Research Highlight

Hexokinase 1 and Retinitis Pigmentosa: Insights Into the Retina and the Molecule

J. Fielding Hejtmancik

Ophthalmic Molecular Genetics Section, Ophthalmic Genetics and Visual Function Branch, National Eye Institute, National Institutes of Health, Bethesda, Maryland, United States; f3h@helix.nih.gov

Retinitis pigmentosa (RP) represents a group of inherited retinal dystrophies characterized by night blindness followed by progressive narrowing of the visual fields, often culminating in vision loss. Retinitis pigmentosa is genetically heterogeneous; currently mutations in at least 63 genes have been implicated.[1] Identification of these genes and mutations causing RP has provided unique insights not only into the pathophysiology of retinal degenerations, but also into the basic biology of the retina and the visual pathways within it.

Sullivan et al.[2] identified a Glu847Lys hexokinase 1 (HK1) mutation in five families with autosomal recessive retinitis pigmentosa (adRP), all of which shared a common extended haplotype, suggesting common ancestry. The severity of RP in affected family members was highly variable, with one individual homozygous for the mutation having severe retinal disease, although no extraocular abnormalities were identified in any individual affected with RP. The Glu847Lys mutation is on the surface of the HK1 molecule, far from any identified functional site, and is not predicted to impair either enzymatic activity or protein stability.

Absence of the nonspherocytic hemolytic anemia seen in autosomal recessive HK1 deficiency in affected individuals is consistent with preservation of kinase activity and normal glucose metabolism in the Glu847Lys mutant HK1, and the absence of extraretinal abnormalities suggests gain of a deleterious property specific to the retina. There is precedent for this, as mutations in HK1 have also been associated with Russe hereditary motor and sensory neuropathy,[3] and HK1 is known to interact with a number of proteins active in regulating apoptosis, including VDAC1, DREAM, RANBP2, and COX11. While requiring functional confirmation, in addition to expanding our understanding of the genetic architecture of RP, this report suggests that although heavily studied for decades, HK1 has a previously unknown molecular function perhaps active in a novel metabolic or regulatory pathway critical to retinal homeostasis and function.

References

1. RetNet. Retinal Information Network. Available at: https://sph.uth.edu/Retnet/. Accessed September 5, 2014.
2. Sullivan LS, Koboldt DC, Bowne SJ, et al. A dominant mutation in hexokinase 1 (*HK1*) causes retinitis pigmentosa. *Invest Ophthalmol Vis Sci*. 2014;55:7147–7158.
3. Hantke J, Chandler D, King R, et al. A mutation in an alternative untranslated exon of hexokinase 1 associated with hereditary motor and sensory neuropathy – Russe (HMSNR). *Eur J Hum Genet*. 2009;17:1606–1614.

DOI: 10.1167/iovs.14-15621

www.iovs.org | ISSN: 1552-5783

Investigative Ophthalmology & Visual Science