Supplementary Material

Phenotype Summary for Individuals Harboring L/M Interchange Mutants  All four subjects with L/M interchange mutants were examined at the time of advanced retinal imaging. Given the unique nature of their phenotype, we provide here a summary of clinical findings as well as self-reported observations.

JC_0347 (LVAVA, examined by author T.B.C.) The subject is a 32-year-old white male who presented with progressive vision loss beginning in grade school. His current examination demonstrated best-corrected visual acuity of 20/125 OU and subtle retinal pigment epithelial stippling at the macula. Extraocular movements were full with no nystagmus. Past medical history was unremarkable. He has 2 brothers with normal visual acuity with their myopic correction, one having a red-green color vision deficiency and the other having normal color vision.

The subject recalls a gradual decline in visual acuity, stabilizing in the last few years. He complains of difficulty with reading, distance vision, adjusting from a bright to dark environment, and greater difficulty with daytime vision and denies nyctalopia. He can no longer drive (though he had a driver’s license until the age of 28). In 2004 the subject had a recorded best-corrected visual acuity of 20/100 OD and 20/70 OS, with symmetrical macular retinal pigment epithelial granularity OU. An electroretinogram in 1996 demonstrated normal rod responses with moderately reduced cone responses. The subject’s symptoms, history, and clinical findings are consistent with a cone dystrophy.

JC_0564 (LVAVA, examined by author G.A.F.) The subject is a 45-year-old Hispanic male, with best-corrected visual acuity of 20/100 OU. Anterior segment exam was unremarkable, and fundus exam showed a blunted foveal reflex and subtle RPE mottling in both eyes. Anomaloscopic color matching (Oculus HMC, Wetzlar, Germany) was consistent
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with protanopia. Goldmann visual field testing showed central scotomas OU. Full-field ERG showed normal rod responses and reduced cone responses (approximately 60-70% below the lower limit of normal). The diagnosis was cone dystrophy with protanopia.

JC_0118 (LIAVS, examined by author E.B.) This subject was previously reported as subject MOL0250 III:2 in the paper by Mizrahi-Meissonnier et al. (2010). The subject is a 32-year-old male who first noted mild visual impairment at age 5-6, when he experienced reading problems. Glasses were fitted with some improvement, and he attended regular elementary and high schools. He does not recall significant difficulty until age 13, as he could sit anywhere in the classroom (and not necessarily in the front of the class) and participated in sports activities, including basketball at the school team level. At age 13 he felt the need for improved contrast, and switched to writing with a rather thick black pen. Despite this increasing difficulty, there are records that he had distance logMAR visual acuity at the 0.5-0.63 level until the age of 16-17, and even received a driver's license at age 16 and a half (this requires a minimum of 0.5 acuity). The main deterioration in central vision occurred between the ages of 17-20, and particularly during his military service. During this time acuity dropped to 0.2-0.3 in both eyes. An ERG at the age of 19 demonstrated cone dysfunction for the first time, with a normal fundus exam. The subject feels that since this significant and rapid deterioration, which occurred in his late teens, the disease has continued to progress but at a slower pace. He notes increasing color vision disturbances, and is particularly bothered by glare and photophobia. This was not apparent early on, and there was no photophobia or nystagmus during childhood. There are no complaints related to peripheral visual fields, his mobility remains good, and he feels his night vision is quite stable. Interestingly, however, repeat ERG recordings done over the span of 8 years, between the ages of 24-32, show progressive deterioration of cone and rod ERG responses and maculopathy has also became clinically evident.
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KS_0577 (LVVVA, examined by author K.E.S.) The subject is a 38-year-old African American male, who presented with a 10-year history of gradual progressive bilateral central vision loss. Additionally he had noted color vision loss since childhood. Despite evaluation by several different eye doctors with substantial work-up, no diagnosis had been made. He stated that he was still able to read, but needed to hold things very close to his eyes in order to focus. He denied any nyctalopia, severe photophobia, nystagmus or floaters. No previous family history of vision problems was reported.

Past ocular history was unremarkable. On clinical exam, Snellen visual acuity without correction was 20/70 right eye and 20/100 left eye. Dilated fundus exam revealed a central linear horizontal area of macular atrophy in both eyes. ERG showed a mildly depressed photopic response and normal scotopic response.

He states that his vision was good throughout his teenage years, declaring vision "was not an issue" at that time. He was able to see the chalkboard and read textbooks. He played sports without issues. He passed all vision screening tests and did not have any special accommodation due to vision while in school, though he remembers issues with color since elementary school. He first noted vision declining in his early 20s when he started to notice central scotomas. He recalls doing visual field testing and not being able to see the central fixation target.