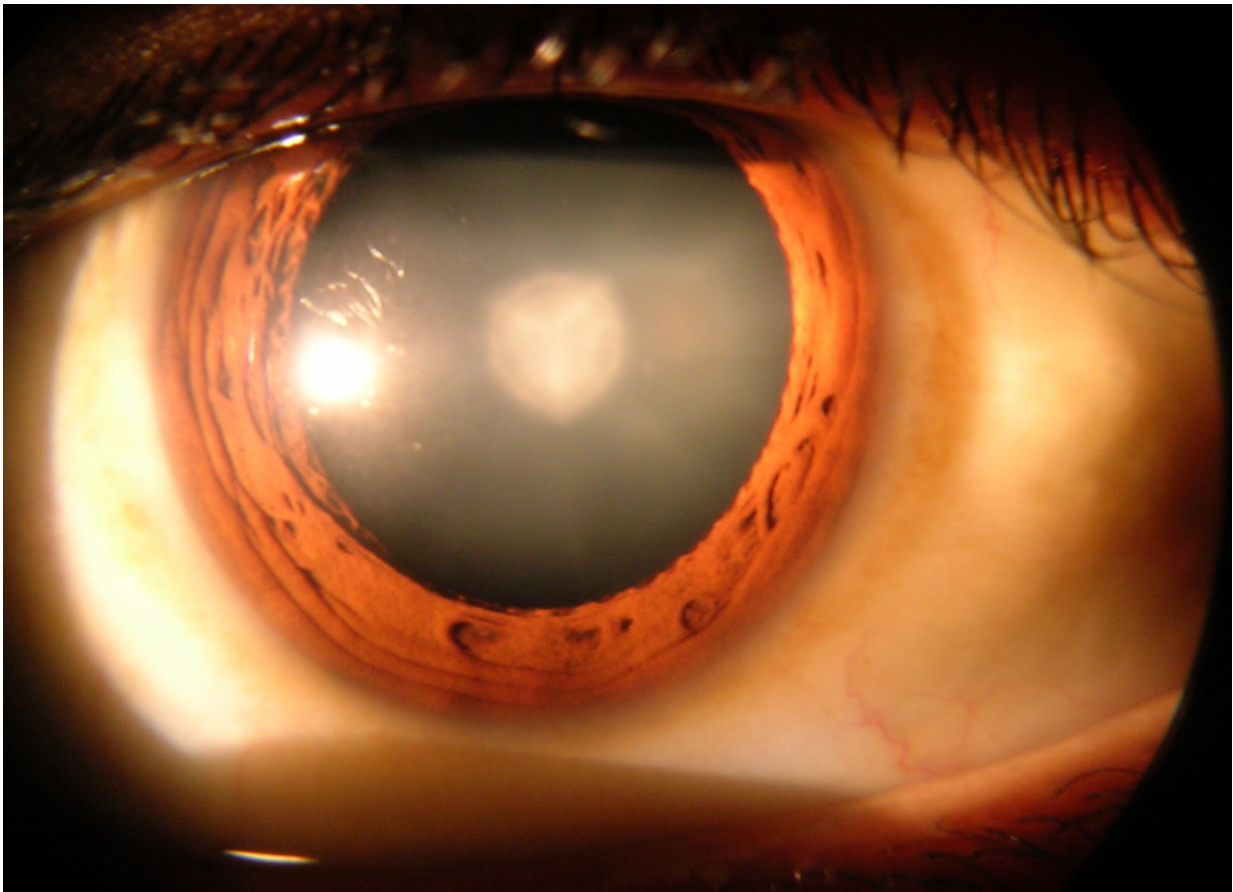


Dynamin-binding protein linked to congenital cataracts

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Cataract in human eye. Credit: Wikipedia.

Cataracts, a condition in which the eyes' natural lenses get clouded, are the most common cause of vision loss in older people and can be

corrected by routine surgery. But congenital cataracts, which occur in infants and children, are particularly serious since they can inhibit visual development leading to permanent vision loss or impairment that cannot be entirely reversed with cataract surgery. A new study has now found compelling evidence that links dynamin-binding protein (DNMBP) to congenital bilateral cataracts and severe vision loss. The study appears in the *American Journal of Human Genetics*.

This discovery is an outcome of an international collaboration between researchers in the laboratories of Dr. Hugo Bellen, professor at Baylor College of Medicine, investigator at the Howard Hughes Medical Institute and the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital in Houston, Texas, USA and Dr. Stylianos E. Antonarakis, professor and chairman of Genetic Medicine at the University of Geneva Medical School, and director of iGE3, the Institute of Genetics and Genomics of Geneva, Switzerland.

"We were intrigued when 12 individuals from three unrelated consanguineous families of Pakistani descent presented with congenital cataracts and severe to partial loss of vision in both eyes. It was even more puzzling that they showed additional signs of improper visual development. Despite having undergone cataract surgeries, they exhibited no improvement in their visual acuity. This led us to suspect this was a genetic disorder that was affecting more than just the opacity of the eye lens," said Antonarakis, one of the corresponding authors.

The researchers in Antonarakis lab compared the whole exome sequences of multiple patients from this cohort to the exome sequences obtained from a control cohort of similar ethnicity. This helped them to rule out all the non-pathogenic variants and hone in on the culprit.

"We found all 12 patients had mutations in the DNMBP gene on chromosome 10, and even though each of the three families had a

distinct type of mutation, it was obvious that the loss of DNMBP was the underlying cause of infantile cataracts and vision loss in these patients," said Dr. Muhammad Ansar, postdoctoral fellow in Antonarakis lab and one of the lead authors of the study. "Also, every patient had two defective copies of this gene, indicating that this was likely a recessive disorder, which is common in inbred populations."

The [eye lens](#) is a transparent tissue through which light and images are focused on the retina. A single type of epithelial precursor cell undergoes many stages of differentiation, elongation and migration to eventually form the lens fiber [cells](#). Actin cytoskeleton, a complex intracellular network of filaments that governs cell shape and motility, plays a crucial role in these complex morphogenetic and migratory steps.

The DNMBP protein regulates actin assembly and maintenance of tight junctions between adjacent cells; however, not much was known about its role in [eye development](#). So, to understand how loss of DNMBP was causing cataracts and vision loss in these patients, the researchers turned to the world-renowned fly biologist, Dr. Hugo Bellen.

"It is striking to see how the fruit fly that looks and behaves completely different from a human has proved time and again to be an excellent model to study human disease. Since the function of many human genes is highly conserved in flies and a plethora of powerful genetic tools is already available in this system, it is becoming increasingly common for human geneticists to employ flies to quickly understand the function of human disease genes," said Bellen.

The eye of an adult fly comprises approximately 750 small optical units called ommatidia. Each unit consists of eight photoreceptors and 11 accessory cells, one of which, the pigment cell, secretes the corneal lens. The fly eyes undergo similar developmental steps as the human eye—the pupal precursor cells differentiate, the photoreceptors elongate, [pigment](#)

[cells](#) at the apical area of the photoreceptors secrete a lens and bristle cells at the apical end start forming hair-like protrusions that depend on extensive actin polymerization.

"First, we used MiMIC technology to tag the still life (*sif*) gene, the fly homologue—that is, the fly's functional counterpart—of human DNMBP, with green fluorescent protein (GFP). This showed us that the Sif protein is normally expressed in photoreceptor cells and bristle cells. Then, to understand the role of Sif protein in eye development, we specifically deleted *sif* gene expression from pupal eyes. The resultant adult flies had subtle rough eyes, a clear indication that the stereotypical arrangement of ommatidia was altered," said Dr. Hyung-lok Chung, postdoctoral associate in the Bellen lab and the other lead author of the paper.

Upon further examination of the subcellular architecture of the ommatidia, they found that the septate junctions (analogous to vertebrate tight junctions) between different types of neighboring [photoreceptor cells](#) in the ommatidia were disorganized. Moreover, pigment cells that secrete the corneal lens were distorted or absent and bristles, a readout of actin cytoskeletal dynamics, were in the wrong position or missing. Most importantly, similar to what had been observed in some of the patients in this cohort, the visual input from the retina was impaired in *sif* mutant flies. Together, these findings pointed to an evolutionarily conserved role for DNMBP/Sif in regulating actin assembly during eye development.

"This study has uncovered the gene responsible for a recessive Mendelian disorder that causes infantile cataracts and blindness of varying severity. We think our pedigree and molecular analyses will help clinicians and geneticists provide accurate genetic counseling and diagnosis to other similarly affected patients," Bellen said. "Moreover, by generating the first fly model of congenital cataract and [vision loss](#), we have embarked on a journey to understand the precise molecular

mechanism behind this genetic disorder, which we are hopeful will lead us to promising therapeutic interventions and better quality of life for these patients."

More information: *American Journal of Human Genetics* (2018).
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