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A novel gelsolin variant associated with Familial Amyloidosis of the Finnish type in an Australian family

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Abstract

Purpose : This study identified and sought to validate the association between a novel gelsolin (*GSN*) variant and the phenotype of Familial Amyloidosis of the Finnish type (FAF) in three first degree relatives harbouring a previously undocumented variant, and manifesting multiple clinical and ophthalmic features consistent with systemic gelsolin (GSN) amyloidosis.

Methods : Three first degree relatives presenting to a single tertiary ophthalmic outpatient clinic exhibiting clinical features consistent with FAF including cutis laxa and vision-affecting corneal stromal changes were enrolled in a genetic study of corneal disease. DNA extracted from whole blood samples collected from two individuals was subjected to exome sequencing. Genes associated with corneal disease were assessed for rare and potentially deleterious variants. Histopathological and immunohistochemical studies of proband corneal tissue collected at the time of corneal graft surgery were performed to investigate for the presence of GSN within corneal deposits.

Results : A previously undocumented *GSN*:c.1477T>C variant resulting in a predicted p.(Trp493Arg) missense variant was identified in the two individuals who underwent exome sequencing. This variant was subsequently confirmed in all three affected individuals through Sanger sequencing. This rare variant which was absent from the Genome Aggregation Database (gnomAD), a large population-based database of 125,748

exomes and 15,708 genomes, was predicted to be damaging by in silico tools (Phred scaled CADD score: 20.8). Histopathological studies performed on the proband cornea demonstrated irregular stromal inclusions which manifested classic amyloid features when subjected to Congo red staining, and intense GSN labelling in immunohistochemical studies.

Conclusions : This study is the first to describe an association between the *GSN*:c.1477T>C,p.(Trp493Arg) variant and FAF. This novel variant which affects a GSN region distant from the classic p.Asp214Asn variant and the gelsolin 2 (G2) domain, may lead to insights into the amyloidogenic mechanisms of FAF-associated GSN variants.

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