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A second gene for color blindness

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Abstract

Analysis of families suffering from total color blindness has revealed one potential cause of the condition - mutations in a gene encoding a α subunit of the retinal cone cGMP-gated ion channel.

Significance and context

Total color blindness, or achromatopsia, is a rare inherited disorder whose victims are completely unable to differentiate between different colors. This disorder also results in low visual acuity, especially within the central region of the visual field. The general public has became familiar with the disorder through television documentaries and *Island of the Colorblind*, a book by Oliver Sacks, describing a Pacific Island population in which the incidence of achromatopsia is much higher than in the general world population. A subset of achromats have mutations in the gene *CNGA3* on chromosome 2q11, which encodes the α subunit of a cGMP-gated ion channel in retinal cone cells - the photoreceptors for color vision. The cGMP-gated channels are major components of the signaling cascades in the visual systems of most species. A second locus associated with the disease has also been identified - *ACHM3* on chromosome 8q21. Kohl *et al*. have now studied achromat families who do not contain mutations in *CNGA3* in order to identify mutations at the *ACHM3* locus that could be responsible for the disorder.

Key results

The authors defined the group of achromat families for study by excluding all families that carried mutations in the *CNGA3* gene. This left 11 achromat families, on which a linkage analysis was performed. Through this analysis, Kohl *et al*. localized the *ACHM3* locus to a 3.7 centiMorgan (cM) region bounded by the markers D8S1838 and D8S273. They constructed a physical map of the *ACHM3* region by collecting yeast artificial chromosome (YAC) clones mapping to chromosome 8q21. Analysis of the sequences identified from these YACs gave a database match with two overlapping high-throughput genomic sequencing phase (HTGS) entries. These contained sequences highly homologous to the murine *cng6* gene, which encodes a putative α subunit for the retinal cone cGMP-gated channel. The authors then cloned the human homolog of *cng6* (*CNGB3*) using reverse transcriptase-couple PCR (RT-PCR) and rapid amplification of cDNA ends (RACE) on human retinal RNA.

CNGB3 gene structure across the 11 achromat families was analyzed by direct sequencing of PCR products obtained from amplification of exon sequences with primers located in flanking intron or untranslated region (UTR) sequences. Six different mutations were found in this gene. These included a missense mutation, two frameshift deletions and a putative splice-site mutation. None of the mutations was found in the 100 non-achromat controls. Most of the mutations would result in severely truncated proteins that lacked essential elements of functional ion channels, such as a pore region and a ligand-binding domain. Kohl *et al*. speculate that these mutations probably completely abolished protein function. But one mutation, S435F, is a change of amino-acid identity in a transmembrane region of the protein at a position that is usually conserved between the human and mouse proteins. This mutation was found in the one patient from the Pacific Island population described by Sacks, and Kohl *et al*. suggest that this population of achromats in particular must all contain mutations in *CNGB3*.

Conclusions

The authors conclude that along with a previously described mutation in the *CNGA3* gene, mutations in *CNGB3*, which is located at the *ACHM3* locus, also cause achromatopsia.

Reporter's comments

The authors used standard techniques in positional genomics to isolate a genetic factor in the development of achromatopsia. The fact that the gene implicated encodes a α subunit of the cGMP-gated channel has exciting implications for future functional studies of this protein. The cGMP-gated family of ion channels have received intense biophysical scrutiny over the past decade, and a great deal of information is available on the relationship between secondary structure and functional properties. Electrophysiological investigation of the *CNGB3* mutants will thus add to our knowledge of the molecular components of the signaling cascades of visual systems by providing a link between the amino-acid structure of an ion channel and its subsequent role in a sensory system.

Table of links

Human Molecular Genetics

References

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