**Evolutionary origin of high frequency deleterious mutations in the human cone opsins and their role in the most common eye disorders**

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More than 99.9% of species that have existed in the 3 billion years of life on earth have become extinct. Organisms and organs, seemingly magnificently suited for their purpose, are not so as a result of careful planning, but rather as the consequence of serendipitous genetic changes that may be adaptive in the short-term, but in the face of a continuously changing environment, will ultimately prove to be evolutionary wrong moves with the predictable endgame being extinction. We tested the idea that human X-chromosome opsin genes bear the unmistakable hallmark of evolution—chance genetic changes that initially proved adaptive but have since been countered by environmental changes, in this case, relaxation of selection against color vision defects, that have placed the L and M cone opsins on an irretrievable path to self-destruction. We sequenced 76 OPN1LW genes and 102 OPN1MW genes from Caucasian males, all of whom had normal color vision as demonstrated by performance on color vision tests. The genes encoded nineteen different amino acid sequence variants of L opsin and nine variants of M opsin. The nearly perfect association between vision loss and non-synonymous amino acid changes in the other two human visual pigments, rhodopsin and the S cone opsin, predicts by analogy that most of the amino acid sequence variation in L and M cone opsins will cause vision disorders. We tested for an association between OPN1LW haplotypes and AMD and found a clear association. We also found OPN1LW, and alleles to be a major genetic factor underlying simple myopia. We conclude that common sequence variants of L opsin are associated with two of the most prevalent human vision disorders, age-related macular degeneration (AMD) and myopia and conclude that degenerative mutations of the opsin genes contribute to most common eye disorders that plague modern humans.

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