Cone Mosaic Disruption Caused by L/M Opsin Mutations in Bornholm Eye Disease

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Summary

Bornholm eye disease (BED) is characterized by dichromacy and cone dysfunction and was mapped to Xp11 in 1990 by Schwimmer et al. Subsequent studies have not identified mutations within the L/M gene array believed to account for both the color vision defect and cone dysfunction. We have previously found that a specific lozenge mutant of human cone photoreceptor, leading to dichromacy. This provides a potential mechanism whereby the color vision defect and the cone dysfunction can have a common origin. Recently similar variants (LIAVA or LVAVA) were found in X-linked cone dysfunction and high myopia may depend on the relative number of cones expressing the aberrant pigment. Michaelides et al. (2006) noted that in BED, “other genetic factors... within which the primary disease causing mutation is expressed may determine the final phenotype.” Our anatomical data indicate that these “other factors” could include genes or sequences that affect L:M cone ratio, which is known to be highly variable.

L/M Opsin Variation: A Source of Cone Dysfunction in Bornholm Eye Disease?

The L and M genes are known to be highly variable. Shown below on the left is a frequency histogram of the different L/M opsins observed in 120 males with normal color vision. The widespread genetic diversity can arise from point mutations, which can be experimentally induced in vitro and associated with altered visual function in animal models. In most patients, the fundus images were consistent with a myopic phenotype. Volumetric SD-OCT images (Cirrus; Carl Zeiss Meditec) showed significant retinal thinning across the 6x6 mm macula scan, shown in the ETDRS thickness plots below. High-resolution scans through the fovea (Biograph or Cirrus) revealed all SD-OCT scans are 2.7 mm in length.

Fundus Imaging and SD-OCT Imaging of the Retina

In most patients, the fundus images were consistent with a myopic phenotype. Volumetric SD-OCT images (Cirrus; Carl Zeiss Meditec) showed significant retinal thinning across the 6x6 mm macula scan, shown in the ETDRS thickness plots below. High-resolution scans through the fovea (Biograph or Cirrus) revealed all SD-OCT scans are 2.7 mm in length.

Patient Characteristics

We examined 7 males, whose clinical phenotype had been previously reported. All had a protanopic color vision defect. No obvious retinal abnormalities were observed from a direct fundus exam in any of the patients, except for typical myopic features (tilted disc and blonde fundus). In most patients, the fundus images were consistent with a myopic phenotype. Volumetric SD-OCT images (Cirrus; Carl Zeiss Meditec) showed significant retinal thinning across the 6x6 mm macula scan, shown in the ETDRS thickness plots below. High-resolution scans through the fovea (Biograph or Cirrus) revealed all SD-OCT scans are 2.7 mm in length.

Patient ID  Age  Axial length  Refractive error  L/M Gene Array  Initial Case Presentation

JC-0195  24  27.32 OD  -9.0 D  L-M-M (L gene→LIAVA)  Patient B1; ref. 10

JC-0196  28  22.88 OD  +0.9 D  L-M-M (L gene→LIAVA)  Patient B2; ref. 10

JC-0432  23  27.08 OD  -18.0 D  L-M-M (L gene→LIAVA)  Patient A2; ref. 10

JC-0433  16  25.90 OD  -6.3 D  L-M-M (L gene→C203R)  Patient A1; ref. 10

JC-0447  13  27.15 OD  -7.7 D  M-M-M (1st gene→LIAVA)  Subject 35; ref. 11

JC-0448  11  26.50 OD  -5.5 D  M-M-M (1st gene→C203R)  Subject 36; ref. 11

Patient Variation

We used adaptive optics retinal imaging tools (fundus camera and a scanning laser ophthalmoscope) to image the cone photoreceptor mosaic in the 7 patients. This imaging data provides a direct link between disruption of the cone mosaic (reported by the LIAVA variant) and the cone dysfunction and color vision defect observed in BED.

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