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Scientists identify mutations that cause congenital cataracts

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New research identifies genetic mutations that cause an inherited form of cataracts in humans. The study, published online June 2 by Cell Press in the *American Journal of Genetics*, provides new insight into the understanding of lens transparency and the development of cataracts in humans.

A cataract is a clouding of the crystalline lens in the eye. Opacity of the normally transparent lens obstructs the passage of light into the eye and can lead to blindness. Congenital cataracts (CCs) are a significant cause of vision loss worldwide and underlie about one-third of the cases of blindness in infants. "Autosomal-recessive CCs form a clinically diverse and genetically heterogeneous group of lens disorders," explains senior study author Dr. J. Fielding Hejtmancik from the National Eye Institute in Bethesda, Maryland. "Although several genes and genetic regions have been implicated in the rare nonsyndromic form of autosomal-recessive CCs, in many cases the mutated gene remains unknown or uncharacterized."

One candidate gene that has been identified as playing a role in lens biology and in the pathogenesis of autosomal-recessive CCs is FYCO1. As part of an ongoing collaboration between the National Eye Institute in Bethesda MD and the National Center for Excellence in Molecular Biology and the Allama Iqbal Medical College in Lahore, Pakistan, Dr. Hejtmancik and colleagues performed a sophisticated genome-wide analysis of unrelated consanguineous families (in which both parents are descended from the same ancestor) of Pakistani origin and identified

mutations in FYCO1 in 12 Pakistani families and one Arab Israeli family with autosomal-recessive CCs. The researchers went on to show that FYCO1 is expressed in the embryonic and adult mouse lens.

Both the high frequency of FYCO1 mutations and the recessive inheritance pattern seen in the families support the idea that autosomal-recessive CCs might result from a loss of FYCO1 function. The FYCO1 protein has been shown to play a role in "autophagy," a process that is necessary for degrading unwanted proteins. To become transparent, lens cells must get rid of some of their protein components, and the researchers suggest that as lens cells lose their organelles during development, abnormal accumulation of protein aggregates might play a role in the loss of lens transparency.

Taken together, the results implicate FYCO1 in lens development and transparency in humans and FYCO1 mutations as a cause of autosomal-recessive CCs in the Pakistani population. "Our study provides a new cellular and molecular entry point to understanding lens transparency and human cataract," concludes Dr. Hejtmancik. "In addition, because of the frequency of FYCO1 mutation in the Pakistani population, it might be useful in genetic diagnosis and possible even improved future cataract treatment and prevention."

Provided by Cell Press