A HISTORY OF MOLECULAR VISION

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Novel mutations of the carbohydrate sulfotransferase-6 (CHST6) gene causing macular corneal dystrophy in India

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Purpose: Macular corneal dystrophy (MCD) is an autosomal recessive disorder characterized by progressive central haze, confluent punctate opacities, and abnormal deposits in the cornea. It is caused by mutations in the carbohydrate sulfotransferase-6 (CHST6) gene, encoding corneal N-acetylglucosamine-6-O-sulfotransferase (C-GlcNAc-6-ST). We screened the CHST6 gene for mutations in Indian families with MCD, in order to determine the range of pathogenic mutations.

Methods: Genomic DNA was isolated from peripheral blood leukocytes of patients with MCD and normal controls. The coding regions of the CHST6 gene were amplified using three pairs of primers and amplified products were directly sequenced.

Results: We identified 22 (5 nonsense, 5 frameshift, 2 insertion, and 10 missense) mutations in 36 patients from 31 families with MCD, supporting the conclusion that loss of function of this gene is responsible for this corneal disease. Seventeen of these mutations are novel.

Conclusions: These data highlight the allelic heterogeneity of macular corneal dystrophy in Indian patients.

The corneal dystrophies are a heterogeneous group of disorders that may lead to severe visual impairment [1]. Macular corneal dystrophy (MCD, OMIM 217800) is an autosomal recessive disorder clinically characterized by bilateral corneal opacification. Initially the patients have diffuse, fine superficial clouding in the central stroma. The opacities extend through the entire thickness of the cornea and involve the central and peripheral corneal stroma. The central stroma is often thinner than normal [2-4]. The corneal endothelium is involved and a gutter form on the Descemet's membrane [5]. The prevalence of MCD varies immensely in different parts of the world but in most populations the condition is rare. In some countries MCD accounts for 10-75% of the corneal dystrophies requiring corneal grafting [6,7].

Keratan sulfate (KS) is the major corneal glycosaminoglycan [8] and is a component of three corneal proteoglycans (lumican, keratocan, and mimecan). Sulfate ions contribute significantly to the negative charge of proteoglycans and in the cornea this highly anionic charge on KS is believed to

due to a failure to synthesize normal keratan sulfate proteoglycan within the cornea [11-13] and corneas with this disorder accumulate a glycosaminoglycan within the keratocytes, corneal endothelium, Bowman's layer, Descemet's membrane, and extracellularly in the stroma.

MCD is divided into three immunophenotypes (MCD types I, IA, and II) based on the reactivity of the patient's serum and corneal tissue to an antibody that recognizes sulfated KS, although these subtypes are clinically indistinguishable from each other [14-16]. In MCD type I neither the serum nor the corneal tissue contain antigenic KS (AgKS). In MCD type IA, sulfated KS is absent in the cornea and the serum but can be detected in the keratocytes [16]. MCD type II is characterized by the presence of AgKS in the corneal tissue and normal levels of AgKS in the serum. After identifying the locus for MCD on chromosome 16 [17] and fine mapping the gene [18,19], mutations in the carbohydrate sulfotransferase gene (CHST6) encoding corneal N-acetylglucosamine-6-O-sulfotransferase (C-GlcNAc-6-ST) were identified as the cause
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• Winning acceptance in the vision science community

• Indexing in PubMed

• Impact Factor from ISI

• Software
Conclusions (4 major points)

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(Scholars need to volunteer to run peer-review and edit scholarly journals).
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3. It takes several years to jump through all the hoops: Acceptance, PubMed, Impact Factor. Stick with it.

4. Software: share your software. Quality software is key.
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