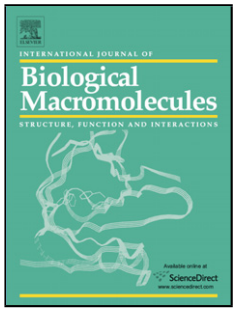

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Increasing susceptibility to oxidative stress by cataract-causing crystallin mutations

Running Title: Susceptibility to oxidative stress of crystallin mutants

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Abstract

Cataract, a crystallin protein aggregation disease, is the leading cause of human blindness worldwide. Congenital cataract may be induced by many factors and genetic disorders accounts for about half of the cases. Inherited mutations can promote cataract formation by affecting crystallin structure, solubility, stability, protein interactions and aggregatory propensity. In this research, we investigated the potential role of oxidative damage in congenital cataracts caused by six mutations in γC- and γD-crystallins, the predominant structural proteins in the lens. H_2O_2 treatment induced structural changes for both the wild type and mutated proteins. Oxidization by H_2O_2 or UV light facilitated protein oligomerization and thermal aggregation. H_2O_2 treatment promoted thermal aggregation of all proteins. By increasing the susceptibility, cataract-causing mutations amplified the deleterious effects of oxidative damage. Our results suggested that oxidative damage might play an important role in the onset and/or progression of congenital cataract caused by both Cys and non-Cys substitutions.