

Functional characterization of canine CNGA3 and cone degeneration-associated mutation in CNGB3

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Abstract

Cyclic nucleotide-gated (CNG) ion channels have an essential role in the transduction of visual stimulus among vertebrate species. In cone photoreceptors, each channel is comprised of CNGA3 and CNGB3 subunits in a two plus two configuration around the central pore. Mutations in the genes encoding these subunits can cause serious visual disorders such as cone dystrophy/cone degeneration (CD), macular degeneration and achromatopsia. Recently, a mutation in the canine CNGB3 subunit, an aspartic acid to asparagine change (D262N), has been linked to CD in German Short Haired Pointers. We have isolated a cDNA clone for canine CNGA3 and initiated an electrophysiological characterization of these specialized proteins. Here we show that canine CNGA3 subunits can form functional homomeric channels when expressed alone, and functional heteromeric channels when co-expressed with CNGB3 subunits. Expression of heteromeric channels containing the CD-associated mutation in CNGB3 gave rise to heteromeric channels that exhibited significant decreases in apparent agonist affinity for cGMP and cAMP, relative agonist efficacy, and current density. The mutation also resulted in a reduction of cell surface expression of green fluorescent protein tagged subunits and a reduction in relative CNGB3 protein amounts. These results are consistent with the idea that CNGB3 subunits are necessary for cone photoreceptor function and viability.