Research team finds genetic clue to 'emergency' glaucoma

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Jackson Laboratory researchers and their collaborators have reported their discovery of a gene implicated in an acute and severe form of glaucoma known as angle-closure glaucoma (ACG). The gene's activity points to previously unsuspected mechanisms involved in both ACG and infant eye development.

Glaucoma is one of the most common eye diseases and a leading cause of blindness. An increase in fluid pressure in the eye (intraocular pressure or IOP) leads to damage to the optic nerve, causing loss of vision. Most people with the more familiar chronic (open-angle) glaucoma don't even know they have the disease until it's detected in an eye exam. The condition develops slowly and can usually be managed with eyedrops and laser surgery.

But ACG can be another story: acute attacks of ACG are a medical emergency. Sudden, debilitating symptoms include severe eye pain, headache, blurred vision, nausea and vomiting, and without prompt intervention to reduce IOP, very rapid loss of vision can occur.

Simon W.M. John, Ph.D., the Jackson Laboratory professor and Howard Hughes Medical Investigator who led the glaucoma research team, describes ACG as "a particularly severe and debilitating subtype of glaucoma, which is very poorly understood at the molecular level." ACG, which affects about 16 million people worldwide, accounts for half of all glaucoma blindness.

ACG patients typically have eyes that are slightly smaller than normal, with a lens that is large for the size of the eye, and an abnormally short axial (front-to-back) length of the eye. These features predispose to blockage or closing of the angle of the eye, which contains an important drain for ocular fluid. As a result, the fluid does not drain properly and can quickly build up, sharply raising IOP. However, notes study author Sai Nair, Ph.D., project head and associate research scientist in the John lab, "It's now clear that the mechanisms of IOP elevation are more complicated than simple blockage by the iris, and must include other physiological disturbances."

The research team identified a mouse strain that has anatomical features similar to those seen in patients with ACG, and that develops high IOP. Because this IOP elevation causes the optic nerve to degenerate, these mice represent an important and much needed mouse model for ACG.

Further, studies in the mouse suggest that depending on genetic background, the mutated gene can cause variable reduction in axial length, ranging from modest to severe. In collaboration with Mounira Hmani-Aifa and colleagues at Université de Sfax in Tunisia, they found that mutation in the same gene can result in severe reduction in axial length in people with extreme hyperopia.

In finding a genetic mutation in the mice that produces a previously unknown protein (one that acts as a protease to break down other proteins), the researchers make the first link between the protein's activity and ACG, as well as eye development in infants.

The John research group also included Zain Ali, Alison Kearney, Danilo Macalinao, Ioan Cosma, Gareth Howell and Richard Smith. Funding was provided by the National Eye Institute, the Barbara and Joseph Cohen Foundation and the Tunisian Ministère de l'Enseignement Supérieur, de la Recherche Scientifique et de la Technologie.

This is the third major paper on glaucoma to come out of the John lab since early March. In the *Journal of Clinical Investigation*, the researchers reported on their new analysis technique that detects early stages of glaucoma in mice, and on their success in blocking the disease by targeting some of the molecular events in those early stages. And a paper in *Science* demonstrated their findings that RNA granules—key players in messenger RNA (mRNA) processing—can affect eye development, leading to juvenile cataracts and glaucoma in humans and mice.

More information: Alteration of the serine protease PRSS56 causes angle-closure glaucoma in mice and posterior microphthalamia in humans and mice. *Nature Genetics*, May 1, 2011, dx.doi.org/10.1038/ng.813

Abstract
Angle-closure glaucoma (ACG) is a subset of glaucoma affecting 16 million people1, 2, 3. Although 4 million people are bilaterally blind from ACG4, 5, the causative molecular mechanisms of ACG remain to be defined. High intraocular pressure induces glaucoma in ACG. High intraocular pressure traditionally was suggested to result from the iris blocking or closing the angle of the eye, thereby limiting aqueous humor drainage. Eyes from individuals with ACG often have a modestly decreased axial length, shallow anterior chamber and relatively large lens, features that predispose to angle closure6. Here we show that genetic alteration of a previously unidentified serine protease (PRSS56) alters axial length and causes a mouse phenotype resembling ACG. Mutations affecting this protease also cause a severe decrease of axial length in individuals with posterior microphthalmia. Together, these data suggest that alterations of this serine protease may contribute to a spectrum of human ocular conditions including reduced ocular size and ACG.

Provided by Jackson Laboratory