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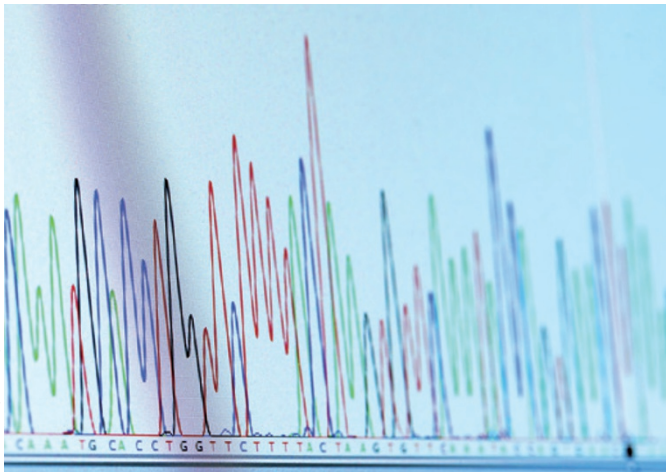
GENETICS

Hidden intronic mutations in *DGKE* are causative of aHUS



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Recessive mutations in diacylglycerol kinase ε (*DGKE*) can cause atypical haemolytic uraemic syndrome (aHUS)—a common cause of acquired acute renal failure in children. New research by Giuseppe Remuzzi and colleagues extends this association, with the identification of a novel aHUS-causative intronic mutation in *DGKE* located well beyond the exon–intron boundaries.

The researchers performed whole-exome and whole-genome sequencing in two families (one from Italy and one from the USA) with infantile recessive familial aHUS of unknown genetic origin. "Analysis of the data using conventional variant filtering parameters did not reveal any obvious candidate mutations in the Italian family, and only a heterozygous nonsense *DGKE* mutation in the US family that alone could not explain the disease," says researcher Marina Noris. "Given that deep intronic mutations can result in abnormal splicing, we examined the intronic variants in the whole-exome sequencing data of the Italian family."

The *DGKE* locus was analysed in detail because of similarities with regard to the mode of disease inheritance, age of onset, and clinical phenotype between the affected patients of the two families and those with known *DGKE* aHUS-causative mutations. A novel *DGKE* mutation located in intron 5 (c.888+40A>G), was identified and segregated with the disease in a recessive pattern.

Sequencing *DGKE* mRNA obtained from blood leucocytes of the two affected siblings in the Italian family, demonstrated that the intronic mutation affected splicing of exon 5, resulting in the production of three aberrant *DGKE* isoforms. The wild-type *DGKE* mRNA was absent.

Further analyses showed that the most abundant *DGKE* mRNA isoform retained an additional 39 nucleotides that immediately follow exon 5 and encoded a DGKE protein that was 13 amino acids longer than the wild-type. Structural 3D modelling predicted that this 13 amino acid insertion would affect DGKE kinase activity. The other two isoforms were not detected at the protein level. Strikingly, the same mutation was found in compound heterozygosity with the nonsense *DGKE* mutation in the three affected siblings of the US family.

"We now plan to design next-generation sequencing panels that target the introns of *DGKE* and other complement-associated aHUS genes, to identify novel disease-associated mutations," says Noris. "Sequencing intronic regions of known disease-associated genes followed by analysis of the mRNA sequence could be a valuable tool to resolve aHUS cases with an unknown genetic basis." The researchers propose that this study might be an example for other rare diseases where exon screening fails to identify any causative mutation.

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Original article Mele, C. *et al.* Characterization of a new DGKE intronic mutation in genetically unsolved cases of familial aytpical hemolytic uremic syndrome. *Clin. J. Am. Soc. Nephrol.* doi:10.2215/CJN.08520814