UNRAVELING A NEW MACULAR DISEASE: INDEL MUTATION IN *GUCA1A* GENE LEADS FROM SUSPECTED CACD TO GARGANTUA'S DISEASE

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Introduction

Malfunctioning of the eye and its inner structures disturb the processes of receiving, processing, and interpreting visual information, often associated with genetic defects. Considering that the retina covers 75% of the bulb and begins the visual process, any deviation in the sensible interaction between different cells that compose this structure is prone to cause visual impairments We investigated the causal genetic variant of a previously unknown macular disease in a South Brazilian family with four affected individuals, exhibiting symptoms suggestive of autosomal dominant central areolar choroidal dystrophy (CACD).

Objective

To establish a comprehensive understanding of the inheritance pattern and to determine a precise diagnosis of the probands.

Methods

We constructed a heredogram spanning four generations, consisting of 56 individuals. All members underwent ophthalmologic exams of electroretinogram, electrooculogram, optical coherence tomography, visual field, color test, and visual acuity to ensure the phenotype of this new disease. DNA samples were extracted from 14 family members for genotyping, while exome sequencing was performed for the identification of candidate variants, later confirmed by Sanger sequencing.

Results

Whole exome sequencing revealed a heterozygous 6-nt in-frame deletion (rs1554185944) within the coding region of guanylate cyclase-activating protein 1 (GUCA1A, also known as GCAP1) in all affected patients. Sanger sequencing confirmed the identified variant in both patients and two symptomatic relatives. Two out of ten asymptomatic relatives also tested positive (p=0.015). Deep phenotyping led to the suggestion of a new progressive macular disease, with characteristic bipartite lesions in the patients (resembling the "Gargantua" black hole) identified by autofluorescence, low visual acuity, tritanopia, rarefaction in the photoreceptors, and foveal atrophy. An interesting finding was that all patients exhibited normal color vision, which differs from most CACD cases, normally associated with at least moderate defects in color distinction.

Conclusion

We identified a rare, likely pathogenic GUCA1A variant in a family with a new macular disease that shares some similarities with CACD but clearly differs from it and other macular diseases. The causative nature of the variant was supported by biochemical analysis, as well as clinical and genetic data.

Descritores: Retinal degeneration, Retinopathies, Photoreceptors, CACD.