GUCA1A encodes guanylate cyclase-activating protein 1A (GCAP1), which is a calcium-binding protein located within the inner segments of the photoreceptors. It regulates guanylyl cyclase 1 by sensing calcium concentrations, which is important for the recovery of rod photoreceptors after light exposure and for the overall phototransduction cascade. Mutations in *GUCA1A* cause autosomal dominant cone and cone-rod dystrophy [1–4].

Onset of visual symptoms for *GUCA1A*-related autosomal dominant cone dystrophy generally occurs after the first two decades of life, between the 20s and 50s. Initial symptoms include reduced visual acuity, loss of color vision, and mild photophobia. Nystagmus is uncommon. Visual acuity usually deteriorates to between 20/200 and count fingers. A range of macular phenotypes may be observed; changes at the level of the retinal pigment epithelium (RPE) at the macula may be observed prior to vision loss. Funduscopic changes are minimal at an early age but may consist of subtle granularity of the RPE. Older patients may exhibit macular atrophy, bone-spicule like pigmentation, and retinal vascular attenuation. Goldmann Visual Fields (GVF) reveal full peripheral fields with central scotomas. Full-field electroretinography (ERG) exhibits significant loss of cone function over time, usually in the context of normal rod parameters [1–7]. Some patients may exhibit rod abnormalities later in life. Intra-familial variability has been shown in some studies, with members of some families exhibiting symptoms of cone-rod dystrophy while others exhibit isolated macular dysfunction [3, 4].

Patients with cone-rod dystrophy experience similar symptoms to cone dystrophy patients but are more likely to experience nyctalopia and peripheral vision loss earlier in the disease process. In one study, symptoms (photophobia, poor acuity) were seen within the first decade in a Chinese family. Full-field ERG in these patients revealed a cone-rod pattern of degeneration. Fundus examination may reveal optic disc pallor, attenuated retinal arterioles, macular atrophy, or pigmentary changes in the macula [7, 8].

References

1. Payne AM, Downes SM, Bessant DA, Taylor R, Holder GE, Warren MJ, et al. A mutation in guanylate cyclase activator 1A (GUCA1A) in an autosomal dominant cone dystrophy pedigree mapping to a new locus on chromosome 6p21.1. Hum Mol Genet. 1998;7(2):273–7.
2. Michaelides M, Hardcastle AJ, Hunt DM, Moore AT. Progressive cone and cone-rod dystrophies: phenotypes and underlying molecular genetic basis. Surv Ophthalmol. 2006;51(3):232–58.
3. Downes SM, Holder GE, Fitzke FW, Payne AM, Warren MJ, Bhattacharya SS, et al. Autosomal dominant cone and cone-rod dystrophy with mutations in the guanylate cyclase activator 1A gene-encoding guanylate cyclase activating protein-1. Arch Ophthalmol. 2001;119(1):96–105.
4. Michaelides M, Wilkie SE, Jenkins S, Holder GE, Hunt DM, Moore AT, et al. Mutation in the gene GUCA1A, encoding guanylate cyclase-activating protein 1, causes cone, cone-rod, and macular dystrophy. Ophthalmology. 2005;112(8):1442–7.
5. Sokal I, Dupps WJ, Grassi MA, Brown J Jr, Affatigato LM, Roychowdhury N, et al. A novel GCAP1 missense mutation (L151F) in a large family with autosomal dominant cone-rod dystrophy (adCORD). Invest Ophthalmol Vis Sci. 2005;46(4):1124–32.
6. Jiang L, Katz BJ, Yang Z, Zhao Y, Faulkner N, Hu J, et al. Autosomal dominant cone dystrophy caused by a novel mutation in the GCAP1 gene (GUCA1A). Mol Vis. 2005;11:143–51.
7. Huang L, Li S, Xiao X, Jia X, Sun W, Gao Y, et al. Novel GUCA1A mutation identified in a Chinese family with cone-rod dystrophy. Neurosci Lett. 2013;541:179–83.
8. Kitiratschky VB, Behnen P, Kellner U, Heckenlively JR, Zrenner E, Jägle H, et al. Mutations in the GUCA1A gene involved in hereditary cone dystrophies impair calcium-mediated regulation of guanylate cyclase. Hum Mutat. 2009;30(8):E782–96.

S. Zahid et al., *Retinal Dystrophy Gene Atlas*, https://doi.org/10.1007/978-3-319-10867-4_35