Autosomal Dominant *FAR1*-Related Disorder

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BACKGROUND

- *FAR1* is associated with an autosomal dominant (AD) disorder, first described in 2021 and characterized primarily by cataracts, spastic paraparesis, and speech delay.[1]
- Other variable features include seizures, developmental delay, and intellectual disability.[1]
- Almost all described individuals are in the pediatric age range, with oldest known individual being 19 years old.[1]
- All known probands harbor a *de novo* variant resulting in a change in arginine at codon 480 to cysteine, histidine, or leucine.[1,2,3,4,5]
- Heterozygous *de novo* variants cause gain-of-function in fatty acyl-CoA reductase resulting in elevated plasmalogen levels.[5]
- *FAR1* is also associated with autosomal recessive peroxisomal fatty acyl-CoA reductase-1 disorder, which has a partially overlapping phenotype.[1,2,4,5]

WE REPORT THE OLDEST KNOWN INDIVIDUAL WITH AD *FAR1*-RELATED DISORDER, A 28-YEAR-OLD MALE, WHO SHARES CORE FEATURES BUT ALSO PRESENTS WITH UNIQUE FINDINGS.

PATIENT DESCRIPTION

- 28-year-old male with a history of congenital cataracts, gross motor delay, spastic paraparesis, mild speech delay, and seizures. He completed community college and is employed part-time.
- Additional phenotypic features not seen in other individuals with *FAR1*-related disorder include dysmorphic features (pectus excavatum, bilateral elliptical coloboma, full lips, large hands and feet with bluish discoloration, tapered fingers, tapered neck), strabismus, and scoliosis.
- 2015: non-diagnostic chromosomal microarray and proband exome sequencing

Figure 1: 2024 exome reanalysis

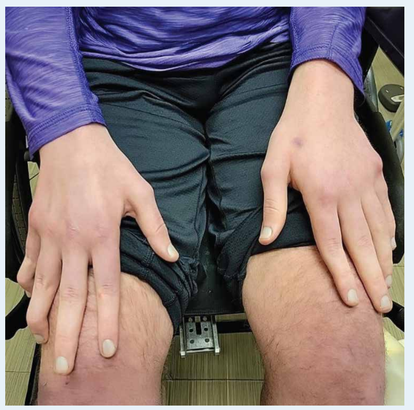
DISEASE	INHERITANCE PATTERN	GENE / VARIANT	VARIANT TYPE	GENOTYPE	INHERITED FROM	VARIANT CLASSIFICATION
Cataracts, Spastic Paraparesis, And Speech Delay	Autosomal Dominant	FAR1: c.1438C>T, p.R480C	Sequence Variant	Heterozygous	De Novo	Pathogenic

Figure 2: Face

Figure 3: Profile view

Figure 4: Lower extremities

Figure 5: Hands



Pictures of the patient shared with written permission from the family

CONCLUSION

This case expands the known phenotypic range among the limited number of described individuals with molecular *FAR1* findings. It also highlights the utility of reanalysis of genomic sequencing for patients suspected to have *FAR1*-related disorder prior to the disease's description, and of reanalysis to provide diagnoses even years after initial testing was performed. The presence of the same codon change in this patient as others documented also improves efforts to identify future patients as well as potential research opportunities.

References

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