

# Aetiology of congenital and paediatric cataract in an Australian population

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**Background/aim:** Paediatric cataract is a major cause of childhood blindness. Several genes associated with congenital and paediatric cataracts have been identified. The aim was to determine the incidence of cataract in a population, the proportion of hereditary cataracts, the mode of inheritance, and the clinical presentation.

**Methods:** The Royal Children's Hospital and the Royal Victorian Eye and Ear Hospital have a referral base for almost all paediatric patients with cataracts in south eastern Australia. The database contains cases seen over the past 25 years. The medical histories of these patients were reviewed.

**Results:** 421 patients with paediatric cataract were identified, which gives an estimated incidence of 2.2 per 10 000 births. Of the 342 affected individuals with a negative family history, 50% were diagnosed during the first year of life, and 56/342 (16%) were associated with a recognised systemic disease or syndrome. Unilateral cataract was identified in 178/342 (52%) of sporadic cases. 79 children (from 54 nuclear families) had a positive family history. Of these 54 families, 45 were recruited for clinical examination and DNA collection. Ten nuclear families were subsequently found to be related, resulting in four larger pedigrees. Thus, 39 families have been studied. The mode of inheritance was autosomal dominant in 30 families, X linked in four, autosomal recessive in two, and uncertain in three. In total, 178 affected family members were examined; of these 8% presented with unilateral cataracts and 43% were diagnosed within the first year of life.

**Conclusions:** In the paediatric cataract population examined, approximately half of the patients were diagnosed in the first year of life. More than 18% had a positive family history of cataracts. Of patients with hereditary cataracts 8% presented with unilateral involvement. Identification of the genes that cause paediatric and congenital cataract should help clarify the aetiology of some sporadic and unilateral cataracts.

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Cataract is a major cause of blindness throughout the world, particularly in developing countries.<sup>1</sup> Cataract is defined as any opacity of the lens, although clinically it usually refers to opacities that reduce visual acuity. Most cataracts occur in elderly members of our community, but a small percentage of the paediatric population is affected.<sup>2–4</sup> Blindness from cataracts is less common in children compared with adults; however, the impact is severe in terms of vision years lost. Even in developed countries, where treatment is readily available, paediatric cataract is responsible for a high proportion of childhood blindness. There are significant costs associated with the diagnosis and management of these children, as well as with long term rehabilitation, visual assistance, and lost productivity.

Since the discovery by Gregg in 1941<sup>5</sup> that maternal rubella commonly causes congenital cataract, widespread immunisation programmes in the developed world have resulted in a dramatic decrease in the incidence of rubella embryopathy. The incidence of congenital cataract has been calculated at 2.49–3.46 per 10 000.<sup>6</sup> Many textbooks have long lists of syndromes possibly associated with cataracts, but none lists the relative frequencies of these causes. Although pedigrees of cataract were described long ago in the literature,<sup>7</sup> there are no data on the relative frequency of different modes of cataract inheritance. The recent discovery of 10 cataract genes (and localisation of at least another nine cataract gene loci) suggests that genetic factors play a significant part in cataract aetiology (OMIN) (Table 1).<sup>8–31</sup> Even in adult cataract where environmental factors (for example, lower socioeconomic status, ultraviolet light, allopurinol or corticosteroid use, smoking, trauma<sup>32–45</sup>) have a role, family history and twin studies suggest a genetic contribution.<sup>45–47</sup> It may be hypothesised that

more deleterious mutations usually result in the paediatric onset diseases while "mild" mutations in the same gene may predispose to the common adult variety of the disease, as has been shown to be the case with glaucoma.<sup>48</sup>

A problem during embryonic lens development can lead to abnormalities in the transparency of the lens. Anterior polar cataract can arise from abnormal separation of the lens vesicle in early pregnancy. Persistent pupillary membranes, a remnant of tunica vasculosa lentis, may also be associated with anterior polar cataracts. Persistent hyperplastic primary vitreous (PHPV) is related to the persistence and secondary fibrosis of the primitive hyaloid vascular system.<sup>49</sup> This fibrovascular membrane may be quite small, such as a Mittendorf's dot, or can extend from the centre of the posterior lens capsule to the ciliary processes.

Developmental genes affecting the lens development include PAX6 and PITX3, which are critical for formation of the lens architecture.<sup>50</sup> Mutations of these genes cause congenital cataract often, but not exclusively, and are associated with other anterior segment anomalies.<sup>51</sup> One family with congenital cataracts due to a PITX3 mutation, but without anterior segment mesenchymal dysgenesis, has been described.<sup>29</sup> Mutations in PAX6, located on chromosome 11p13, are usually responsible for aniridia and an associated clinical spectrum that may include anterior polar cataract, Peters' anomaly, Axenfeld anomaly, lens dislocation, foveal hypoplasia, optic nerve hypoplasia, dominant keratitis, and nystagmus.<sup>52</sup> Reported atypical phenotypes include a compound heterozygote with congenital cataracts and late onset corneal dystrophy,<sup>30</sup> and foveal hypoplasia plus presenile cataract with onset before 40 years of age.<sup>33</sup> Cataract is present in 50–80% of patients, with aniridia, by the age of 20 years.

**Table 1** Mapped autosomal dominant and X linked cataract loci predominantly involving the eye

Phenotype	Chromosome	Gene	Abbreviation	Reference
Volkman	1p36	–	–	9
Posterior polar	1pter-p36.1	–	–	10
Zonular pulverulent	1q21-25	Connexin 50	CX50 (GJA8, MP70)	11, 12
Coppock-like	2q33-35	$\gamma$ crystallin C	CRYGC	13
Aculeiform/punctate	2q33-35	$\gamma$ crystallin D	CRYGD	13, 14
Polymorphic (lamellar)	2q33-35	–	–	15
Nuclear sutural	3q21.2-22.3	–	–	16
Congenital cataract plus or minus anterior segment mesenchymal dysgenesis	10q25	Paired-like homeodomain transcription factor 3	PITX3	29
Aniridia and cataract	11p13	Paired box gene 6	PAX6	30
Pulverulent	13q	Connexin 46	CX46 (GJA3)	17
Anterior polar	14q24-qter	–	–	18
Marnier (pulverulent)	16q22	–	–	19
Anterior polar	17p13	–	–	20, 21
Zonular sutural (lamellar)	17q11-12	$\beta$ A3/A1-crystallin	CRYBA1	22
Cerulean	17q24	–	–	23
Zonular central nuclear	21q22.3	$\alpha$ crystallin	CRYAA	24
Cerulean/Coppock-like	22q	$\beta_2$ crystallin	CRYBB2	25, 26
Hyperferritinaemia cataract syndrome	19q13.3-13.4	Ferritin light chain	FTL	27, 31
Nance-Horan syndrome	Xp22.3-21.1	–	–	28

In 1894 Marner<sup>54</sup> first described the crystallins as heterogeneous structural proteins found in high concentrations in the lens. The first crystallin ( $\delta$ ) was found in reptilian lenses and was cloned in 1979.<sup>55</sup> The crystallins comprise over 90% of the soluble protein of the lens and provide cellular cytoplasm that is transparent and of a consistent refractive index.  $\alpha$  Crystallins are synthesised early in development and act as molecular chaperones.<sup>56</sup>  $\beta$  And  $\gamma$  crystallins both consist of four “Greek key”  $\beta$  sheet motifs. The polypeptides of each class associate in various combinations to form polymers, except for the  $\gamma$  crystallins and one  $\beta$  crystallin which remain as monomers. Synthesis of the  $\beta$  and  $\gamma$  crystallins increases as anterior epithelial cells move into the lens nucleus to form lens fibre cells. All human cataract crystallin mutations, except one, are predicted to disrupt tertiary structure, resulting in an increased tendency of  $\alpha$ ,  $\beta$ , and  $\gamma$  crystallins to aggregate and precipitate.

Gap junction channels, termed connexons, modulate exchange of ions and metabolites between lens fibre cells, epithelial cells, and the extracellular space. Connexons are each composed of six subunits of connexin proteins. Lens fibre cells are interconnected by a network of gap junctions containing CX46 and CX50, while CX43 expression is restricted to lens epithelium. Two of the connexin mutations are predicted to alter the extracellular loop of the protein products, disrupting connexon formation and interaction. Mutations have also been associated with increased crystallin proteolysis and shown to function in a dominant negative manner.<sup>11, 12, 17</sup>

Many rare syndromes are associated with cataract. However, the hereditary hyperferritinaemia cataract syndrome (HHCS) (Craig *et al*, manuscript submitted) and Nance-Horan syndrome (NHS)<sup>57</sup> are two familial syndromes in which cataract predominates. HHCS results from a range of mutations in the iron responsive element (IRE) of the 5' non-coding region of the ferritin light chain (FTL) gene,<sup>31, 38</sup> and accumulation of ferritin in the lens is believed to be responsible for the observed cataract. HHCS is probably rare in infancy and unlikely to cause congenital cataracts as lens opacities seem to develop progressively through the second and third decade of life. Even in adults with early onset cataract it is underdiagnosed. NHS is an X linked syndrome involving cataracts, dental anomalies, shortened metacarpals, and sometimes mental retardation. Carrier females are also affected, although with a milder phenotype than hemizygous males. While males typically exhibit severely impaired vision, females often

display sutural cataracts and experience only mild visual loss. The gene for this syndrome has been localised to Xp22.3–21.1, but the gene has not yet been identified.

The most common aetiologies of all paediatric cataract include intrauterine infections, metabolic disorders and genetically transmitted syndromes.<sup>39</sup> To date there has been no major series of consecutive paediatric and congenital cataracts studied to determine the relative frequencies of different subgroups of cataract. The aim of this study was to determine the prevalence of familial cataracts among the congenital and paediatric cataracts seen at the Royal Children's Hospital, Royal Victorian Eye and Ear Hospital and associated clinics in Melbourne over the past 25 years. In addition we looked at the aetiology and associated diseases of congenital and paediatric cataracts that were not familial.

## METHODS

We reviewed all the paediatric cataract cases managed over the past 25 years at the Royal Children's Hospital and associated clinics in Melbourne. These clinics have a referral base for paediatric cataracts in south eastern Australia, a population of 5–6 million. Outpatients and inpatients had been diagnostically coded and we cross referenced this with children requiring contact lenses. We recorded the following data from the medical histories of these patients: family history, age at diagnosis, morphology of cataract (where mentioned), laterality, age at surgery of either eye, visual acuity before and after surgery and at last visit, associated findings (for example, nystagmus, strabismus, preoperative or postoperative glaucoma, anterior segment abnormalities, other eye abnormalities), systemic disorders and events during pregnancy, delivery, and the neonatal period. Those with a family history of cataract were contacted to participate in further genetic studies. The families that agreed to participate were examined to record the actual visual acuity, slit lamp findings, further family and personal history, and information on relatives. The likely mode of inheritance was determined from the pedigree. Buccal mucosal swabs were collected from affected familial cases, spouses, and many unaffected relatives.<sup>60</sup> All cases of aniridia were also identified in addition to those who had been identified from the cataract samples. Further pedigrees of adult cataracts were sought from ophthalmologists in the state.

To calculate the incidence of cataract, we used a formula similar to previous studies estimating the incidence of retinoblastoma.<sup>61</sup> Over the 25 year period the referral patient

**Table 2** Inheritance patterns of cataract in 39 pedigrees of our original cohort

Inheritance	Number of pedigrees
Autosomal dominant	30
Autosomal recessive	2
X linked	4
Not determined	3

**Table 3** Laterality of cataracts

	Bilateral	Unilateral
Sporadic cataracts (342)	47% (164)	52% (178)
Inherited cataracts (178)	92% (164)	8% (14)

11% (19) of the unilateral sporadic cataracts had PHPV.  
40% (72) of the unilateral sporadic cataracts had surgery.

population had a total of 75 000 births per year (Victoria: average 61 415 births annually; Tasmania: average 6782 births annually; and the southern part of New South Wales estimated to be the same as Tasmania).<sup>62</sup>

## RESULTS

Over 25 years, 421 index cases with congenital or paediatric cataract were identified (16.8 per year) giving an incidence of 2.2 per 10 000 (one in 4500). This is approximately four times the incidence of retinoblastoma.

### Familial cases

Seventy nine children from 421 (18.8%) had a positive family history of cataract. These 79 cases came from 54 nuclear families. Of these 54 families, five could not be contacted and four declined to participate. Genealogical research revealed that 10 of the nuclear families formed four larger pedigrees. Thus, we identified a total of 39 cataract pedigrees from this cohort. Thirty pedigrees were autosomal dominant, four X linked, two autosomal recessive, and in three pedigrees the inheritance is uncertain (Table 2). A total of 178 affected family members have been examined, and 14 (8%) had unilateral cataract (Table 3). Seventy six of the 178 patients (43%) were diagnosed within the first year of life (Table 4). There was remarkable variability of phenotype and severity within the same family. From this set four of the dominant pedigrees had anterior polar cataract and at least one family member with clinical criteria to suggest the diagnosis of "aniridia." From the notes of the other cases in our clinic diagnosed with aniridia a further two pedigrees had members with cataract and three

**Table 4** Age at diagnosis

Age at diagnosis	Number of patients	Number of patients
	Inherited (178) (79 index cases plus a further 99 family members)	Sporadic (342)
Birth–1 month	37 (20.8%)	102 (29.8%)
>1 month–12 month	39 (22%)	90 (26.3%)
>1 year–2 years	8 (4.5%)	25 (7.3%)
>2 years–3 years	7 (3.9%)	19 (5.6%)
>3 years–4 years	5 (2.8%)	12 (3.5%)
>4 years–5 years	10 (5.6%)	12 (3.5%)
>5 years–10 years	32 (18%)	28 (8.2%)
>10 years	28 (15.7%)	9 (2.6%)
No information	12 (6.7%)	45 (13.2%)

**Table 5** Cataracts in aniridia

Aniridia	Number of patients	Number with cataract
With family history	9 (in 7 pedigrees)	6/9
Without family history	12	5/12 (3 WAGR syndrome)
Total	21	11/21

**Table 6** Systemic disorders associated with sporadic cataracts in our series

Disease	Number of patients
Down's syndrome	18
Rubella embryopathy	9
Aniridia	5
Juvenile chronic arthritis with uveitis	4
Diabetes	3
Galactosaemia	3
Craniosynostosis	2
Hallerman-Streiff syndrome	1
Smith-Lemli-Opitz syndrome	1
X linked dominant chondrodysplasia punctata	1
Achondroplasia	1
Marshall syndrome	1
Mosaic trisomy 8	1
Partial duplication of chromosome 1	1
Lowe syndrome	1
Unspecified collagen disorder	1
Goldenhar syndrome	1
Treacher-Collins syndrome	1
Hereditary hyperferritinaemia cataract syndrome	1

pedigrees had no members with cataract (Table 5). From the adult cataract patients a further nine dominant pedigrees (two of whom had hereditary hyperferritinaemia cataract syndrome in addition to one sporadic case), one recessive pedigree, and one X linked pedigree were identified. On cross reference no members of these families had been seen in the Children's Hospital clinics during the period of our study.

### Sporadic cases

Of 342 children without family history, 56/342 (16%) had a systemic disorder as a possible cause of their cataract (Table 6). Another 19 children were mentioned to have general developmental delay or cerebral palsy. Of the 342 children without family history, 84 (25%) were diagnosed within 1 month of birth, and a further 85 (25%) during the first year of life (Table 4). Sixty one (18%) of these patients were documented to have manifest nystagmus at the time of diagnosis and 37% strabismus. Unilateral cataract was found in 178/342 (52%) (Table 3). Of the unilateral sporadic cataracts 19/178 (11%) had PHPV. In unilateral cataract 40% (72/178) had surgery.

## DISCUSSION

The Royal Children's Hospital and the Royal Victorian Eye and Ear Hospital have a referral base for almost all paediatric cataracts in south eastern Australia. They are the tertiary referral centres for children in Victoria, Tasmania, and southern New South Wales. We receive very few referrals from outside this region. Almost every child requiring surgery will have been seen at the hospital although some children with mild cataracts not requiring surgery may not have been referred. The diagnostic coding database contains cases seen over the past 25 years. When families were examined we identified other adults with cataract born outside the study period, and children who at the time of initial diagnosis were living in

other states. For purposes of establishing the relative frequencies of cataract subtypes and associations we only analysed data for those index cases identified from the database.

Familial cases account for almost one fifth of paediatric and congenital cataract. This is a significant proportion and thus examining the parents and other family members is clearly the "investigation" most likely to explain the aetiology of a child's cataract. A higher proportion may be genetic. As cases were ascertained from a retrospective case notes review and a family history may not always have been elicited, there is likely to be an underestimate of autosomal recessive cases. The majority of cataracts are sporadic, though this does not exclude genetic causes in these cases. In comparison, the majority of retinitis pigmentosa cases are sporadic and most likely recessive in inheritance in the Australian population.<sup>63</sup>

Down's syndrome was the most common systemic association with sporadic cataract. Six per cent of 300 Down's syndrome patients on our database were also known to have cataracts. This figure is lower than the 13% of Down's syndrome cases with cataract that was found in a Brazilian study.<sup>64</sup> It is possible that a gene dosage effect of one of the cataract genes on chromosome 21, such as CRYAA at 21q22.3, may be responsible for these cataracts. The incidence of births of rubella damaged children in Australia has fallen to one in 67 000 live births.<sup>65</sup> Although rubella embryopathy is a less common cause for congenital cataract than in the past, it is still seen, especially in new immigrants who have not been immunised. The mothers of three of the nine children with rubella embryopathy originated from Malta, Mauritius, and the Philippines. The babies were born in Australia in 1983, 1991, and 1995, respectively. There are reports of babies born with congenital rubella infection and malformations after their previously vaccinated mothers were exposed to wild virus during pregnancy. In this study one child was previously reported as reinfection of an immunised mother.<sup>66</sup> The other five children born between 1969 and 1974 are Australian. In our series one family had originally been mislabelled as rubella cataract although there were three affected members in two generations.

No child who was otherwise well and had cataract was found to have an associated syndrome on further investigations. The panel of screening tests has now been greatly reduced in our hospital. The previous bank of studies included: "TORCH" antibody screening, karyotyping, random blood glucose, galactose, RBC galactokinase, full blood count, electrolytes (particularly calcium and phosphate), liver function tests, joint x rays, urine for reducing substances, and amino acids.<sup>67</sup> Now the first investigation of any paediatric cataract is examination of the parents, thus avoiding unnecessary further investigations if hereditary cataracts are found. If the child is dysmorphic, failing to thrive, or developmentally delayed, they are reviewed by a paediatrician or geneticist and many of the tests mentioned above are performed depending on the clinical picture. In male babies with total cataract who are otherwise well, but too young to show signs of mental retardation from Lowe syndrome, urine amino acids are usually tested. In children with the scattered axial and peripheral cystic flecks in cortex and nucleus, as seen in hereditary hyperferritinaemia cataract syndrome, serum ferritin should be measured. Down's syndrome, the most common association, is usually obvious. Of the 21 children with aniridia, three were found to have Wilms' tumour, Aniridia, Genitourinary anomalies, mental Retardation (WAGR) syndrome. These three were non-familial cases of aniridia. With 25% (3/12) sporadic cases of aniridia having WAGR, this would justify chromosome analysis and FISH analysis to detect deletion of both the PAX6 and the Wilms' tumour genes and abdominal ultrasound to detect Wilms' tumour in sporadic cases of aniridia. Inflammatory, metabolic, and dysmorphic syndromes were seen, but did not usually present as a diagnostic problem.

Although most cases with a positive family history tended to be bilateral in this series, 8% of the inherited cataracts presented as unilateral or asymmetric bilateral. These asymmetric bilateral cases were not recognised until later slit lamp examination of children, where very mild cataract was detected. The UK study found that, overall, 34% of congenital and paediatric cataracts were unilateral.<sup>6</sup> Of their sporadic cataracts, 76/136 (56%) were unilateral compared with 178/342 (52%) in our study. Of their hereditary cases, 5/95 (5%) were unilateral, similar to the 8% found in our study. PHPV was the most common association with unilateral cataracts. It is possible that a somatic mutation in the developing lens may cause unilateral cataract, in a similar fashion to sporadic retinoblastoma, but further study of the lens material of these cataracts will be required. Full explanation of the aetiology of congenital cataracts will require the identification of further cataract genes. Cataract genes identified and mapped regions are given in Table 1. The identification of a large number of cataract pedigrees will allow us to do further work on the identification of cataract genes and will eventually give a more precise indication of the true genetic component to cataract in this and other populations.

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