confirmed the variants with a second method and replicated the results in an independent sample, ensuring that their associations meet typical standards for significance and replication.

The consortium suggests that the proximity of one of the variants to *SIRT1* implicates abnormalities in mitochondria (the cell's energy-producing centres) in MDD, because one role of the SIRT1 protein is to regulate mitochondrial function. If this assertion holds up, it is likely to imply that many other genetic variants are involved in altered mitochondrial function and have associations with MDD that near the threshold for significance. A standard way to evaluate such a hypothesis is to investigate whether a specific genetic pathway, such as that involving the genes that affect mitochondrial function, is statistically more likely to have smaller *P*-values for association with MDD than expected by chance. This analysis was not reported in the current study. A previous systematic pathway analysis of MDD and other major psychiatric disorders did not implicate mitochondrial biology[5]. As such, although the researchers' hypothesis is intriguing, it requires replication, extension, integrated analysis and more biological evidence.

I wish the authors had formally tested their fundamental premise, namely that their sample was more homogeneous than those studied previously. If that is the case, then the heritability of the common variants (the proportion of variance contributing to MDD that can be accounted for by the genetic variation they measured) should be notably high. But although several methods exist to check this[6,7], the authors did not report such an analysis.

More unsettling, the two variants identified have almost no association signal in samples taken from European populations[8]. The reasons for this discrepancy are unclear. Perhaps these variants are truly causative for MDD only in severe cases from China. However, many other common associations for complex illnesses hold across the world. The authors tested the comparability of their findings with European samples and found some evidence of overlap, but more-refined analyses would be of keen interest.

This first identification of replicable, significant genome-wide associations for MDD is exceptional. Although further work is required, it is to be hoped that these results will provide therapeutic targets for MDD. The drug-discovery pipeline for MDD has never been based on solid biological foundations, but the work begun here could improve the focus of the field.

The authors' study marks the beginning of the beginning for the genetic dissection of MDD. The CONVERGE consortium has provided an excellent starting point for what should be an intriguing voyage of discovery. ■ See go.nature.com/lsghoc for a related News story.

**Patrick F. Sullivan** *is in the Departments of Genetics and Psychiatry, University of North Carolina, Chapel Hill, North Carolina 27599-7264, USA, and in the Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden.*
*e-mail: pfsulliv@med.unc.edu*

1. Levinson, D. F. *et al. Biol. Psychiatry* **76,** 510–512 (2014).
2. CONVERGE consortium. *Nature* **523,** 588–591 (2015).
3. Whiteford, H. A. *et al. Lancet* **382,** 1575–1586 (2013).
4. Kendler, K. S. *Arch. Gen. Psychiatry* **54,** 299–304 (1997).
5. The Network and Pathway Analysis Subgroup of the Psychiatric Genomics Consortium. *Nature Neurosci.* **18,** 199–209 (2015).
6. Cross-Disorder Group of the Psychiatric Genomics Consortium. *Nature Genet.* **45,** 984–994 (2013).
7. Bulik-Sullivan, B. K. *et al. Nature Genet.* **47,** 291–295 (2015).
8. Major Depressive Disorder Working Group of the Psychiatric GWAS Consortium. *Mol. Psychiatry* **18,** 497–511 (2013).

**This article was published online on 15 July 2015.**

OPHTHALMOLOGY

# Cataracts dissolved

**Mutations underlying hereditary cataracts in two families impair the function of an enzyme that synthesizes the lens molecule lanosterol. The finding may lead to non-surgical prevention and treatment of cataracts.** SEE LETTER P.607

J. FIELDING HEJTMANCIK

In this issue, Zhao *et al.*[1] (page 607) identify a mutation in the gene encoding the enzyme lanosterol synthase (LSS) as the cause of inherited cataracts in two families. LSS, which is produced in the lens, synthesizes lanosterol, a molecule that is amphipathic (that is, it has both hydrophilic and hydrophobic properties). The authors show that lanosterol can dissolve the precipitates, and even the amyloid-like fibril structures, of mutant lens crystallin proteins that are the cause of cataracts in some individuals. Furthermore, lanosterol effectively treated naturally occurring cataracts in rabbit lenses and in dogs *in vivo*. In addition to elucidating the visual process, this work promises to continue in the tradition of lens research by expanding scientific insight into broad and often seemingly unrelated areas of enquiry.

The eye lens has been intensively studied for almost two centuries. In 1833, optics scientist David Brewster deduced the fine structure of the cod lens, calculating that it contained 5 million fibre cells, each 4.8 millimetres long, using only a candle and a finely ruled steel bar[2]. In 1901, embryologist Hans Spemann's study of lens development resulted in the concept of inductive cellular interactions during embryonic development[3]. Studies of lens biochemistry began in the late nineteenth century with descriptions of the high concentrations of heterogeneous structural proteins now known as crystallins[4]. Subsequently, one of the first genetic locations on a non-sex chromosome to be associated with disease was linked to cataract susceptibility[5], and messenger RNA molecules encoding chicken lens δ-crystallins were among the first mRNAs to be isolated, cloned and studied[6].

The function of the eye lens is to transmit light and focus it on the retina. The lens accomplishes this through a single cell type that follows a developmental pattern, beginning as a member of the germinative zone in the single layer of anterior epithelial cells overlaying a mass of fibre cells. The epithelial cells then migrate laterally towards the lens equator, where they elongate and invert to form secondary fibre cells, arranged in a curved, onion-like configuration. As they do this, the cells synthesize large amounts of crystallins, such that they contain perhaps the highest concentration of proteins found in any tissue. They also degrade organelles, minimize extracellular space and increase the density of their cell membranes to levels approaching that of the cell's cytoplasm, all of which decrease light scattering[7]. Thus, transparency is accomplished largely through a combination of the microarchitecture of the lens and, on a molecular level, the densely packed lens crystallins (Fig. 1).

Human crystallins are divided into two families, α- and βγ-crystallins; together, these make up 90% of the water-soluble proteins in lens cells[8]. They are extremely stable, highly ordered and provide a relatively constant refractive index, which allows lens transparency[9]. Because differentiated lens fibre cells lack the synthetic apparatus to produce new proteins, crystallins are not turned over, and those in the centre of the lens are among the oldest proteins in the body. Preserving crystallin structure and function is therefore crucial for prevention of lens opacities. Other biological activities of the lens serve primarily to protect the complementary systems of crystallin packing and fibre-cell arrangement from disruption and damage by age and external insults, especially ultraviolet light, oxidative stress and glycation.

The genes that cause cataracts when mutated

PAUL FITZGERALD/REF. 16

tend to encode proteins that are involved in one of these biological pathways or functional groupings of proteins that are critical for lens homeostasis. In families at risk of congenital cataracts for which the mutant gene is known, slightly less than half have mutations in lens crystallins, with others having mutations in growth or transcription factors, membrane proteins, chaperone proteins and proteins involved in protein degradation, among others[10]. Zhao and colleagues' identification of LSS mutations as a cause of congenital cataracts adds a new pathway.

The catastrophic structural changes in crystallins seen in many hereditary cataracts can overwhelm the defensive systems of the lens, and might also be refractory to the solubilizing activity of lanosterol identified by the authors. Nevertheless, this agent might be more therapeutically applicable to the slow progressive denaturation of crystallins seen in age-related cataracts. In age-related cataracts, damaged βγ-crystallin proteins are bound by α-crystallins, which act like chaperones — proteins that assist the folding or unfolding of other proteins — except that, instead of refolding the denatured βγ-crystallins, α-crystallins solubilize them[11], thereby reducing light scattering. However, as more crystallins are damaged and bound over time, the protein complexes themselves become large enough to scatter light[11,12]. Eventually, the complexes precipitate, forming the insoluble protein fraction (termed high molecular weight aggregates) that increases with normal ageing and especially in cataractous lenses. This identifies cataracts, in at least some cases, as a protein-misfolding disease[13].

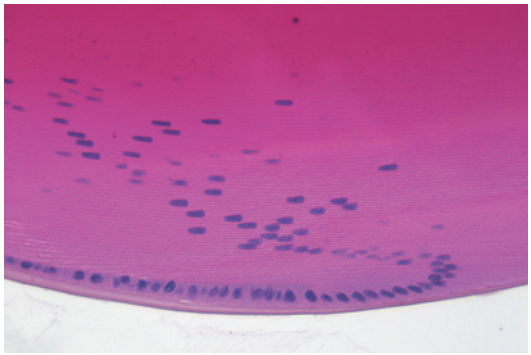

**Figure 1 | The eye lens.** This cross-section of a mouse eye lens shows the curved, onion-like configuration of fibre cells, which are packed close together and lose subcellular structures such as nuclei (coloured blue) as they mature and move to the centre of the lens. Fibre cells contain highly ordered crystallin proteins, the intracellular concentration of which increases towards the interior of the lens (seen as darkening pink). This combined cellular and intracellular structure gives transparency to the lens. Denaturation and aggregation of crystallin proteins can result in the lens opacity known as a cataract. Zhao *et al.*[1] show that the molecule lanosterol can redissolve crystallin aggregates and alleviate cataracts.

Although surgery to remove cataracts is efficacious and safe, ageing populations around the world are predicted to require a doubling of cataract surgery in the next 20 years[14]. The same population demographics suggest that, if development of age-related cataracts in susceptible individuals could be delayed by even ten years, the need for surgery could be reduced by almost half[15]. Pre-symptomatic screening of age-related cataracts is easy, and the eye is easily accessible for topical application of drugs. Zhao and colleagues show that eye drops containing lanosterol successfully treated natural cataracts in dogs. The potential for this finding to be translated into the first practical pharmacological prevention, or even treatment, of human cataracts could not come at a more opportune time. Furthermore, this approach might serve as a model for other protein-misfolding diseases affecting a variety of tissues and organ systems. ■

**J. Fielding Hejtmancik** *is in the Ophthalmic Molecular Genetics Section, Ophthalmic Genetics and Visual Function Branch, National Eye Institute, Rockville, Maryland 20892-9402, USA.*
*e-mail: hejtmancikj@nei.nih.gov*

1. Zhao, L. *et al. Nature* **523,** 607–611 (2015).
2. Brewster, D. *Phil. Trans. R. Soc. Lond.* **123,** 323–332 (1833).
3. Spemann, H. *Vehr. Anat. Ges.* **15,** 61–79 (1901).
4. Zhang, T. *et al. Hum. Mutat.* **30,** E603–E611 (2009).
5. Renwick, J. H. & Lawler, S. D. *Ann. Hum. Genet.* **27,** 67–84 (1963).
6. Zelenka, P. S. & Piatigorsky, J. *Proc. Natl Acad. Sci. USA* **71,** 1896–1900 (1974).
7. Michael, R., van Marle, J., Vrensen, G. F. & van den Berg, T. J. *Exp. Eye Res.* **77,** 93–99 (2003).
8 Bloemendal, H. *et al. Prog. Biophys. Mol. Biol.* **86,** 407–485 (2004).
9. Benedek, G. B. *Appl. Optics* **10,** 459–473 (1971).
10 Shiels, A. & Hejtmancik, J. F. *Clin. Genet.* **84,** 120–127 (2013).
11. Rao, P. V., Huang, Q.-L., Horwitz, J. & Zigler, J. S. Jr *Biochim. Biophys. Acta* **1245,** 439–447 (1995).
12. Datiles, M. B. III *et al. Arch. Ophthalmol.* **126,** 1687–1693 (2008).
13. Moreau, K. L. & King, J. A. *Trends Mol. Med.* **18,** 273–282 (2012).
14. Taylor, H. R. *Br. J. Ophthalmol.* **84,** 1–2 (2000).
15. Kupfer, C. *Invest. Ophthalmol. Vis. Sci.* **28,** 2–8 (1987).
16. Sun, N., Shibata, B., Hess, J. F. & FitzGerald, P. G. *Mol. Vis.* **21,** 428–442 (2015).

**This article was published online on 22 July 2015.**

STRONG-FIELD PHYSICS

# Harmonic radiation from crystals

**Electrons in a crystal can tunnel between energy bands when a strong electric field is switched on. It emerges that electron pathways interfere almost instantaneously, giving rise to ultra-short, pulsed emission of light.** SEE LETTER P.572

PETER HOMMELHOFF & TAKUYA HIGUCHI

The puzzling but experimentally verified fact that particles can propagate through walls is a hallmark of quantum mechanics. In crystalline solids, the motion of electrons is restricted by the presence of the atomic lattice, which limits their energy to certain ranges known as energy bands. Because an electron's energy cannot exceed these limits, gaps are formed between bands. In the heyday of quantum theory, the physicist Clarence Zener showed[1] that the electrons in a solid that is subjected to a strong electric field can tunnel between energy bands, traversing the classically imposed barrier. On page 572 of this issue, Hohenleutner *et al.*[2] report an experimental and theoretical study showing that, when a strong electric field oscillating at terahertz frequencies (1 THz is $10^{12}$ Hz) is applied to a crystal, various bands can be coupled together by electron tunnelling, and the crystal emits ultra-short bursts of high-harmonic radiation.

The frequency of this oscillating driving field, which corresponds to mid-infrared wavelengths, is much lower than any of the frequencies required for straightforward electron jumps between different energy bands. Because of its large strength, however (greater than 1 volt per nanometre), the field drives electrons to tunnel from one band to another[3,4] on femtosecond timescales (1 fs is $10^{-15}$ seconds), that is, almost instantaneously with the switching-on of the field. The electrons' dynamics are complex and include not only tunnelling to different energy bands, but also acceleration within each band; these processes result in the radiation of electromagnetic waves at a much higher frequency than that of the driving terahertz-frequency field. The emitted radiation is called high-harmonic radiation because its spectrum usually displays peaks at harmonics (integer multiples) of the driving field's frequency, reflecting the field's temporal periodicity.

The observed high-harmonic radiation consists of pulses of ultra-broadband visible