

SCIENTIFIC CORRESPONDENCE

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.

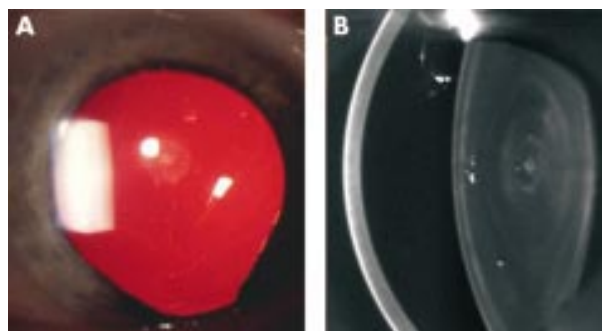


Figure 1 Pulverulent cataract in patient III-3. (A) White punctate nuclear lens opacities. (B) Scheimflug view.

toms from the cataracts were juvenile in onset, progressive, with extraction required from the third decade. These findings point to the importance of *MAF* in maintenance of lens clarity and suggest a potential contribution to later onset and age related cataract.

PATIENTS AND METHODS

Family members underwent ophthalmic examination with particular attention to cataract morphology by direct examination and photography. Examination also included measurement of corneal diameter and axial length, slit lamp examination, and gonioscopy.

RESULTS

Five affected members over three generations of this family were examined. They were a grandmother (I-1), three of her daughters (II-2, II-3, and II-5), and one of the daughter's sons (III-3). Cortical pulverulent opacities were present in I-1, II-2, II-3, and II-5, who all had juvenile onset of symptoms. These were described as round white and refringent green/blue opacities. I-1 also had nuclear pulverulence. III-3 has bilateral lamellar pulverulent cataracts of the embryonic nucleus (1.2 mm in diameter) (Fig 1A, B). In all affected adults there has been progression to additional posterior subcapsular cataracts. The grandmother and her daughters underwent cataract removal at ages 25–29 years. The grandson at the age of 16 years has only minor reduction in vision (visual acuity right eye 0.8 and left eye 0.9), perhaps related to the presence of iris colobomas.

Microcornea (10–10.25 mm) is present in II-2 and II-3. Bilateral iris colobomas in the 6 o'clock position are present in the grandson. Neither iridocorneal anomalies nor glaucoma were observed. Axial length and fundal examination were normal.

MAF is a proto-oncogene whose expression may be altered in multiple myeloma¹² of which there was no history in this family. There was no strong evidence of a genetic predisposition to malignancy. I-1 was treated for a right uveal

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.¹ 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 crystallins² 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.⁴ 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.^{5–7} Two *PAX6* mutations have been identified in patients with microcornea and cataract in association with anterior segment abnormality.^{8–9} A mutation in the crystallin gene, *CRYAA*, has been identified in a family with cataract, microcornea, and microphthalmia.¹⁰ 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*.¹¹ Symp-

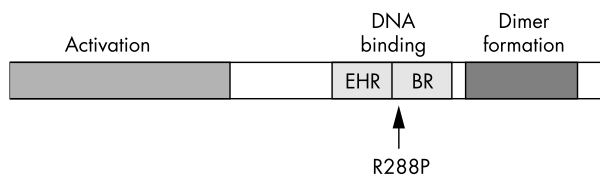


Figure 2 Schematic representation of the MAF protein showing the functional domains and the position of the R288P (arginine to proline substitution) mutation in the basic region of the DNA binding domain. The arginine in this position of the DNA binding domain is conserved in all known large Maf proteins.¹¹ EHR = extended homology region, BR = basic region.

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 identified as the cellular homologue of an avian oncogene isolated from a spontaneous musculo-aponeurotic fibrosarcoma.¹³ While the gene may be dysregulated in multiple myeloma,¹² 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.¹⁴ *Maf* regulates expression of crystallin genes.¹⁵ 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).¹¹

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 segment¹⁶ 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 glaucoma and corneal dystrophy.^{17,18} 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.¹¹ 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.^{2,3} These findings identify *MAF* as an attractive candidate gene to contribute to later onset and age related forms of cataract.

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