Pulverulent cataract with variably associated microcornea and iris coloboma in a MAF mutation family

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Aims: To report the detailed clinical findings in a three generation pedigree with autosomal dominant cataract, microcornea, and coloboma resulting from mutation of the lens development gene, MAF.

Methods: Five members of a three generation pedigree with progressive cataracts underwent detailed ophthalmic examination to characterise associated ocular phenotypic features.

Results: The cataracts present in all affected individuals were cortical, and/or nuclear, pulverulent opacities. Corneal diameters of 10–10.25 mm were present in two family members. Axial lengths were in the normal range. Bilateral iris coloboma in the 6 o’clock position was present in one patient. Uveal melanoma was present in one patient, with uveal naevi in this and one other patient.

Conclusion: The bZIP transcription factor MAF is a key lens development gene that regulates the expression of the crystallins. Individuals with a mutation in MAF may have pulverulent cataract alone or cataract in association with microcornea or iris coloboma.

Congenital, infantile cataract has an estimated incidence of three per 10 000 births. A large proportion is inherited and a number of underlying genes have been identified. Causative mutations, in particular in lens membrane and crystallin genes, have been characterised in congenital often non-progressive cataract requiring early surgical management. Age related cataract also has a significant heritable contribution and twin studies indicate that ~50% of the contribution is genetic. Such genetic factors remain undefined but variants in genes causing rare monogenic forms of congenital cataract represent attractive candidates. Mutations found in later onset cataracts, such as defects of β B2 and γ D crystallins suggest that these molecules in particular are worthy of study.

Microcornea, a small cornea in a normal sized eye, is defined by a horizontal corneal diameter below 11.00 mm. Cataract and microcornea are described in rare autosomal dominant pedigrees. Recognition of microcornea may be important as a potential contributor to the development of aphakic glaucoma. Other ocular associations include Peters’ anomaly, sclerocornea, aniridia, and ectopia pupillae. Two BLY6 mutations have been identified in patients with microcornea and cataract in association with anterior segment abnormality. A mutation in the crystallin gene, CRYA4, has been identified in a family with cataract, microcornea, and microphthalmia. However, the underlying genetic aetiology in individuals and families with microcornea and cataract without anterior segment anomalies or microphthalmia, remains unknown.

We describe detailed phenotypic features in a family with cataract and microcornea without microphthalmia, resulting from mutation in the bZIP transcription factor MAF. Symp-
melanoma, and has a uveal naevus on the left. II-5 is in remission from Hodgkin’s disease and she has three uveal naevi on the left.

**DISCUSSION**

In this three generation family five members have autosomal dominant progressive cataract. All have a mutation in the DNA binding domain of the bZIP transcription factor, MAF. In one case the pulverulent opacities are nuclear, in three they are cortical, while the fifth has both nuclear and cortical opacities. Two individuals have microcornea and in one case there are bilateral iris colobomata. Maf was initially identified as the cellular homologue of an avian oncogene isolated from a spontaneous musculo-aponeurotic fibrosarcoma. While the gene may be dysregulated in multiple myeloma, a role for MAF has not been proposed in Hodgkin’s disease or in uveal melanoma, which were each seen in two different members of this family. Therefore, the oncogenic significance, if any, of this MAF mutation remains unknown. Maf is expressed in early eye development and the homozygous knockout mouse demonstrates microphthalmia with abnormal lens fibre formation. Maf regulates expression of crystallin genes. In this three generation family, a mutation, R288P, has been identified in the basic region DNA binding domain in a highly conserved arginine residue (Fig 2).

The phenotypic heterogeneity, as observed in this family with variable cataract, microcornea, and iris abnormality, is a common feature of families with cataract and anterior segment anomalies. However, this is the first description of a gene mutation identified in a patient with a typical iris coloboma. The lens is known to be important for development of the anterior segment and this family emphasises the complexity likely to be present in these early developmental processes. The presence of microcornea and iris coloboma suggests that MAF may have a broader role, in development of the anterior segment of the eye and optic fissure closure, than one confined to lens fibre development and elongation.

The MAF mutation in this family may be associated with isolated cataract. The majority of identified cataract mutations are in genes encoding lens membrane and crystallin proteins. Isolated cataract has been described in individuals from families with mutations in the transcription factors PITX3 and PAX6 and in all cases these were detected in early infancy with later onset findings including glucoma and corneal dystrophy. By contrast the MAF mutation causes cataracts with symptoms in mid to late childhood and in two cases there was no other anterior segment abnormality. It is noteworthy that a balanced translocation occurring close to MAF, that is hypothesised to alter MAF expression, also caused isolated pulverulent, childhood onset cataract with progression of symptoms. This suggests that in addition to its developmental role in the lens, MAF may be important in the maintenance of lens clarity. It is likely that this is through its known role in crystallin gene regulation. Interestingly, mutations found in two crystallin genes, CRYBB2 and CRYGD, are also associated with childhood or early adult onset cataracts, highlighting their role in lens maintenance. These findings identify MAF as an attractive candidate gene to contribute to later onset and age related forms of cataract.

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