SCIENTIFIC CORRESPONDENCE

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

R V Jamieson, F Munier, A Balmer, N Farrar, R Perveen, G C M Black

Br J Ophthalmol 2003;**87**:411–412

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.[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 crystallins[2 3] 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] Symptoms 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.

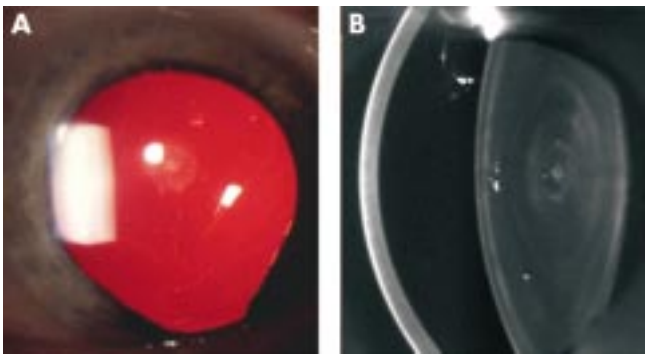

Figure 1 Pulverulent cataract in patient III-3. (A) White punctate nuclear lens opacities. (B) Scheimflug view.

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 myeloma[12] 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

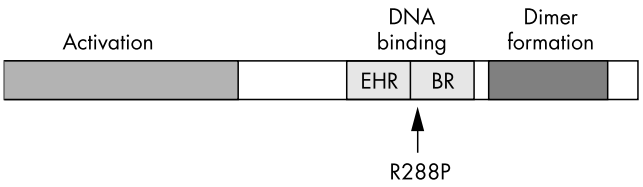

Figure 2 Schematic representation of the MAF protein showing the functional domains and the position of the R288P (arginine to proline substitution) mutation in the basic region of the DNA binding domain. The arginine in this position of the DNA binding domain is conserved in all known large Maf proteins.[11] 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 segment[16] 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.

ACKNOWLEDGEMENTS

We thank the family for their collaboration. RVJ is a Neil Hamilton Fairley Research Fellow (Reference 997006) with the National Health and Medical Research Council of Australia and also acknowledges a Paediatric Travelling Fellowship from the Royal Australasian College of Physicians. NF is supported by the Birth Defects Foundation (Grant Reference 2000/25). RP is supported by Action Research and GCMB is a Wellcome Trust Clinician Scientist Fellow (Reference 51390/Z).

Authors' affiliations

R V Jamieson, N Farrar, R Perveen, G C M Black, Academic Unit of Medical Genetics and Regional Genetic Service, St Mary's Hospital, Manchester M13 0JH, UK
R V Jamieson, Department of Clinical Genetics and Sydney University Department of Paediatrics and Child Health, The Children's Hospital at Westmead, Sydney, NSW, 2145, Australia
F Munier, A Balmer, Hopital Ophtalmique Jules Gonin, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland
G C M Black, Academic Unit of Ophthalmology, Manchester Royal Eye Hospital, Manchester M13 9WH, UK

Correspondence to: R V Jamieson; robynj@chw.edu.au

Accepted for publication 4 September 2002

REFERENCES

1 **Hammond CJ**, Duncan DD, Snieder H, *et al*. The heritability of age-related cortical cataract: the twin eye study. *Invest Ophthalmol Vis Sci* 2001;**42**:601–5.
2 **Gill D**, Klose R, Munier FL, *et al*. Genetic heterogeneity of the Coppock-like cataract:a mutation in CRYBB2 on chromosome 22q11.2. *Invest Ophthalmol Vis Sci* 2000;**41**:159–65.
3 **Stephan DA**, Gillanders E, Vanderveen D, *et al*. Progressive juvenile-onset punctate cataracts caused by mutation of the gammaD-crystallin gene. *Proc Natl Acad Sci USA* 1999;**96**:1008–12.
4 **Duke-Elder S**, ed. Normal and abnormal development. Congenital deformities. In: *System of ophthalmology*. Vol 3. St Louis: CV Mosby, 1963:497–539.
5 **Salmon JF**, Wallis CE, Murray AD. Variable expressivity of autosomal dominant microcornea with cataract. *Arch Ophthalmol* 1988;**106**:505–10.
6 **Yamamoto Y**, Hayasaka S, Setogawa T. Family with aniridia, microcornea, and spontaneously reabsorbed cataract. *Arch Ophthalmol* 1988;**106**:502–4.
7 **Mollica F**, Li Volti S, Tomarchio S, *et al*. Autosomal dominant cataract and microcornea associated with myopia in a Sicilian family. *Clin Genet* 1985;**28**:42–6.
8 **Azuma N**, Yamaguchi Y, Handa H, *et al*. Missense mutation in the alternative splice region of the PAX6 gene in eye anomalies. *Am J Hum Genet* 1999;**65**:656–63.
9 **Hanson I**, Churchill A, Love J, *et al*. Missense mutations in the most ancient residues of the PAX6 paired domain underlie a spectrum of human congenital eye malformations. *Hum Mol Genet* 1999;**8**:165–72.
10 **Litt M**, Kramer P, LaMorticella DM, *et al*. Autosomal dominant congenital cataract associated with a missense mutation in the human alpha crystallin gene CRYAA. *Hum Mol Genet* 1998;**7**:471–4.
11 **Jamieson RV**, Perveen R, Kerr B, *et al*. Domain disruption and mutation of the bZIP transcription factor, MAF, associated with cataract, ocular anterior segment dysgenesis and coloboma. *Hum Mol Genet* 2002;**11**:33–42.
12 **Chesi M**, Bergsagel PL, Shonukan OO, *et al*. Frequent dysregulation of the c-maf proto-oncogene at 16q23 by translocation to an Ig locus in multiple myeloma. *Blood* 1998;**91**:4457–63.
13 **Nishizawa M**, Kataoka K, Goto N, *et al*. v-maf, a viral oncogene that encodes a "leucine zipper" motif. *Proc Natl Acad Sci USA* 1989;**86**:7711–5.
14 **Kawauchi S**, Takahashi S, Nakajima O, *et al*. Regulation of lens fiber cell differentiation by transcription factor c- Maf. *J Biol Chem* 1999;**274**:19254–60.
15 **Ogino H**, Yasuda K. Induction of lens differentiation by activation of a bZIP transcription factor, L-Maf. *Science* 1998;**280**:115–18.
16 **Collinson JM**, Quinn JC, Buchanan MA, *et al*. Primary defects in the lens underlie complex anterior segment abnormalities of the Pax6 heterozygous eye. *Proc Natl Acad Sci USA* 2001;**98**:9688–93.
17 **Semina EV**, Ferrell RE, Mintz-Hittner HA, *et al*. A novel homeobox gene PITX3 is mutated in families with autosomal-dominant cataracts and ASMD. *Nat Genet* 1998;**19**:167–70.
18 **Glaser T**, Jepeal L, Edwards JG, *et al*. PAX6 gene dosage effect in a family with congenital cataracts, aniridia, anophthalmia and central nervous system defects [published erratum appears in *Nat Genet* 1994;**8**:203]. *Nat Genet* 1994;**7**:463–71.