, high myopia, strabismus and normal fundus appearance. Clinically this form of CSNB can be diagnosed by full-field electroretinogram. The mode of inheritance can be X-linked and autosomal recessive with mutations in genes coding for proteins mainly present at the dendritic tips of ON-bipolar cells. Mutations in NYX, GRM6, GPR179, LRIT3 and TRPM1 lead to this condition. The latter gene defect represents the major form underlying cCSNBC. It codes for the melastatin-related transient receptor 1 expressed in the inner nuclear layer of the retina, with the protein localized in ON-bipolar cells. To date, various homozygous or compound heterozygous mutations in TRPM1 have been reported. Small chromosomal rearrangements are frequent cause of mental retardation. In rare cases deletions can overlap with a mutation on the remaining chromosome and lead to a recessive disorder. Here, we describe a patient with mild neurological deficiencies and cCSNB caused by a microdeletion on 15q32 overlapping with a TRPM1 variant.

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Introduction

The complete form of congenital stationary night blindness (cCSNB) represents a non-progressive retinal disorder characterized by night vision problems and often congenital nystagmus, reduced vision, high myopia, strabismus and normal fundus appearance (1). Clinically this form of CSNB can be diagnosed by full-field electroretinography (2). The ffERG shows severely reduced or absent scotopic responses to a dim flash. At low light intensities (dark adaptation (DA) 0.01) the b wave is absent. At a bright flash, the b wave is reduced, while the a-wave is normal (DA 10.0), which is consistent with normal rod function, and results in an electronegative ERG waveform (3). The photopic responses are less altered: the light adaptation (LA) 3.0 30 Hz ERG is often of normal amplitude but it has a pathognomonic flattened trough and mild implicit time shift. The single-flash cone ERG (LA 3.0) displays a normal amplitude of the a-wave with a broadened trough; the waveform has a sharply rising b wave with no oscillatory potentials and a reduced b/a ratio. Long-duration stimulation shows selective abnormalities of the ON-responses (2). The mode of inheritance of the cCSNB can be X-linked and autosomal recessive with mutations in genes coding for proteins mainly present at the dendritic tips of ON-bipolar cells. Mutations in *NYX* (MIM: 300278) (4,5), *GRM6* (MIM: 604096) (6,7), *GPR179* (MIM: 614515) (8,9), *LRIT3* (MIM: 615004) (10) and *TRPM1* (MIM: 603576; NM_001252020.1) (11–13) lead to this condition. The complete form of CSNB is distinct from the incomplete CSNB caused primarily by *CACNA1F* gene (5).

Mutations in *TRPM1* represent the major cause underlying cCSNB (1). It codes for the melastatin-related transient receptor 1 expressed in the inner nuclear layer of the retina, with the protein localized in ON-bipolar cells (14). To date various homozygous or compound heterozygous mutations in *TRPM1* have been reported (1).

Small chromosomal rearrangements are frequent cause of mental retardation. In rare cases deletions can overlap with a mutation on the remaining chromosome and lead to a recessive disorder (15). Here, we describe a patient with mild developmental delay and cCSNB caused by a microdeletion on 15q32 overlapping with a *TRPM1* variant.

Clinical description

The patient was a girl of one-year old referred for ophthalmological examination because of congenital nystagmus and convergent strabismus. The nystagmus appeared before the fourth month of age. It was horizontal with low amplitude and present in all directions of gaze. The child had preserved ocular movements. Right esotropia of 30 diopters was noted. Cycloplegic refraction showed myopia and mild astigmatism of −5(−1/170°) and −5(−1/20°). Anterior segment examination was unremarkable. Ocular fundus showed findings compatible with the myopia. The patient was followed clinically and at the age of two years the strabismus was still present, while the nystagmus decreased. Correction was given for the myopia and alternating occlusion therapy was started. Best-corrected visual

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acuity was possible at the age of 6 y. and was 0,5 and 0,4 for the right and left eye, respectively. Nystagmus and convergent strabismus persisted. The anterior segment examination and ocular fundus remained normal.

General findings consisted of anxiety crises and mild developmental delay. At 6 years, her development was of a 4 year old child. She also had microcephaly, congenital hip luxation and torticollis.

Electroretinography (ERG) was performed at 4 years of age and showed severely reduced dim light (0,01) dark-adapted response, bright flash (10,0) dark-adapted response with reduced A/B ratio (indicating electronegativity), reduced oscillatory responses, present but reduced light-adapted response with enlarged A and delayed B wave, and reduced and mildly delayed 30 Hz flicker response (Figure 1).

Based on the ERG results a diagnosis of cCSNB was made. Genetic testing was performed for the CSNB genes and for the developmental delay of the patient.

Material and methods

Clinical examination was performed with age appropriate tests including – hand held refractometer Retinomax, visual acuity. Electroretinography (Metrovision) was done following the International Society for Clinical Electrophysiology of Vision recommendations (16), under general anesthesia.

After informed consent was obtained, blood was taken and DNA was extracted following standard procedures. The Microarray Comparative Hybridisation experiments were performed by external certified laboratory. Sequencing of the CSNB related genes was done by direct Sanger sequencing.

Results

Mutation analyses of genes implicated in cCSNB revealed a hemizygous variant in exon 24: c.3262 G > A p.(Ala 1088Thr) of *TRPM1*. The variant was never found to be homozygous and very rare in the heterozygous state with a frequency of 0.00002136 in common databases (gnomAd). It was previously described in a patient with high myopia and reduced vision, however, the patient was not available for ERG testing (17).

Array CGH showed a heterozygous micro deletion of chromosome 15q13.2 – q13.3.

Segregation analysis in the parents showed that the mother carries the deletion and the father carries the *TRPM1* mutation in a heterozygous state. Both parents were asymptomatic.

These results demonstrate that the patient carries deletion on one 15q13 chromosome. The *TRPM1* gene is located on 15q13 within the deletion region, thus the patient has only one *TRPM1* gene with a mutation in a hemizygous state on the remaining 15q13 chromosome.

Discussion

We describe a patient compound heterozygous for a large deletion of 15q13 and a sequence variant in *TRPM1* gene.

The identification of sequence change in *TRPM1* in a combination with a deletion of the other allele most likely explains the ocular phenotype of the patient. The same *TRPM1* variant has been previously described in a patient with most likely cCSNB (17).

We also found that the patient is a heterozygous carrier of a deletion on chromosome 15. Heterozygous microdeletion 15q13 leads to variable degree of mental retardation, autism spectrum disorder, epilepsy and hypotonia (18). The deletion has variable clinical expressivity. Our patient presents with mild developmental delay, no other neurological problems and no facial dysmorphism. The deletion was also present in the normal mother. Hassfurther et al. reported the inheritance of 15q13 deletions from normal parents to be up to 81% (18). The same group hypothesizes that the maternal inheritance enhances the clinical phenotype in the patients. Homozygous deletions of the 15q13 locus have also been reported (19) The

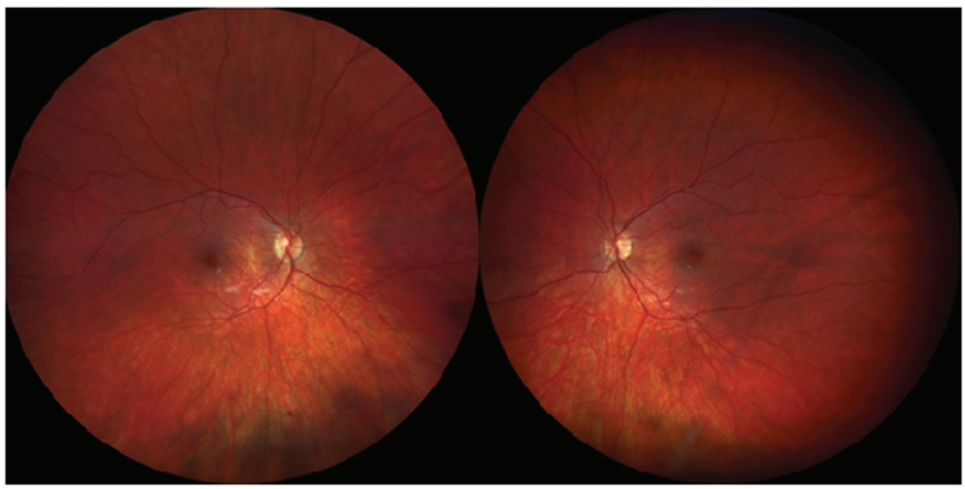
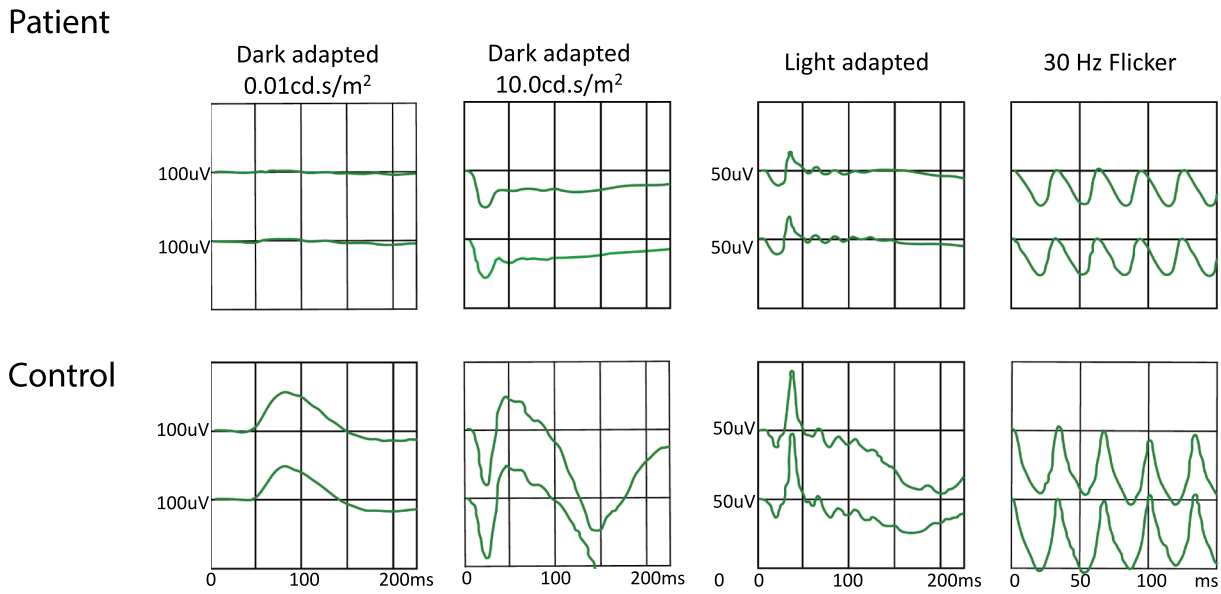


Figure 1. Electroretinography recordings of the patient and a normal control *. The upper recording of each patient is from the right eye and the lower from the left eye. The type of examination is indicated above each recording. The y-axis shows the amplitudes for the right and left eye. The scale is in 100uV in scotopic conditions and 50uV in photopic conditions. The x-axis shows the msec. Each division equals 50msec.
The ERG of the patient shows severely reduced dim light (flash strength of 0.01 cd.s/m^2) dark-adapted response, electronegative bright flash (flash strength of 10.0 cd.s/m^2) dark-adapted response, light-adapted response with broadened a wave and reduced b wave and the 30 Hz flicker is reduced and mildly delayed.*The normal control was a patient of 30y. The ERG was recorded without anesthesia.



two affected siblings had abnormal electroretinography with negative scotopic and atypical photopic responses probably indicative for cCSNB.

Compound heterozygote for a chromosomal microdeletion and a mutation as a cause of a recessive ocular disease were previously described in a patient with Peters Plus syndrome (15). While current testing for retinal dystrophies is often not sensitive for heterozygous deletions and duplications, their importance becomes clear from different reports. Huang XF and coauthors detected four copy number variants in 50 previously negative for genetic testing patients with retinal dystrophies (20). Bujakowska et al. increased diagnostic yield with 18% by testing for deletions and duplications (21). In order to identify loci with higher risk for copy number changes, Van Schill K. performed analysis of 256 genes underlying retinal disorders for genomic features leading to more frequent deletions and duplications (22). All these reports focus on the identification of intragenic deletions and duplications. Here, we show an unusual finding of a larger deletion combined with a recessive mutation. The phenotype of the patient is a combination of the clinical features associated with both genetic defects. With this report, we would like to raise attention to this type of complex genetic defects with atypical phenotypes. Inversions or smaller duplications disrupting retinal dystrophy genes will be similarly difficult to detect while leading clinically to less severe systemic phenotype. Application of bio-informatic algorithms allowing better interpretation of WES and WGS data for detecting small or larger structural variants in patients with retinal dystrophies will help to improve the diagnosis in these patients.

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