

Review

The iris – a window into the genetics of common and rare eye diseases

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ABSTRACT

Visual examination, without instruments, of the eye allows inspection of the iris, sclera, cornea and, through the iris, some abnormalities of the lens and retina. Several hereditary disorders can easily be recognised by characteristic iris changes. This review discusses changes in the iris, visible lens anomalies, and changes in the cornea surrounding the iris. A genetic diagnosis can help with management of diseases. Some conditions are single gene disorders, some are chromosomal rearrangements, and some are abnormalities of fetal development.

INTRODUCTION

When NHS evidence (www.evidence.nhs.uk) was being set up last year, the logo chosen was a picture of a normal iris (figure 1). At the meeting of the board where the logo was presented for discussion and approval, Sir Michael Rawlins, the chairman of NICE, asked “how do we know is it a normal iris?” I mentioned that we could say there were at least 25 genetic disorders that the person probably did not have, although we could not necessarily say the iris was normal. The result, having been asked to name them, was a presentation to the board on the disorders, and now this paper. Several genetic

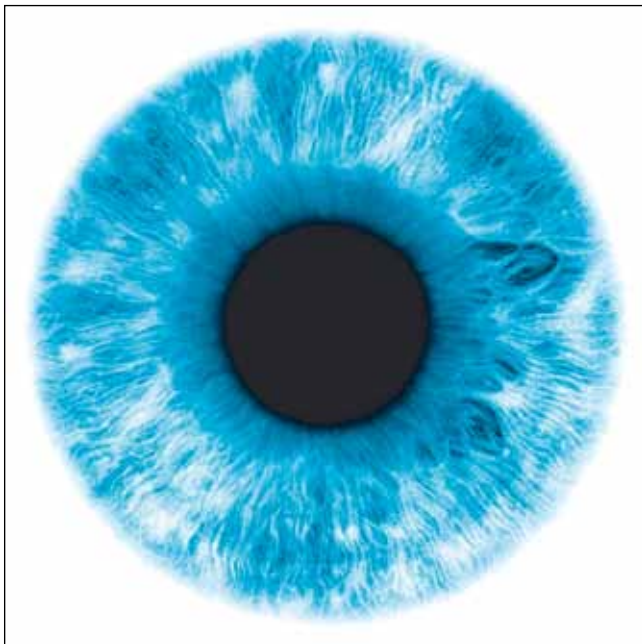


Fig 1. NHS evidence ‘normal’ iris.



Figs 2-10. From left to right, abnormal irides – see text for diagnoses.

conditions can be detected by just looking at the iris or the overlying cornea or intervening lens, and I use this article to illustrate how recognition of some common and some rare diseases that can be identified by direct visualisation in the outpatient clinic or GP surgery, can lead to prevention and management of underlying complications.

GENERAL IRIS DISORDERS.

Glaucoma, uveitis, conjunctivitis and iritis may all be discernable by ocular examination. Most of these disorders are caused by common somatic disease, often caused by infection or trauma, and usually are not heritable. Glaucoma does occur in some autosomal dominant families. Pupillary anomalies may also give a clue to the diagnosis (a dilated iris occurs naturally with death or with drugs such as mydriatics or cocaine) Similarly pupillary constriction can be a marker of heroin and other drug use, or other neurological abnormalities. The list is too long to deal with in this review.

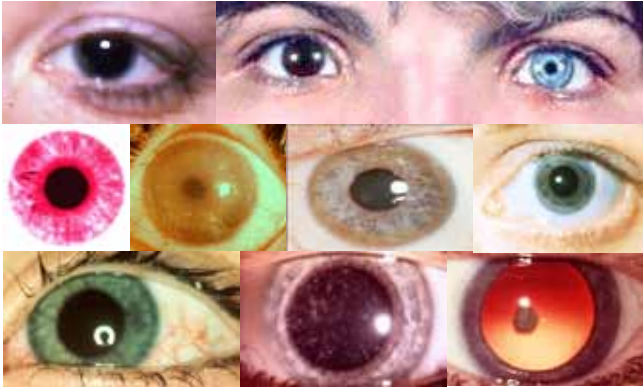
CHROMOSOMAL ANOMALIES

Humans have 23 pairs of chromosomes, most of which have a clearly defined short (p) and a long (q) arm. Cytogenetic

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Figs 11-19. From left to right, abnormal irides – see text for diagnoses.

analysis has improved over the last few years with small duplicated or deleted segments now being more easily detected by automated karyotyping techniques. Some chromosome disorders have characteristic iris findings including trisomy 21 (Down syndrome) where Brushfield spots may occur (figure 2), and Williams syndrome – a condition caused by a missing segment (deletion) at chromosome 7q11.23 (deletion is on chromosome seven on the long arm, at segment 11, sub-band 23). Affected individuals have a characteristic phenotype including a recognisable facial appearance, and typical behavioural traits (including moderate learning difficulties), along with hypercalcaemia in childhood. The Williams syndrome iris is described as ‘stellate’ lace-like appearance (figure 3). A coloboma (small missing segment) of the iris may be present sporadically, or due to a developmental anomaly, or be a marker of an underlying chromosome disorder (figure 4) such as ‘cat-eye’ syndrome (caused by an extra segment of chromosome 22, and having ocular coloboma and anal atresia). Such abnormalities should prompt investigations for a chromosome karyotype and a thorough ophthalmic examination as the coloboma may extend into the retina. Severe cyclopia may occur as a developmental or chromosomal abnormality (figure 5) with fusion of the two optic globes and a single iris.

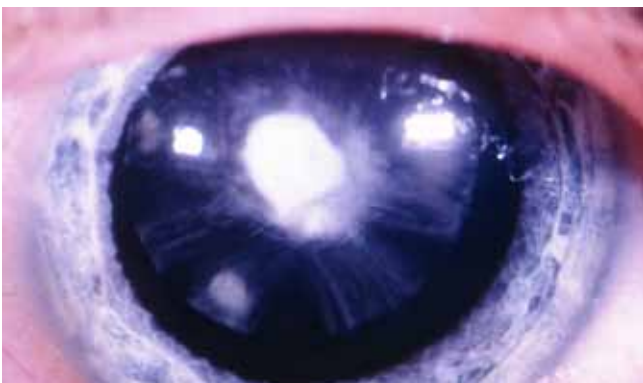


Fig 20. X-linked cataract.

SINGLE GENE DISORDERS

The twenty-three sets of chromosomes carry DNA wrapped carefully in a compact form. ‘Unwinding’ the DNA into its double helix allows analysis of genes, where mutations (changes in a small segment of DNA base pairs) can change the structure and function of a particular amino acid and thus

inactivate or change the expression of a gene product – usually a protein or enzyme. Several genetic disorders have clearly autosomal dominant or autosomal recessive inheritance. Some have recognisable iris signs.



Fig 21. Epibulbar dermoid overlying the iris.

Autosomal Dominant.

Autosomal dominant disorders generally require a mutation in one of the two sets of genes, and often code for proteins. Such protein abnormalities make take time to build up or process within cells, and unlike recessive disorders where often an enzyme is the gene product and thus present early in life, dominant disorders are often not present until adulthood. One example is Marfan syndrome, a disorder of connective tissue with abnormalities in the fibrillin protein, causing hyperelasticity of fibrillin and a propensity to aortic dissection. Patients can have a series of eye abnormalities, the most easily recognisable is a dislocated lens (figure 6). Dislocation occurs because the zonules holding the lens in place are weaker and careful examination by an ophthalmologist is helpful. Other dominant causes of dislocated or abnormal lens include familial ectopia lentis, and Weill-Marchesani syndrome.

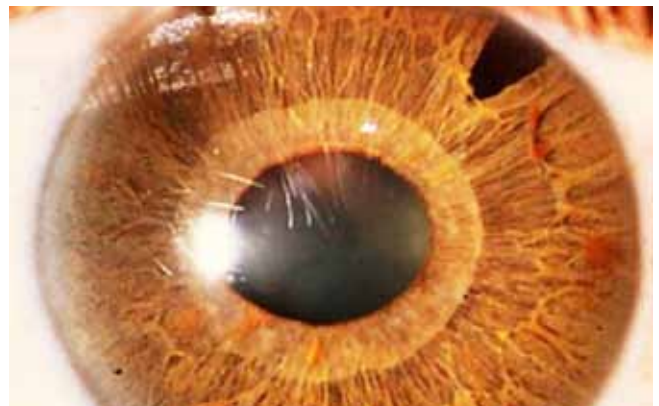


Fig 22. Rieger anomaly.

Neurofibromatosis type I, a neurocutaneous disorder causing pigmentation of the skin (café au lait spots, and skin neurofibromas), may exhibit clumps of pigment (Lisch nodules) within the iris (Figure 7). Some patients may develop optic nerve compression, and females are at moderate risk of breast cancer. Markers of systemic disease such as raised cholesterol may be familial – dominant familial hypercholesterolaemia may cause cholesterol and lipid

deposits – arcus senilis - around the iris (Figure 8). Autosomal dominant cataract may be familial or isolated (figure 9) or part of other disorders including Myotonic dystrophy. Virtually all modes of inheritance have been recognised for hereditary cataract including recessive and X-linked types. Occasionally some cancers may be hereditary and retinoblastoma (figure 10) and Wilms' tumour (hypernephroma, figure 11) are examples of tumour suppressor genes that may fail to normally function if one of the pair is abnormal, and can occur in early childhood. These may present in autosomal dominant familial forms with a white retinal reflex and aniridia respectively. Curious differences in the colour of the iris (heterochromia) are found normally in the population, but may be inherited (figure 12) as autosomal dominant, and more rarely in syndromic forms such as Waardenburg syndrome with underlying hearing loss and a white forelock being characteristic. The pop star David Bowie is said to have heterochromia.

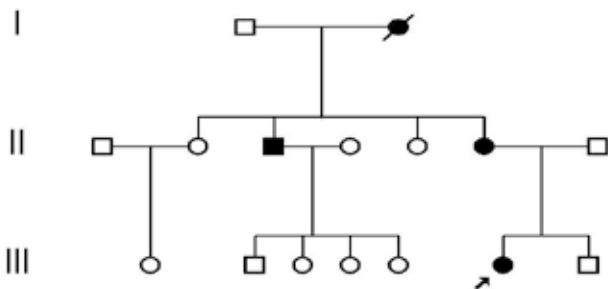


Fig 23. Autosomal dominant family tree.
Affected cases are shaded.

Autosomal recessive.

Albinism – lack of melanin pigment, may manifest as a pink coloured iris (figure 13). Several metabolic diseases produce characteristic iris findings with the mucopolysaccharidoses producing a build up of mucopolysaccharide within the cornea making the iris appear cloudy (figure 14). Enzyme replacement therapy started early will improve lifespan. Cystinosis may cause crystals to build up in the overlying layers, as does Wilson disease with abnormal copper metabolism. Characteristic Kayser-Fleischer rings (figure 15) may be detectable and treatment initiated. Patients with osteogenesis imperfecta (brittle bone disease) may have thin sclerae and this may show around the iris (figure 16), particularly in the more severe autosomal recessive types, or sometimes in the more common later onset autosomal dominant type. The rare ataxia disorder ataxia-telangiectasia – causing early unsteadiness with radiosensitivity, and immune problems, may present with childhood unsteadiness, and telangiectasia around the iris (figure 17), rather than just hyperaemic blood vessels at the periphery of the eye as may be normal or due to irritation or trauma. Iris hypoplasia may occur in a syndrome of immunodeficiency and autoimmunity associated with STIM1 mutations.

X-Linked (Sex-linked recessive)

Sex linked recessive disorders usually only affect males as females have two X chromosomes (46XX karyotype) and males one X chromosome and one Y chromosome (46XY). Mutations involving one X chromosome therefore are masked by the corresponding normal X in most females so the majority of female carriers may have no or markedly

reduced signs, unlike males who have no normal X as the Y chromosome generally has different genes from the X chromosome. Lowe syndrome – (oculocerebrorenal syndrome) – a disorder causing renal abnormalities and lenticular cataract in males (figure 18, and minor lens opacities in carrier females, shows the variation in X-linked disorders (figure 19). Similarly X-linked cataract is more severe in males with minor lens opacities sometimes visible in female carriers on close ophthalmic investigation (figure 20).

DEVELOPMENTAL DISORDERS

Some conditions may have a genetic basis not yet recognised. Epibulbar dermoids – white-grey fleshy overgrowths on the cornea - may occur in Goldenhar syndrome (oculoauriculovertebral dysplasia – heart, skeletal and facial abnormalities) and overgrow the lens (figure 21). Similarly a pterygium may occur with excess sun exposure or may be a feature of some rare genetic diseases. Rieger anomaly - a small outer segmental iris defect caused by abnormal cleavage of the anterior chamber, is mainly sporadic (figure 22), but autosomal dominant and chromosomal anomalies may be a cause. Teratogens may cause abnormal development of the eye during pregnancy, and include infections causes such as fetal varicella, and drug exposure such as anti-epileptic drugs, and also alcohol. Careful examination of an infant may give a clue to the cause of problems in a baby, and may also reveal undisclosed drugs taken during the pregnancy.

DIAGNOSIS AND MANAGEMENT

Genetic testing for mutations in the appropriate gene can be carried out in an affected case and if a mutation found, will allow predictive (presymptomatic) gene testing for single gene disorders for autosomal dominant disorders, or for carrier testing in autosomal recessive or X-linked diseases. This can help patients determine the exact risk and seek early diagnosis which may assist in treatment or prevention of complications in other organ systems. For example in the pedigree in figure 23, the shaded members are affected with medullary thyroid cancer. The arrowed proband (the first family member that draws the family to the attention of the clinician – often an affected member) was tested for mutations in the RET gene causing medullary thyroid cancer in which the rare type 2B can manifest with tongue neuromas and prominent corneal nerves on close ocular examination. Having identified the mutation, other at risk family members can be offered genetic testing and either given definitive reassurance if normal, or appropriate preventative surgical treatment such as early thyroidectomy or biochemical screening using serum calcitonin if mutation carriers wish.

CONCLUSIONS

Early clinical diagnosis of genetic disorders can allow accurate advice to be given to families and molecular genetic testing may allow better management and treatment options in patients. A brief examination of the iris may give a clue to diagnosis.

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