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CASE REPORT

Two different homozygous mutations in two Turkish siblings: *DGUOK* and *HPS5*

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ABSTRACT

Background: Genetic disorders are enormously diverse both in terms of genotype and phenotype. Each case requires a careful and cautious investigation.

Case Presentation: In this paper, we report two siblings who were admitted to our clinic with various symptoms. The older one, a 13-year old boy, presented with mental retardation, lack of speech, autistic behavior, and self-mutilation. And the younger one, a 6-month old girl, presented with growth retardation, dysmorphic face, and strabismus. We used next generation sequencing for our definitive diagnoses and followed a path from genotype to phenotype.

Conclusion: We found homozygous changes in *DGUOK* (NM_080916.2 c.566T>G) and *HPS5* (NM_181507.1 c.219G>A) genes in the siblings. In the literature review, we did not find any article that investigates two different autosomal recessive disorders in two siblings. On this aspect, we present a different approach.

Keywords: Intellectual disability, genetic heterogeneity, DNA mutational analysis.

Introduction

Deoxyguanosine Kinase (*DGUOK*) is a gene located in 2p13.1 and is known to be associated with three syndromes: Mitochondrial DNA depletion syndrome 3 (hepatocerebral type); Portal hypertension, noncirrhotic; Progressive external ophthalmoplegia with mitochondrial DNA deletions, autosomal recessive 4 (*PEOB4*).

The first syndrome we are going to discuss is chronic progressive external ophthalmoplegia (CPEO). CPEO is an eye disorder characterized by slowly progressive inability to move the eyes and eyebrows (1). It is often the only feature of the mitochondrial disease, in this case the term CPEO may be given as the diagnosis. In some cases suffering from the mitochondrial disease, CPEO occurs as part of a syndrome involving more than one part of the body, such as Kearns–Sayre syndrome. Occasionally, CPEO may be caused by conditions other than mitochondrial diseases.

CPEO is a slowly progressing disease. It may begin at any age and progress over a period of 5–15 years. The first presenting symptom of ptosis is often unnoticed by the patient until the lids droop to the point of producing a visual field defect. Often, patients will tilt the head backward to adjust for the slowly progressing ptosis of the lids. In addition, as the ptosis becomes complete, the patients will use the frontalis muscle to help elevate the lids. The ptosis is typically bilateral but may be unilateral for a period of months to years before the fellow lid becomes involved.

Autosomal recessive progressive external ophthalmoplegia with mitochondrial DNA deletions-4 (*PEOB4*) is an autosomal recessive subtype of CPEO. It normally has adult onset and progresses with weakness in eye muscles and proximal extremity muscles. It is associated with mtDNA deletions on skeletal muscle biopsy, which results in defective mtDNA replication in post-mitotic muscle tissue (2).

The other syndrome we are going to discuss is Hermansky–Pudlak Syndrome-5 (*HPS5*). This syndrome progresses with oculocutaneous albinism, a bleeding diathesis, and lack of platelet dense bodies. *HPS5* has autosomal recessive inheritance and is a milder form of Hermansky–Pudlak Syndrome because the complications

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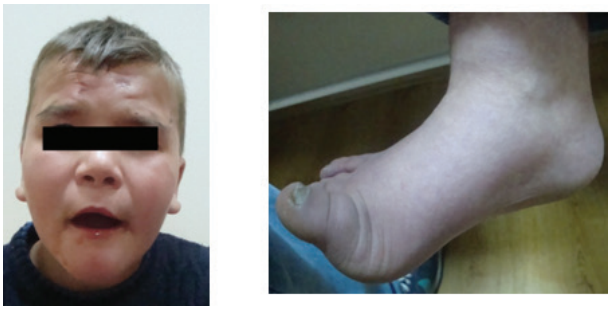

Figure 1. *Dysmorphic features of case 1.*

present in other forms of HPS, such as pulmonary fibrosis, neutropenia, and granulomatous colitis, have not been reported in patients with *HPS5* (3).

The syndrome is caused by homozygous mutation in the *HPS5* gene on chromosome 11p14.

CASE Presentation

Case 1

A 13-year old boy presented with severe mental retardation, microcephaly, lack of speech, autistic behavior, self-mutilation, lack of self-care, seizures, ptosis, brachydactyly, and flatfoot. We noticed that he was using his forehead muscles in order to keep his eyes open and he was tilting his head backward to be able to see properly. He had had seizures when he was 2- and 6-month old. Her parents were relatives; her mother was her father's first cousin. He had a 6-month old sister (Case 2) with growth retardation, dysmorphic face, and strabismus. His physical examination revealed pes valgus, pathologic lines on the left hand, hypotonic face, carp-like mouth, short stature (118 cm, <3 p), microcephaly, and brachydactyly. His MRI scan revealed cerebral atrophy in the brain sulci in supratentorial images and enlargement in lateral ventricles and the third ventricle.

Because of mental retardation, dysmorphic features, consanguinity between his parents and existence of a syndromic sibling, we assumed "X-Linked Mental Retardation-Hypotonic Facies Syndrome (MRXHF1)" and planned an ATRX gene-sequencing test. This test result was negative for MRXHF1. After that next generation sequencing (NGS) (Trusight One Sequence panel) was performed and it revealed a homozygous change in *DGUOK* gene NM_080916.2 c.566T>G (p.F92C) (p.Phe92Cys). This change is considered PM2, PP2, and PP3 in Varsome database, which support its pathogenity (4,5).

Both of his parents also underwent an NGS test and the results revealed both of them were carriers for that mutation.

Case 2

A 6-month old girl presented with growth retardation, dismorphic face, and strabismus. Her mother had

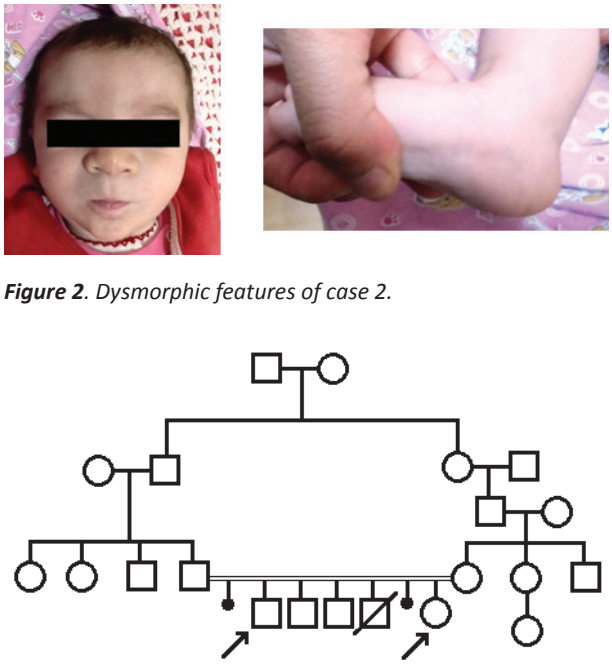

Figure 2. *Dysmorphic features of case 2.*

polyhydramnios during her pregnancy. Her parents were related; her mother was her father's first cousin. She had a 14-year old brother (Case 1) with mental retardation and lack of speech. Her physical examination revealed a relatively small head circumference of 40,5 cm (5–10 p), a low body weight of 5,450 g (<3 p), hypertelorism, epicanthus inversus, strabismus, broad and depressed nasal bridge, broad nasal tip, flattened philtrum, thin upper vermillion, and slight rocker bottom feet.

Her PT and aPTT were normal. Her platelet count was high (405,000/µl) and her hematocrit was low (32%) In follow up, she had an echocardiography when she was 11-month old, which showed an aberrant band in the left ventricle and a physicological mitral insufficiency. She had a cranial and lumbar MRI scans when she was 12-month old. Her cranial MRI scan revealed fluid deposits in both temporal fossas due to a previous otitis, an 8 mm long colloid cyst in the third ventricle, a slight enlargement in the fourth ventricle, asymmetrical nodular Virchow Robin spaces in the right basal ganglia and right capsula interna. Her lumbar MRI scan revealed loss of lumbar lordosis and fullness and dilatation in the sisterns in distal lumbosacral region. She had a urinary US scan when she was 20-month old which revealed a 10 mm stone in the left proximal ureter and grade 2 hydroureteronephrosis in the left ureter secondary to the stone.

Because of growth retardation, dysmorphic face, consanguinity between her parents and existence of a syndromic sibling, we assumed an autosomal recessive genetic disorder; but the clinical findings didn't lead us to a specific syndrome. Therefore, we planned an NGS test for the patient. NGS (Trusight One Sequence panel) was performed and revealed a homozygous change in *HPS5* gene NM_181507.1 c.219G>A (p.R73=) (p.Arg73=).

***Table 1**. Clinical findings of HPS5 reported in previous studies and in our study.*

Features	Zhang et al. (2003)	Huizing et al. (2004)	Ringeisen et al. (2013)	Stephen et al. (2017)	Our case
Oculocutaneous albinism	+	+	+	+	
Easy bruising	+	+		+	
Reduced platelet count	+				
Prolonged bleeding time	+	+	+	+	
Epistaxis				+	
Menorrhagia		+			
Reduced visual acuity		+	+	+	
Nystagmus		+	+	+	
Iris transillumination		+		+	
Strabismus					+
Broad nasal bridge					+
Hypertelorism					+
Epicanthus inversus					+
Flattened philtrum					+

This change is considered pathologic in ClinVar (6) and VUS (PM2 and BP4) in Varsome database, which supports its pathogenicity (5,7). The same test also revealed a heterozygous change in *DGUOK* gene c.566T>G (p.F92C) (p.Phe92Cys). The NGS her brother underwent revealed a homozygous change in the same gene.

The pedigree of the patients is shown below.

Discussion

Clinical heterogeneity is the phenomenon in which different mutations at the same locus lead to different phenotypes. Our case 1 is a great example for that phenomenon since the *DGUOK* gene, which we detected a homozygous mutation, causes three different autosomal recessive disorders. At this point, his clinical findings had a key role to make a diagnosis. This has once again proven the fact that the way to make an accurate diagnosis goes through taking a good history and performing a good physical examination.

Studies have shown numberless mutations in the *DGUOK* gene. However, the pathogeny of most of them and their relation with phenotype is yet to be known. The homozygous mutation we found in the *DGUOK* gene in our patient may explain some of the findings he has, such as cerebral atrophy, mental retardation, and ptosis.

HPS5 is a rare genetic disorder that has autosomal recessive inheritance. It is a subtype of Hermansky–Pudlak Syndrome which has quite variable signs and symptoms. In our patient, we didn't find most of the findings listed in the table above. Therefore, there were not enough clinical findings to suspect HPS at first. However, the growth retardation and the dysmorphic face lead us to perform genetic testing. After receiving the result of the NGS that was performed, we compared our patient's physical examination findings with the clinical features in literature. The only common feature we found is strabismus. The clinical features table and earlier studies do not mention any facial anomalies, but in our case, we spotted several of them.

Table 1 is a comparison between earlier studies and our case.

Our patient's mother had polyhydramnios during her pregnancy. This is a feature that was not reported in any HSP5 patients before. Furthermore, while the literature points out bleeding tendency in *HPS5*, our patient didn't have such a symptom; moreover, her PT and aPTT was normal. Besides, she had a low hematocrit which is also a finding that wasn't reported in *HPS5* patients before.

Conclusion

Genetic syndromes have broad phenotypic and clinical spectrum. In our literature scan, we did not come across with an article about two different homozygous mutations in two siblings. On this aspect, our article is unique. Syndromes also have heterogeneity inside themselves. Again, our cases are decent examples of it. Because some of the phenotypical findings correspond with the literature, while some don't. As a result, it is once again proven that patients with genetic disorders should be assessed by a multidisciplinary team. Besides that, a good clinical assessment is essential.

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Declaration of conflicting interests

The authors of this article have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

Consent for publication

The parents of the patients were informed and their written consent was obtained for publication of this case report. The family of the patients agreed to publish this paper, and have read and approved the final version of this manuscript including photos of the patients.

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