CRIM1 haploinsufficiency causes defects in eye development in human and mouse.

Colobomatous macrophthalmia with microcornea syndrome (MACOM, Online Mendelian Inheritance in Man (OMIM) 602499) is an autosomal dominantly inherited malformation of the eye, which is characterized by microcornea with increased axial length, coloboma of the iris and of the optic disc, and severe myopia. We performed whole-exome sequencing (WES) in two affected individuals from the 2p23-p16-linked MACOM family, which includes 13 affected individuals in 3 generations. As no shared novel variation was found on the linked haplotype, we performed copy number variation (CNV) analysis by comparing the coverage of all exons in the WES data sets of the 2 patients with the coverage of 26 control exomes. We identified a heterozygous deletion predicted to span 22 kb including exons 14-17 of CRIM1 (cysteine-rich transmembrane bone morphogenetic protein (BMP) regulator 1). Quantitative PCR (qPCR) analysis confirmed the deletion, which was present in 11 affected individuals. Split-read analysis of WES data followed by breakpoint PCR and Sanger sequencing determined both breakpoints flanked by a 4-bp microhomology (CTTG). In the mouse, Crim1 is a growth-factor-binding protein with pleiotropic roles in the development of multiple organs, including the eye. To investigate the
role of Crim1 during eye development in mice, we crossed a Crim1(flox) mouse line with the Ap2?-cre mouse line, which expresses Cre in the head surface ectoderm. Strikingly, we observed alterations of eye development in homozygous mice leading to severe anatomical and morphological changes overlapping with the anomalies observed in MACOM patients. Taken together, these findings identify CRIM1 as the causative gene for MACOM syndrome and emphasize the importance of CRIM1 in eye development.