Mousawi, Z., Chebly, A., Nehme, J., Ibrahim, J. N., Helou, C., Zeitz, C., & El Shamieh, S. Identification of a novel *CABP4* frameshift variant and a secondary *USH2A* missense variant in congenital cone-rod synaptic disorder.

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Background and Objectives

Congenital cone-rod synaptic disease (CRSD) belongs to a group of genetically and clinically heterogeneous retinal disorders. Pathogenic variants in the *CABP4* gene coding for the calcium-binding protein four can lead to this condition. Several disease-causing variants lead to this condition. In support of this, our current study aimed to genetically characterize a consanguineous Lebanese family with two young siblings who show CRSD.

Results

Whole-exome sequencing identified a novel frameshift insertion in both affected siblings; c.363dup, p.(Lys122Glufs *21) in *CABP4*. The elder sibling carried a secondary homozygous missense variant; c.12575 G > A, p.(Arg4192His) in *USH2A* that is known to be associated with retinitis pigmentosa. *CABP4* variant co-segregated with the phenotype in all the available family members. The ACMG guidelines classified *CABP4* and *USH2A* variants as likely pathogenic and pathogenic, respectively. The secondary *USH2A* missense variant may lead to a more pronounced phenotype, necessitating an effective follow-up for better patient management.

Conclusion

The current findings highlight the involvement of *CABP4* pathogenic variants in CRSD.