Case Report

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PERCHING syndrome caused by variant gene KLHL7 in the first Iranian patient: a case report study

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Introduction and importance: PERCHING syndrome is a condition that affects many parts of the body and is caused by genes passed down from both parents. People with this syndrome have delays in their development, unusual facial features, trouble eating and breathing, slow overall growth, weak muscles, and stiff joints.

Case presentation: The child at the age of 6 months suffered from developmental delay, delayed walking, speech delay, and hypotonia and was referred to the Neurologist. Also, he has an abnormal phenotype. Whole-exome sequencing (WES) revealed a missense variant in the KLHL7 gene at a highly conserved genomic Chr7: 23124718T > G; NM_018846:exon3:c.110T > G:p. Val37Gly.

Clinical discussion: One way to explain the difference in physical characteristics caused by recessive KLHL7 mutations might be related to the person's genetic makeup. However, the genes someone has do not always accurately determine their physical traits.

Conclusion: This report will help us learn more about the different traits and characteristics of Perching syndrome. The authors need to do more research on how proteins work and study more about patients with different characteristics to fully understand this.

Keywords: Case report, PERCHING syndrome, KLHL7

Introduction

Kelch family proteins are really important for our cells because they help proteins interact with each other. This is necessary for many cellular activities like growing, changing, moving, keeping the cell structure intact, and controlling how genes work[1,2]. Kelch-like family member 7 (KLHL7) is a gene that makes a protein and is found on chromosome 7. The precise function of its protein product remains unclear; however, it is known to be involved in substrate recognition as part of cullin-3 (CUL3)-containing E3 ubiquitin ligase complexes that mediate proteasome degradation. We are not sure exactly what the protein does, but we do know that it helps identify and break down substances as part of a group of proteins called E3 ubiquitin ligase complexes. KLHL7 is similar to the Kelch family members. It has a BTB/POZ (broad complex Tramtrack bric-a-brac/Pox virus and zinc finger) domain, a BACK (BTB and C-terminal Kelch) domain, and a bunch of Kelch motifs. The BTB domain helps to connect with CUL3 and create a working complex that adds molecules called ubiquitin to proteins. The BACK domain is also necessary for connecting with CUL3 and for the activity of the complex[2,3]. PERCHING syndrome is a rare condition that affects the development of multiple systems in the body. It is caused by certain changes in a gene called KLHL7, which is inherited from both parents. These changes can include truncation or missense variants[4]. Here, for the first time, we report the first phenotypic and molecular description of PERCHING syndrome in a patient from Iran.

HIGHLIGHTS

- Kelch family proteins are really important for our cells because they help proteins interact with each other.
- Even though the diagnosis was confirmed through genetic testing, previous studies show that this disease may be noticeable in patients and could be classified as a brain disorder.
- Our report will help us learn more about the different traits and characteristics of Perching syndrome.
- We need to do more research on how proteins work and study more about patients with different characteristics to fully understand this.

Case presentation

The person who needed medical help was a little boy who was only 1 year old. He lived in Golestan province in Iran. He was the eldest child in the family and was born through a C-section. He was born at the usual time (40 weeks) and had a birth weight of

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3200 g. He was 63 cm tall and his head circumference was 44 cm. He had received all his vaccinations. There were no past cases of diseases that run in the family or are related to the brain, mind, or genetics. The parents were related as cousins. The parents and the daughter's cousins were all part of the same family.

The child at the age of 6 months suffered from developmental delay and hypotonia and was referred to the Neurologist. Also, he has an abnormal phenotype (Fig. 1). In the examination, it was found that the child's heart was healthy. An increase in the signal was observed in the MW and the subcortex in the head MRI. Also, all organs are spastic. The child's test results are written down in Table 1.

The patient was under the supervision of a paediatric neurologist for 6 months. Then, to diagnose the cause of the disorders and neuromuscular manifestation, it was referred to the specialized laboratory of medical genetics, and the results of the interpretation of the laboratory are as follows (Table 2).

According to Table 2, a missense variant in the KLHL7 gene at a highly conserved genomic region (GERP Score: 5.78). This variant is not reported in the ClinVar database (https://ncbi.nih.gov/clinvar/). This variant is absent in population databases of healthy individuals (gnomAD, ExAC, ESP6500, and Iranome). Moreover, the CADD phred score for this variant is 27.6 representing this variant as a rare variation. Multiple lines of in silico computational analysis support the deleterious effects of the variant on gene/protein function. Taken together and based on ACMG standards and guidelines, this variant is classified as a Variant of uncertain significance (VUS) variant.

PERCHING syndrome is a condition that affects many parts of the body and is caused by genes passed down from both parents. People with this syndrome have delays in their development, unusual facial features, trouble eating and breathing, slow overall growth, weak muscles, and stiff joints. The characteristics can be different for different people, even within the same family. They may include eye problems, heart or urinary system issues, and unusual sweating.

Table 1

Routine blood examination performed

	Lab data	Count	Reference	Unit
Haematology	WBC	8.80	4000–10 000	10^3/µl
	RBC	5.16	4.5–6.3	10^6/µl
	Haemoglobin	10.1	14–18	g/dl
	Haematocrit	32.3	39–52	%
	M.C.V	79.1	80–97	fl
	M.C.H	25.2	26–32	pg
	M.C.H.C	34.6	32–36	g/dl
	RDW-CV	13.2	11.5–16	%
	Plateletes	389	140 000–400 000	10^3/µl
	MPV	9.2	6.5–12	
	PDW	14.3	9–17	—
	PCT	3.66	—	—
	Uric acid	2.79	2.5–5.5	mg/dl
Hormone studies	T4	6.4	4.4–11.7	mg/dl
	TSH	2.58	0.39–6.16	iIU/ml
	F-Thyroxine F-T4	1.9	0.8–2.2	ng/dl
	Vitamin D3 (25-OH)	10.8	4.4–11.7	ng/ml
ABG	PH	6.41	7.35–7.45	
	Hco3	30.09	22–26	meq/l
	PCo2	48	35–45	mmHg

ABG, arterial blood gas; MCH, mean corpuscular haemoglobin; MCHC, mean corpuscular haemoglobin concentration; MCV, mean corpuscular volume; MPV, mean platelet volume; PCT, patient care technician; PDW, platelet distribution width; PH, potential of hydrogen; RBC, red blood cell; RDW-CV, red cell distribution width-coefficient of variation; TSH, thyroid-stimulating hormone; WBC, white blood cell.

Figure 1. Abnormal phenotype of the patient.

Discussion

This study reported the patient had a rare mutation KLHL7 gene. The patient showed symptoms of developmental delay, delayed walking, speech delay and hypotonia, and abnormal phenotype.

In 1996, seventeen babies were found to have a rare condition called Crisponi syndrome. This condition caused them to have unusual facial features, bent fingers, and difficulty with eating, such as being unable to suck or swallow. They also had strong and sudden facial contractions during regular care, red skin rashes, and sometimes had high body temperature and seizures, which could lead to death[5]. Neurodevelopmental problems like small corpus callosum, seizures without a fever, and delay in

Table 2

Shows the outcomes of the test called whole-exome sequencing which is used to identify the genetic reasons behind different disorders

Variant nomenclathre	Gene	Zyg	Disease	PI	ACMG classification
Chr7: 23124718T > G; NM_018846:exon3: c.110T > G:p. Val37Gly	KLHL7	Hom	PERCHING syndrome Retinitis pigmentosa 42	ARAD	VUS

AD, autosomal dominant; AR, autosomal recessive; Hom, homozygote; PI, pattern of inheritance; VUS, variant of uncertain significance; Zyg, zygosity.

learning and movement are not often talked about[6–8]. Previously, it was discovered that CS is the baby version of a condition called cold-induced sweating syndrome (CISS). CISS was first identified in grown-up patients[9]. Through the identification of specific genes, CISS was divided into two very similar disorders called CISS1 and CISS2. These disorders are caused by mutations in two separate genes, CRLF1 and CLCF1[7,10].

In 1999, a group of patients was identified who were said to have a more severe form of a condition called C syndrome, also known as Opitz trigonocephaly. This condition includes changes in the shape of the head, unusual facial features, heart problems, and issues with the nervous system[11]. This new syndrome, called Bohring Opitz syndrome (BOS), has some different things compared to C syndrome. These include a red birthmark on the face, a split in the lip and/or roof of the mouth, thick eyebrows that meet in the middle, and a special way of holding the body called the "BOS posture." This posture involves rotating or pulling the shoulders outward, bending the elbows, bending the wrists, and bending the fingers in a certain way[12]. Scientists have discovered that the main cause of BOS is changes in the ASXL1 gene[13]. Even though CS/CISS and BOS are different conditions caused by separate factors, there are some similarities in how they appear in patients. Therefore, it is not surprising that when patients with recessive KLHL7 mutations were first reported, they showed similarities to both syndromes. Because of this, they were given labels such as "BOS-like" and "CS/CISS1-like"[4].

One way to explain the difference in physical characteristics caused by recessive KLHL7 mutations might be related to the person's genetic makeup. However, the genes someone has don't always accurately determine their physical traits. Even though all changes in the genes that cause a specific eye disease are in a specific part of the gene, people with a different type of eye disease also have changes in a different part of the gene. Furthermore, patients with BOS-like disease had various types of genetic mutations that affected how proteins functioned. These mutations included changes in the Kelch domains called nonsense and splice donor variants, as well as a mutation in the BACK domain that affected how proteins interacted with DNA. There is no clear pattern that can explain how recessive KLHL7 gene mutations affect the characteristics of an organism[14].

So, we recommend using the acronym PERCHING for certain common features of the spectrum of recessive KLHL7 disorders. However, these features may not be present in every case. Each letter represents two important phenotypic elements: **P** for Postural and Palatal abnormalities, **E** for Exophthalmos and Enteral-tube dependency/feeding issues, **R** for Respiratory distress and Retinitis pigmentosa, **C** for Contractures and Camptodactyly, **H** for Hypertelorism and Hirsutism, **I** for IUGR/growth failure and Intellectual disability/developmental delay, **N** for Naevus flammeus and Neurological malformations, **G** for facial Gestalt/Grimacing and Genitourinary abnormalities[15].

Conclusions

Even though the diagnosis was confirmed through genetic testing, previous studies show that this disease may be noticeable in patients and could be classified as a brain disorder. Our report will help us learn more about the different traits and characteristics of Perching syndrome. We are not sure if the differences in the PERCHING appearance are caused by different effects on the protein by certain mutations or by unknown genetic, epigenetic, or other environmental factors. We need to do more research on how proteins work and study more about patients with different characteristics to fully understand this.

Ethical approval

Not applicable.

Consent to participate

An written informed consent was obtained from the parents of patient for possible publication of this information as the case report. The whole research was done under the permission of the Ethics committee of Golestan University of Medical Sciences and also Genetic Testing for parents was done because of their.

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Author contribution

S.A.H. and M.G.G. diagnosed, and managed this patient and interpretation. S.D. wrote the first manuscript draft, M.G.G. and S.G. revised the manuscript and finalized the draft

Conflicts of interest disclosure

Not applicable.

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For register of research needs to pay charge. we are in international sanction so unable pay or transfer register fee.

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Data availability statement

The datasets are available from the corresponding author on reasonable request.

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