First genetically characterized mouse model for age-related cataracts is a mutation in the βA2-crystallin encoding gene

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Age-related cataracts are the major cause of blindness worldwide and have been associated with falls and increased mortality, possibly because of associated systemic conditions. Major risk factors for cataracts are diabetes and UV light. However, the suggested contribution of genetics to the etiology of age-related cataracts is largely unknown.

In a large-scale high-throughput ENU mutagenesis screen we analyzed the offspring of paternally treated C57BL/6J mice for malformation of the eye by non-invasive *in-vivo* techniques including slit-lamp biomicroscopy, funduscopy and eye size measurement by laser interference biometry. In total, we screened 1700 F_1 mice; the most efficient screen was the laser interference biometry at the age of 11 weeks. This test detected 77 variations; 13 mutants could be confirmed so far. One of them was characterized by a clear, but significantly smaller lens without any changes for cornea thickness, anterior chamber depth or aqueous humour size. At the age of 11 weeks, the mean lens axis length is 2.1 mm (± 0.01 mm) for wild type mice and 1.9 mm (± 0.03 mm) for heterozygotes. The smaller size of the clear lens was more pronounced in the homozygous mutants (1.7 mm ± 0.03 mm), which were fully fertile and viable. The mutation was mapped to chromosome 1 between the markers *D1Mit251* and *D1Mit253*. Using a positional candidate approach, the βA2-crystallin encoding gene *Cryba2* was sequenced; a T→C exchange at cDNA position 139 leads to an S47P amino acid exchange.

Histologically, the eye of newborn homozygous mutants showed small vacuoles at the anterior pole of the lens. At the age of three weeks, some clefts appeared at the anterior cortical region; the other main tissues of the eye, cornea and retina, appeared without major changes. Later, at the age of 25 weeks, the lenses of the heterozygous mutants develop a subcapsular cortical cataract, but the lenses of homozygous mutants are completely opaque.

These findings demonstrate the first mutation in the *Cryba2* gene in any organism so far. The *Cryba2* gene is very closed to the γ-crystallin gene cluster; mutations in the γ-crystallin genes have been shown to cause congenital dominant cataracts in mouse and man. Surprisingly, no congenital cataract mutation could be attributed up to now to this gene. If the data on our new *Cryba2* allele in the mouse are extrapolated to the situation in human cataract patients, *CRYBA2* should be considered as a strong candidate gene for human age-related cataracts, and the slightly smaller size of the lens might be understood as an early biomarker for age-related cataracts. Moreover,

data from the Allen Brain Atlas (http://mouse.brain-map.org) demonstrate that *Cryba2* is expressed also in the hippocampus. Therefore, mutations in the human *CRYBA2* gene are expected also to modify the function of the hippocampus (mainly long-term memory and spatial navigation), and ophthalmologists have to consider additional neurological deficits in these patients.

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