Pediatr Pol 2025; 100 (4): 394-397
DOI: https://doi.org/10.5114/polp.2025.156306
Submitted: 27.06.2025, Accepted: 17.08.2025, Published: 19.11.2025

PEDIATRIA Polska
PISMO POLSKIEGO TOWARZYSTWA PEDIATRYCZNEGO
Polish Journal of PAEDIATRICS
OFFICIAL JOURNAL OF POLISH SOCIETY OF PAEDIATRICS

CASE REPORT

15q13.2q13.3 microdeletion syndrome with congenital stationary night blindness due to compound deletion and a missense point mutation in *TRPM1* gene

Justyna Pietrasik[1], Marlena Młynek[1], Agata Wiśniewska[2], Danuta Sielska-Rotblum[1], Magdalena Białecka[1], Marta Kotlarek-Łysakowska[3], Krystyna Chrzanowska[1], Agnieszka Madej-Pilarczyk[1]

[1]Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland
[2]Department of Ophthalmology, Professor Jan Bogdanowicz Children's Hospital, Warsaw, Poland
[3]Warsaw Genomics, Warsaw, Poland

ABSTRACT

The 15q13.3 microdeletion syndrome is associated with a variable phenotype, often with incomplete penetrance, characterised by psychomotor developmental delay, intellectual disability, autism spectrum disorders, and nonspecific dysmorphic features. Epilepsy, congenital heart defects, and ophthalmologic abnormalities, including strabismus and/or astigmatism, may also occur. In the case of a homozygous 15q13.3 deletion involving the *TRPM1* gene, symptoms of congenital stationary night blindness additionally appear. A similar clinical effect is associated with compound damage to both copies of the *TRPM1* gene, in the form of a deletion involving this gene on one allele and a point mutation in *TRPM1* on the other allele. We present a patient with a complex 15q13.2q13.3 deletion and a hemizygous *TRPM1* variant c.332A>G, p.Tyr111Cys, in whom neurodevelopmental symptoms coexist with congenital stationary night blindness.

KEY WORDS:
15q13.3 microdeletion syndrome, *TRPM1* gene, congenital stationary night blindness.

INTRODUCTION

The 15q13.3 microdeletion syndrome (ORPHA: 199318) is caused by a partial deletion of the long arm of chromosome 15, typically spanning 1.5 to 2 Mb [1–8], located between the BP4 and BP5 chromosomal breakpoints [1, 2, 6, 7]. This region usually encompasses 7 genes: *ARGHAP11B*, *MTMR15* (= *FAN1*), *MTMR10*, *TRPM1*, *KLF13*, *OTUD7A*, and *CHRNA7* [1–7]. Heterozygous microdeletions of the 15q13.3 region are characterized by highly variable phenotype, even within the same family [1–3]. Due to incomplete penetrance, the deletion may be asymptomatic in carriers or may lead to neurodevelopmental disorders [1–6], manifesting as psychomotor and speech delay, hypotonia, intellectual disability, learning difficulties, autism spectrum disorders, attention deficit hyperactivity disorder (ADHD), and neuropsychiatric conditions. Some patients also present with epilepsy, and more rarely, congenital heart or kidney defects [1–4, 6–8]. Ophthalmologic problems, observed in about 6% of patients with del15q13.3, most commonly include strabismus and astigmatism [1, 7]. Dysmorphic features are non-specific and may include microcephaly or macrocephaly, synophrys, hypertelorism, strabismus, upward slanting palpebral fissures, short or elongated philtrum, thin upper lip, and fifth finger clinodactyly [2, 7]. Biallelic deletion results

ADDRESS FOR CORRESPONDENCE:
Dr. Agnieszka Madej-Pilarczyk, Department of Medical Genetics, The Children's Memorial Health Institute, Warsaw, Poland, e-mail: a.madej-pilarczyk@ipczd.pl

in a more severe phenotype, including hypotonia, intellectual disability, encephalopathy, epilepsy, optic nerve abnormalities, and cortical visual impairment [1–3, 5, 6]. Approximately 15% of heterozygous 15q13.3 microdeletions occur *de novo*, while 85% are inherited from a parent [1]. The *TRPM1* gene is located within the 15q13.3 microdeletion region, and it is linked to congenital stationary night blindness, an autosomal recessive (AR) condition (ORPHA:215) [3, 9]. Patients with homozygous deletions of 15q13.3 involving both copies of the *TRPM1* genes may present with ocular symptoms such as optic nerve atrophy and retinal dysfunction [3, 5, 6].

CASE REPORT

A 2-year-old boy was referred for a consultation at a genetic clinic due to psychomotor delay, hypotonia, nystagmus, rapidly progressing myopia, and alternating strabismus. He was born to healthy parents from the second pregnancy at 39 hbd, with birth weight of 3460 g, length 57 cm, and Apgar score 10. His motor development was delayed: he sat at 9 months and began walking at around 15 months. His gait was clumsy, with frequent falling and difficulties climbing stairs. He spoke his first words at around 12 months, and by age 3 years he had a considerable vocabulary. On physical examination joint laxity was noted, along with a proportionally slim build, hyperextension of the elbow joints, mildly shortened palpebral fissures, subtle downward slanting of the outer corners of the eyes, a low nasal bridge with a slightly upturned nasal tip, jaw asymmetry with mild right-sided deviation, slightly low-set ears with a small skin tag on the right earlobe, flaccid and sagging cheeks, normal palate and dentition, and a small umbilical hernia. At the age of 6 years, scoliosis and increased lumbar lordosis were diagnosed.

At the age of 3.5 years, he began attending a special kindergarten for children with visual impairments. Difficulties with concentration were noted, along with selective compliance with instructions, a tendency to become easily discouraged from completing tasks, reluctance to draw, and persistently reduced fine motor skills. Considering these behavioural problems, difficulties in peer relationships, and aggression toward his mother, autism spectrum disorder was diagnosed at the age of 5.5 years.

Since birth, alternating strabismus was observed, with predominance of the right eye, as well as oblique strabismus of the left eye and nystagmus. At the age of 3 months a progressive myopia was diagnosed, starting from –4.5D in the right eye, –5D in the left eye and reaching –9.0D before the age of 3 years. In addition, the parents reported that the boy had experienced complete vision loss during nighttime awakenings. On electrophysiological testing (electroretinography – ERG) in scotopic conditions (dark-adapted ERG), a markedly flattened b-wave was observed in response to both dim and bright flashes. Under photopic conditions (light-adapted ERG), cone responses were present but showed reduced amplitude. The results indicated rod response dysfunction in both eyes, with milder cone response abnormalities. These findings were consistent with congenital stationary night blindness. Visual evoked potential revealed impaired conduction in the visual pathway of both eyes. Optical coherence tomography of the fundus showed reduced parameters of the retinal nerve fibre layer and the ganglion cell complex thickness in both eyes. Additional changes typical for high myopia in both eyes were visualised, including elongated eyeballs and posterior staphyloma.

From the age of 3 years, episodes of unresponsiveness were observed, although no convulsive seizures were noted. Two EEG recordings were normal. At the age 5 years, during a febrile upper respiratory tract infection, the patient experienced a seizure-like episode characterised by body stiffening, unresponsiveness, and temporary vision loss during transport to the hospital. A cranial computed tomography scan showed no abnormalities. An echocardiographic examination raised suspicion of a bicuspid aortic valve.

MOLECULAR DIAGNOSTICS

After informed consent was obtained, DNA was extracted from peripheral blood following standard procedures. The genetic diagnostics included aCGH (array Comparative Genomic Hybridisation), which revealed a 1.68 Mb deletion on the long arm of chromosome 15 in the q13.2q13.3 region, encompassing 6 OMIM-listed genes: *FAN1*, *TRPM1*, *MIR211*, *KLF13*, *OTUD7A*, and *CHRNA7* (Figure 1). The result was confirmed using MLPA (multiplex ligation-dependent probe amplification) with the P297-D1 probe set. Parental testing showed that the microdeletion occurred in the patient *de novo*. Because the ophthalmologic presentation exceeded the typical phenotypic spectrum of the 15q13.3 microdeletion syndrome and the deleted region included the *TRPM1* gene, which is known to be associated with ocular symptoms, suspicion was raised of a second-hit mutation affecting the second *TRPM1* allele. Next-generation sequencing (NGS) of the coding regions of the *TRPM1* gene revealed a pathogenic variant: c.332A>G (p.Tyr111Cys), most probably present in hemizygous state, further confirmed by Sanger sequencing.

DISCUSSION

The patient's dysmorphia and neurodevelopmental symptoms were consistent with 15q13.3 microdeletion syndrome. However ophthalmologic presentation, with night blindness, nystagmus, and high myopia with the greatest rate of myopathic shift before the age of 5 years exceeded its typical phenotypic spectrum. Detection of the pathogenic variant: c.332A>G (p.Tyr111Cys) on the second allele of the *TRPM1* gene, in addition to

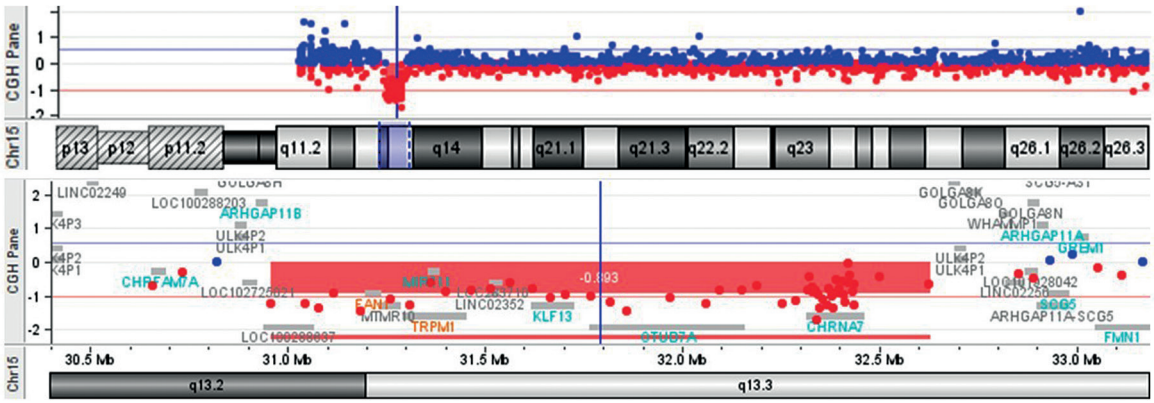

FIGURE 1. Chromosomal microarray analysis revealed a deletion of approximately 1.68 Mb in 15q13.2q13.3. Karyotype according to International System for Human Cytogenetic Nomenclature (ISCN) 2024: arr[GRCh37] 15q13.2q13.3(30,954,726_32,635,959)x1

The deletion encompasses 6 genes listed in Online Mendelian Inheritance in Man® (OMIM®), including TRPM1.

known deletion of one copy of this gene within the deleted 15q13.2q13.3 region, helped to confirm the clinical diagnosis of congenital stationary night blindness (CSNB) in our patient [10].

Congenital stationary night blindness is a clinically and genetically heterogeneous group of retinal diseases, which, according to current knowledge, are associated with defects in 17 genes (as of 2020), with various inheritance patterns: autosomal dominant, AR, X-linked dominant, and X-linked recessive [11]. Pathogenic variants in both copies of the *TRPM1* gene cause subtype 1C of the disease with AR inheritance. The *TRPM1* gene encodes melastatin-related transient receptor 1 expressed in the inner nuclear layer of the retina, with the protein localised in ON-bipolar cells [10]. Mutations in both copies of this gene result in loss of ON bipolar cell responses and manifest as congenital stationary night blindness. This disease is classified as a channelopathy. Patients suffer from strabismus, nystagmus, early-onset progressive myopia, and night blindness (nyctalopia), present at birth [11, 12]. Based on ERG, 2 types of CSNB are distinguished: Schubert-Bornschein type (with a flattened b-wave more pronounced than the a-wave) and Riggs type (with proportional flattening of both b- and a-waves). The Schubert-Bornschein type is associated with reduced visual acuity, myopia, and nystagmus, whereas Riggs type patients have normal visual acuity without myopia or nystagmus. Furthermore, 2 Schubert-Bornschein CSNB subtypes are distinguished: incomplete and complete. In the incomplete subtype, due to dysfunction of both ON and OFF bipolar cells, there is a significantly reduced response from both rod and cone photoreceptors. In the complete subtype, caused by dysfunction of ON bipolar cells, there is a selective, markedly reduced rod photoreceptor response with preserved, slightly reduced cone response. The electroretinogram of patients with *TRPM1*-related CSNB is characteristic of the complete CSNB subtype [13, 14].

In most patients with *TRPM1*-related CSNB an isolated ophthalmological phenotype is seen, with high myopia, nystagmus, strabismus, and nyctalopia. When additional neurodevelopmental symptoms are present, especially in cases when only one *TRPM1* variant is visible in next-generation sequencing, it is worth considering detailed analysis towards copy number variation in the chromosomal region 15q13.3, encompassing locus of the *TRPM1* gene. The combination of del15q13.3 and missense variant c.3017G>A, p.(Arg1006His) or c.3070A>T, p.(Ile1024Phe) on the second allele of the *TRPM1* gene have been described in a patients with CSNB and developmental delay or autism, respectively [12], while del15q13.3 of maternal origin and c.3262G>A, p.(Ala1088Thr) in *TRPM1* have been described in a patient with mild developmental delay, with no facial dysmorphia [15]. The ophthalmological phenotype of our patient was typical for CSNB, but features of del15q13.3 were more pronounced than in another 3 patients with the same deletion and missense *TRPM1* variant; however, this may reflect phenotypic variability, often seen in chromosomal microaberrations.

CONCLUSIONS

The presented patient with 15q13.2q13.3 deletion presented with ophthalmologic symptoms more severe than expected in patients with the aforementioned microaberration. Night blindness, progressive myopia, nystagmus, strabismus, and the clinical diagnosis of CSNB raised suspicion of a mutation in the second copy of the *TRPM1* gene, which was confirmed in further genetic testing. This highlights the necessity for a thorough analysis of the patient's symptoms, correlating them with pathogenic genetic findings, and continuously monitoring the relevant scientific literature and genetic databases.

DISCLOSURES

1. Institutional review board statement: Written informed consent to publish the cases was obtained from the mother of the affected patients.
2. Assistance with the article: None.

3. Financial support and sponsorship: None.
4. Conflicts of interest: None.

REFERENCES

1. Van Bon BW, Mefford HC, de Vries BB, Schaaf CP. 15q13.3 recurrent deletion. GeneReviews 2010 (last update November 17, 2022).
2. Hoppman-Chaney N, Wain K, Seger PR, Superneau DW, Hodge JC. Identification of single gene deletions at 15q13.3: further evidence that CHRNA7 causes the 15q13.3 microdeletion syndrome phenotype. Clin Genet 2013; 83: 345-351.
3. Lepichon JB, Bittel DC, Graf WD, Yu S. A 15q13.3 homozygous microdeletion associated with a severe neurodevelopmental disorder suggests putative functions of the TRPM1, CHRNA7, and other homozygously deleted genes. Am J Med Genet A 2010; 152A: 1300-1304.
4. Shinawi M, Schaaf CP, Bhatt SS, Xia Z, Patel A, Cheung SW, et al. A small recurrent deletion within 15q13.3 is associated with a range of neurodevelopmental phenotypes. Nat Genet 2009; 41: 1269-1271.
5. Prasun P, Hankerd M, Kristofice M, Scussel L, Sivaswamy L, Ebrahim S. Compound heterozygous microdeletion of chromosome 15q13.3 region in a child with hypotonia, impaired vision, and global developmental delay. Am J Med Genet A 2014; 164A: 1815-1820.
6. Liao J, DeWard SJ, Madan-Khetarpal S, Surti U, Hu J. A small homozygous microdeletion of 15q13.3 including the CHRNA7 gene in a girl with a spectrum of severe neurodevelopmental features. Am J Med Genet A 2011; 155A: 2795-2800.
7. Sharp AJ, Mefford HC, Li K, Skinner C, Stevenson RE, Schroer RJ, et al. A recurrent 15q13.3 microdeletion syndrome associated with mental retardation and seizures. Nat Genet 2008; 40: 322-328.
8. Ziats MN, Goin-Kochel RP, Berry LN, Ali M, Ge J, Guffey D, et al. The complex behavioral phenotype of 15q13.3 microdeletion syndrome. Genet Med 2016; 11: 1111-1118.
9. Audo I, Kohl S, Leroy BP, Munier FL, Guillonneau X, Mohand-Saïd S, et al. TRPM1 is mutated in patients with autosomal-recessive complete congenital stationary night blindness. Am J Hum Genet 2009; 85: 720-729.
10. Miraldi Utz V, Pfeifer W, Longmuir SQ, Olson RJ, Wang K, Drack AV, et al. Presentation of TRPM1-associated congenital stationary night blindness in children. JAMA Ophthalmol 2018; 136: 389-398.
11. Zeitz C, Friedburg C, Preising MN, Lorenz B. Overview of congenital stationary night blindness with predominantly normal fundus appearance. Klin Monbl Augenheilkd 2018; 235: 281-289.
12. Iosifidis C, Liu J, Gale T, Ellingford JM, Campbell C, Ingram S, et al. Clinical and genetic findings in TRPM1-related congenital stationary night blindness. Acta Ophthalmol 2022; 100: e1332-e1339.
13. Kabanarou SA, Holder GE, Fitzke FW, Bird AC, Webster AR. Congenital stationary night blindness and a "Schubert-Bornschein" type electrophysiology in a family with dominant inheritance. Br J Ophthalmol 2004; 88: 1018-1022.
14. Langrová H, Gamer D, Friedburg C, Besch D, Zrenner E, Apfelstedt-Sylla E. Abnormalities of the long flash ERG in congenital stationary night blindness of the Schubert-Bornschein type. Vision Res 2002; 11: 1475-1483.
15. Delle Fave M, Cordonnier M, Vallee L, Condroyer C, Zeitz C, Balikova I. 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. Ophthalmic Genet 2021; 42: 296-299.