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Case Report

Two variants of the ferredoxin reductase (FDXR) causing isolated retinitis pigmentosa

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ABSTRACT

Objective: The FDXR gene encodesferredoxin reductase, which is a mitochondrial membrane protein and plays a role in Fe-S cluster synthesis. Loss of function in this gene causes intracellular iron accumulation, leading to dysfunction, especially in nervous system cells. To date, 46 patients with biallelic FDXR variants have been reported. While optic atrophy was a common finding in most of the patients, it was found that many neurological findings were also accompanied.

Method: Two siblings from an unrelated Turkish family and their parents were included. DNA was isolated from the patient's blood sample. Whole exome sequencing was performed using next-generation DNA sequencing.

Results: We described two siblings with the same compound heterozygous variants, but with phenotypically different characteristics. While ataxia, opticatrophy, and minor dysmorphic findings were present in one sibling, we did not detect any finding other than subclinical retinal dystrophy in the other sibling.

Conlusion: Many patients described in the literature have also been reported to show wide phenotypic variability. We would like to report these patients to contribute to the genotype phenotype relationship of the disease and to create resources for future gene therapies.

Keywords: FDXR gene, optic atrophy

INTRODUCTION

Iron is required as an enzymatic cofactor to synthesize many protein complexes, including Fe-S clusters. Incorrect biosynthesis of Fe-S aggregates creates iron overload in tissues and cells. Excessive iron accumulation also causes pathological changes and dysfunction in cells. Due to a decrease in Fe-S clusters, this accumulation is responsible for the pathogenesis of mitochondrial diseases. Ferredoxin Reductase (FDXR) encodes flavoprotein, a mitochondrial membrane protein involved in the biosynthesis of Fe-S clusters and the transfer of electrons from NADPH to the cytochrome p450 system. The flavoprotein interacts with ferredoxin 1 (FDX1) and ferredoxin 2 (FDX2). FDX1 plays a critical role in the steroid biosynthesis pathway, while FDX2 plays a critical role in the biosynthesis of Fe-S aggregates.[1,2] When FDXR activity decreases, the synthesis of Fe-S clusters decreases, and iron overload occurs, resulting in multiorgan dysfunction, especially in the neurons. FDXR is a gene with 12 exons localized at 17q25 and has three main domains: two NAD(P) binding domains and the FAD/NAD(P) binding domain in the middle. FDXR plays a role in the pathogenesis of mitochondrial myopathy, auditory neuropathy, and optic atrophy. It was first

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described by Paul et al.[3] in patients with hereditary auditory neuropathy and optic atrophy. It is among the ten most common genes that cause hereditary optic neuropathy. In this study, we report the different phenotypic features in two siblings with the same variants.

MATERIAL AND METHODS

Subjects

Two siblings from an unrelated Turkish family and their parents were included. The study was approved by the Necmettin Erbakan University Faculty of Medicine Ethics Committee (2023/4118) and performed in accordance with the ethical standards of the Declaration of Helsinki. The parents signed a written informed consent form.

Genetic Studies

The number of GAA repeats for Freidrich's ataxia was evaluated and found to be <33. Mitochondrial sequence analysis revealed no pathogenic variant in Patient 1. DNA was isolated from the patient's blood sample. Whole exome sequencing was performed using next-generation DNA sequencing (NextSeq, Illumina). The data obtained was analyzed using the Franklin Genoux database. Homozygous and heterozygous variants with high sequence read quality were filtered out.

RESULTS

Patient 1

A 5-year-old male patient presented to us with a complaint of walking disorder. The patient's walking had gradually deteriorated over the previous year, resulting in an unbalanced gait. According to the patient's medical history, he was hospitalized because of a walking disorder that developed suddenly when he was 2.5 years old. He was diagnosed with Gullian-Barre and received immunoglobulin treatment for the same. The walking disorder partially improved after the treatment, but it worsened when he was approximately four years old. A pediatric neurology check-up was performed because the patient had frequent falls and an unbalanced gait. The patient's electromyography and electroencephalography were evaluated as normal. Cranial magnetic resonance imaging (MRI) was reported as normal. The patient's nystagmus, which started two weeks after his first hospitalization, continues, and visual field loss and optic atrophy were detected during an ophthalmology check-up. The patient's visual loss was progressive. A hearing test and brainstem auditory-evoked potentials (BAEP) were performed and evaluated as normal. The following findings were reported upon physical examination: body weight – 24 kg (75–90 p), height – 127 cm (99p, +2.4 SDS), head circumference – 51 cm (25–50 p). Other than dysmorphic findings, such as downward slanting palpebral fissures, ptotic eyelids, drooping ears, no eye tracking, and weak deep tendon reflexes were found (Figure 1).

Patient 2

A 9-year-old female patient was born to the same unrelated parents at 40 weeks gestational age. It was learned from the patient's medical history that she had completed her neurodevelopmental milestones without delay and had no disease. An eye examination was performed since optic atrophy was detected in her brother. Retinal dystrophy and optic atrophy were detected in the concerned patient. However, the patient had no complaints about vision. BAEP was evaluated as normal. Cranial MRI was reported as normal. The hearing test was assessed as normal. The following findings were noted upon physical examination: body weight – 35 kg (75–90 p), height – 137 cm (75–90 p), head circumference – 52 cm (25–50 p). Systemic examination revealed no significant finding examination.

Molecular Findings

FDXR c.235C>T, p.Arg79Cys (NM_024417.5), c.980G>A, p.Arg327His variants were detected, which are compatible with the patient's clinical findings. These variants were deemed likely pathogenic based on the American College of Medical Genetics 2015 (ACMG) criteria. According to the ACMG criteria, the FDXR c.235C>T variant is of uncertain clinical significance (VUS), and when evaluated together with family segregation data, it is classified as likely pathogenic (PP1, PM2). In addition, this variant has been reported as deleterious by in silico prediction programs (MT, DANN, SIFT). The DNA was obtained from the blood samples of the family members, after which the PCR product prepared with the target region primers was sequenced. The FDXR c.980G>A variant was detected in the mother, and the FDXR c.235C>T variant was detected in the father. His older sister also had compound heterozygote FDXR variants (Figure 2).

DISCUSSION

Here, we present a case study of a male patient with optic atrophy and ataxia and his sister, who had the same variants but presented with no clinical findings. The literature has reported 46 such patients so far. The most common finding in these patients is optic neuropathy, observed in 93.2% of the cases.[4] The second most common finding reported is acoustic neuropathy, found in 50% of the cases. Developmental delay, developmental regression, peripheral neuropathy, and hypotonia are among the less common findings reported. The rate of ataxia seen in our

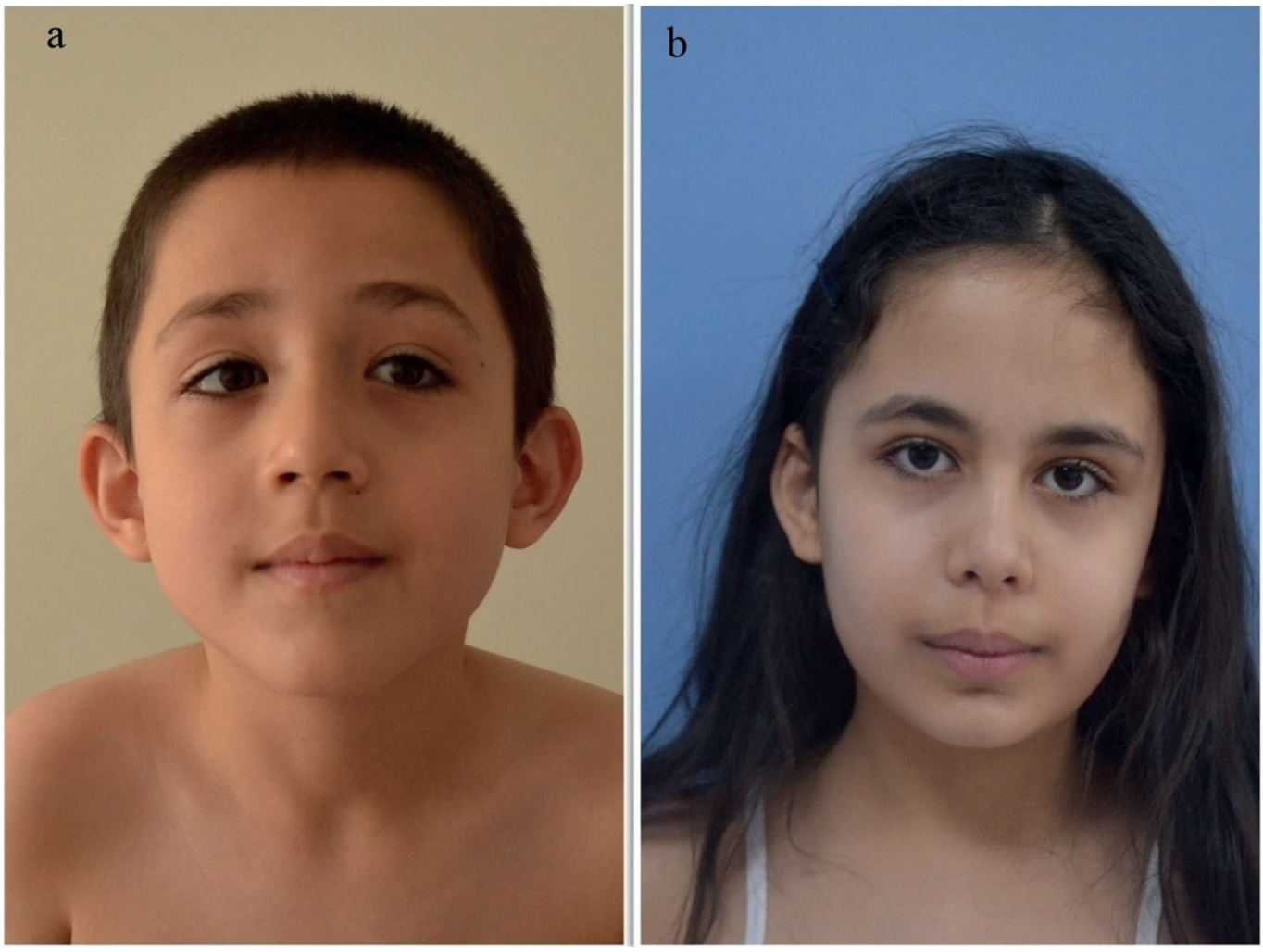


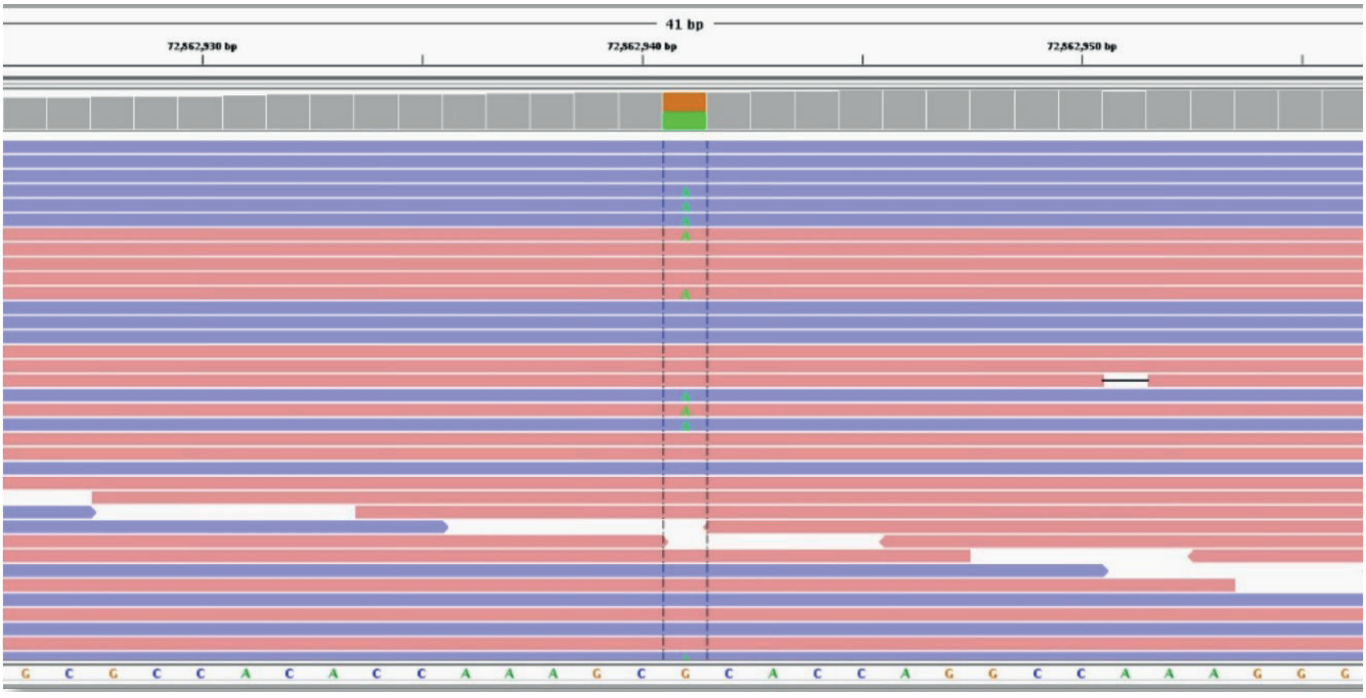
Figure 1. a. Patient 1: Downslanting palpebral fissures, ptotic eyelids, and drooping ears **b. Patient 2:** No dysmorphic features.

Patient 1 was 43.9%. When the genotype of the patients with ataxia was examined, it was determined that the most common variant was c.1115C>A. However, in most of these patients, a compound heterozygous variant was detected.[4] In addition, the rate of retinal dystrophy was reported as 30.4% in this study, and no patient with isolated retinal dystrophy was identified. In our Patient 2, there was no finding other than infraclinical retinal dystrophy.

Dramatic amounts of iron accumulation have been detected in FDXR mutant mice.[3] This accumulation has also been found in the nervous system. Because of the FDX2 median pathway component, it has been thought that pathophysiology similar to Friedrich's ataxia may also occur in FDXR mutants.[5] Therefore, the occurrence of ataxia in Patient 1 was expected.

The literature describes a case involving the FDXR biallelic variant with only optic atrophy but no neurological deficit. It is reported that this patient's symptoms appeared at the age of 12 years, and his visual acuity gradually decreased in 6 months without any apparent trigger.[6] Another study on ten patients did not show retinal dystrophy alone. Optic atrophy was present in all patients, while retinal dystrophy was found in 6 patients. Cataracts, nystagmus, and ophthalmoplegia were among the ocular findings.[7] In the last published study by Jurkute et al.[7], retinal dystrophy was reported in 30.4%, nystagmus in 17.4%, cataracts in 10.9%, and ophthalmoplegia 4.3% (Table 1).[4] Mutant mice retinal cells were functionally reduced.

Further, a reduction in the number of cells in the visual cortex of mutant mice has been observed even at eight weeks of age,



FDXR c.235C>T heterozygous variant above, and below FDXR c.980G>A heterozygous variant below.

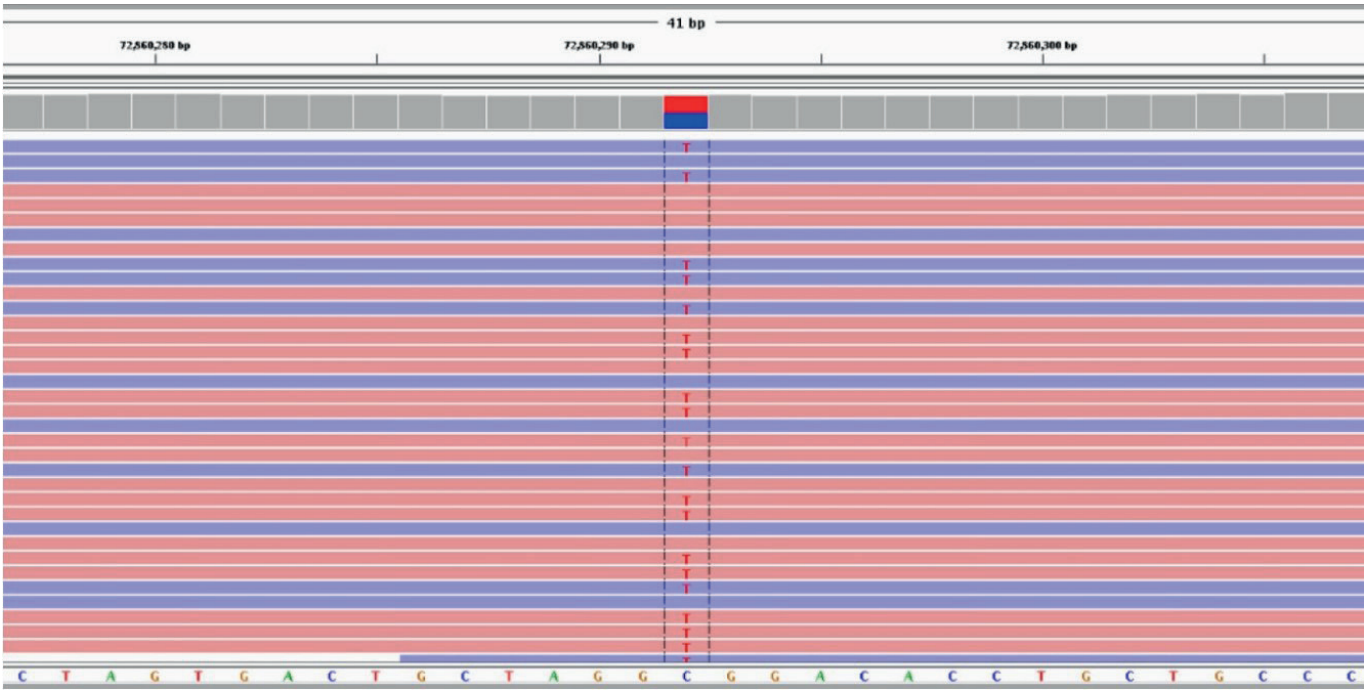


Figure 2. IGV image of variants

suggesting worsening of optic atrophy.[5] Despite this, although retinal dystrophy and optic atrophy were present in Patient 2, no clinical findings were detected. No additional findings were found during the follow-up eye examinations.

In many FDXR mutant patients, an MRI of the brain revealed

Table 1. Clinical findings of patients and literature review

Clinical findings	Patient 1	Patient 2	Review of the literature
Optic neuropathy	+	+	%93,5
Acoustic neuropathy	-	-	%50
Ataxia	+	-	%43.9
Hypotonia	-	-	%41.3
Developmental delay	-	-	%39.1
Developmental regression	-	-	%34.8
Retinal dystrophy	+	+	%30.4
Peripheral neuropathy	+	-	%23.9
Pyramidal signs	-	-	%23.9
Speech issues	-	-	%23.9
Nystagmus	+	-	%17.4
Loss of deambulation	-	-	%15.2
Microcephaly	-	-	%15.2
Cataract	-	-	%10.9
Encephalopathic episodes	-	-	%10.9
Dystonia	-	-	%8.7
Seizures	-	-	%6.5
Ophthalmoplegia	-	-	%4.3
Tremor	-	-	%4.3

findings such as delayed myelination, cerebellar atrophy, cerebral atrophy, and corpus callosum anomalies. Nevertheless, the MRI was normal in many of the other patients.[8] In our patients, both orbital and brain MRI were normal.

CONCLUSION

As the relationship between variants in the FDXR gene and the phenotype is defined, which makes it easier to study it on a molecular level. The FDXR gene may also have an essential role in the genetic etiology of patients with only ophthalmic findings and no additional neurological anomalies. This will increase the number of defined variants, which can guide suitable gene therapy development.

Ethical approval

This study has been approved by the Necmettin Erbakan University Non-Drug and Non-Medical Device Research Ethics Committee (approval date 06.01.2023, number 167). Written informed consent was obtained from the participants.

Author contribution

Study conception and design: FMB; data collection: FMB, MB; analysis and interpretation of results: MB; draft manuscript preparation: FMB, MB. All authors reviewed the results and approved the final version of the manuscript.

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Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Shi Y, Ghosh M, Kovtunovych G, Crooks DR, Rouault TA. Both human ferredoxins 1 and 2 and ferredoxin reductase are important for iron-sulfur cluster biogenesis. Biochim Biophys Acta. 2012;1823:484-92. [Crossref]
2. Sheftel AD, Stehling O, Pierik AJ, et al. Humans possess two mitochondrial ferredoxins, Fdx1 and Fdx2, with distinct roles in steroidogenesis, heme, and Fe/S cluster biosynthesis. Proc Natl Acad Sci U S A. 2010;107:11775-80. [Crossref]
3. Masnada S, Previtali R, Erba P, et al. FDXR-associated disease: a challenging differential diagnosis with inflammatory peripheral neuropathy. Neurol Sci. 2023;44:3037-43. [Crossref]
4. Paul A, Drecourt A, Petit F, et al. FDXR Mutations Cause Sensorial Neuropathies and Expand the Spectrum of Mitochondrial Fe-S-Synthesis Diseases. Am J Hum Genet. 2017;101:630-7. [Crossref]
5. Slone JD, Yang L, Peng Y, et al. Integrated analysis of the molecular pathogenesis of FDXR-associated disease. Cell Death Dis. 2020;11:423. [Crossref]
6. Song SJ, Hong Y, Xu K, Zhang C. Novel biallelic compound heterozygous mutations in FDXR cause optic atrophy in a young female patient: a case report. Int J Ophthalmol. 2021;14:1796-8. [Crossref]
7. Jurkute N, Shanmugarajah PD, Hadjivassiliou M, et al. Expanding the FDXR-associated disease phenotype: retinal dystrophy is a recurrent ocular feature. Invest Ophthalmol Vis Sci. 2021;62:2. [Crossref]
8. Peng Y, Shinde DN, Valencia CA, et al. Biallelic mutations in the ferredoxin reductase gene cause novel mitochondriopathy with optic atrophy. Hum Mol Genet. 2017;26:4937-50. [Crossref]