The Axenfeld syndrome and the Rieger syndrome

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SUMMARY A family is reported in which both the syndrome of Axenfeld and the eye malformations of the syndrome of Rieger occur, indicating that both may be expressions of the same gene. We also review the associated anomalies already reported, emphasise their high incidence, suggest that these are not accidental associations, and propose some possible explanations for the high incidence.

The Rieger syndrome is caused by an autosomal dominant gene which produces malformations of the anterior chamber of the eye and the teeth. Though a wide spectrum of additional malformations is found, they form no recognisable pattern and so their association is considered to be accidental (Alkemade, 1969). The Axenfeld syndrome consists of two of the three major eye malformations found in the Rieger syndrome (Table and Fig. 1) and it is also produced by an autosomal dominant gene. It has been suggested (Hoskins and Shaffer, 1972) that the two syndromes may be different expressions of the same gene. The purpose of this paper is to report a family who support this suggestion. It will also review the associated anomalies already reported, emphasise their high incidence, suggest that they may not be accidental associations, and propose possible explanations for the high incidence.

The Axenfeld and Rieger eye malformations are components of the anterior chamber cleavage group of anomalies, as defined by Reese and Ellsworth (1966).

Table Anterior chamber cleavage malformations

<table>
<thead>
<tr>
<th>Posterior embryotoxon</th>
<th>Axenfeld syndrome</th>
<th>Rieger syndrome</th>
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<tbody>
<tr>
<td>Prominent Schwalbe ring</td>
<td>Prominent Schwalbe ring; iris strands to Schwalbe ring and trabeculum</td>
<td>Prominent Schwalbe ring; iris strands to Schwalbe ring and trabeculum; hypoplasia anterior iris stroma</td>
</tr>
<tr>
<td>No symptoms</td>
<td>± Glaucoma</td>
<td>± Glaucoma</td>
</tr>
<tr>
<td>Occasionally results from autosomal dominant gene</td>
<td>Autosomal dominant gene</td>
<td>Autosomal dominant gene</td>
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</tbody>
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The anterior chamber cleavage anomalies have been classified by Waring et al. (1975) as designated in the Table and Fig. 1. (Definitions of anterior chamber cleavage anomalies vary; we have used the terminology of Duke-Elder, 1964.) Schwalbe's ring is the junction of Descemet's membrane and the trabecular meshwork. It is a whitish ridge with a central core of collagen fibres, which can be seen with a gonioscope and slit lamp. It is prominent in 15% of the normal population and is then referred to as posterior embryotoxon. The Axenfeld eye malformations con-
sist of a prominent Schwalbe ring with attached iris strands. The Rieger eye malformations consist of these two defects plus hypoplasia of the iris stroma. About 50% of children with the syndromes of Axenfeld or Rieger develop glaucoma, that is, the angle anomalies may interfere with the removal of intraocular fluid.

In the published reports, the term 'Rieger anomaly' is used to describe the eye malformations; when the teeth are also involved, the condition is called the syndrome of Rieger. In this paper we have avoided the use of the term 'Rieger anomaly' because of the recommended nomenclature of morphological defects (Smith, 1975). It is recommended that the term malformation be used for primary structural defects and that the term syndrome be used for a recognised pattern of malformations presumably having the same aetiology. In this paper instead of using the term Rieger anomaly, we use 'Rieger eye malformations'.

A wide variety of ocular defects may be associated with those that constitute the syndrome of Rieger (Alkemade, 1969). There may be heterochromia, aniridia, coloboma of the iris, persistent pupillary membrane, displaced pupil, more than 1 pupil, distortion of the shape of the pupil, conical opacities, lens defects (cataract, subluxation, coloboma), conjunctival xerosis, blue sclera, choroidal hypoplasia, and retinal detachment. Hyaline membranes have been described (Falkenstein and Henkind, 1973).

The tooth anomalies (Alkemade, 1969) consist of anodontia vera, microodontia, abnormally shaped teeth, and abnormally implanted teeth.

Alkemade (1969) pointed out that some patients with the Rieger syndrome have distinctive facies, consisting of maxillary hypoplasia, telecanthus, and a broad flat nasal root. A large variety of other malformations has been reported in patients with Rieger's syndrome. Hand malformations include arachnodactyly (Delmarcelle et al., 1958), polydactyly (Delmarcelle et al., 1958), camptodactyly (Delmarcelle et al., 1958; Collier, 1962; Frandsen, 1963; Levy et al., 1973), clinodactyly (Collier, 1962; Breebaart, 1966; Schmidt-Redemann and Vogt, 1976), short middle phalanges (Frandsen, 1963), hypoplastic metacarpals (Kittel, 1956; Henkes, 1965), hallux valgus (Forsius, 1964), and short thumb (Schmidt-Redemann and Vogt, 1976). Feet anomalies include short metatarsals (Frandsen, 1963), short toes (Lemmingson, 1961), and polydactyly (Delmarcelle et al., 1958). A wide variety of other abnormalities has been reported. These include cardiovascular malformations (Falls, 1949; Rossetti, 1952; Delmarcelle et al., 1958; Zygulska-Machowa, 1964; Haye and Blanck, 1965; Alkemade, 1969; Schmidt-Redemann and Vogt, 1976), funnel chest (Gassler and Berthold, 1960), cleft lip and/or palate (Delmarcelle et al., 1958; Forsius, 1964), cryptorchidism (Kittel, 1956; Gassler and Berthold, 1960), deafness (Falls, 1949; Callahan, 1956; Forsius, 1964; Forsius and Eriksson, 1964; Levien, 1966; Wolkowicz et al., 1971), abnormal ears (Lemmingson, 1961; Collier, 1962; Gassler and Berthold, 1960; Crawford, 1967; Summitt et al., 1971), hernia (Braendstrup, 1948; Crawford, 1967; Alkemade, 1969; Feingold et al., 1969), hip dislocation (Breebaart, 1966), hydrocephalus (Saba, 1927; Delmarcelle et al., 1958; von Noorden and Baller, 1963), small kidneys (Delmarcelle et al., 1958), kyphosis and/or scoliosis (von Grosz, 1940; Lemmingson, 1961; Crawford, 1967; Nenquin-Klaassen and Brihaye-van Geertruyden, 1959), mental retardation (Niederegger, 1920; Kittel, 1956; Collier, 1962; Gassler, 1960; Forsius, 1964; Alkemade, 1969; Summitt et al., 1971; Schmidt-Redemann and Vogt, 1976), myopathy (Kittel, 1956; Busch et al., 1960; Summitt et al., 1971), short stature (Braendstrup, 1948; Falls, 1949; Crawford, 1967; Alkemade, 1969; Feingold et al., 1969; Summitt et al., 1971; Nenquin-Klaassen and Brihaye-van Geertruyden, 1959), growth hormone deficiency (Sadeghi-Nejad and Senior, 1974), skin and/or hair anomalies (Sivasubramaniam and Hoole, 1955; Kittel, 1956; Gassler and Berthold, 1960; Alkemade, 1969), speech defect (Summitt et al., 1971) syringomelia (von Grosz, 1940), and goitre (Niederegger, 1920; Gassler and Berthold, 1960).

The practical importance of being aware of the wide spectrum of both the eye and the associated defects in the Rieger syndrome is that unless the eye is examined with a slit lamp and gonioscope, the characteristic prominent Schwalbe's ring, iris strands to Schwalbe's ring, and hypoplastic iris stroma may not be detected. As asymptomatic open angle glaucoma develops in about 50% of patients with the Rieger eye malformations, it is essential to be aware of the expressivity of this gene, so that blindness can be avoided.

Alkemade's extensive review of the literature covers 151 cases, and he adds several of his own patients. Of 159 cases, 49 have one or more 'occasional' anomalies, that is almost 30%.

Alkemade includes face and teeth anomalies as part of the spectrum of expressivity of the gene for the syndrome of Rieger, but he is of the opinion that all the other anomalies are accidental occurrences. We agree that simultaneous occurrence of some of the malformations, especially the more common ones, may be coincidental, but the high incidence of these 'occasional' anomalies makes it extremely unlikely that these are all 'accidents'.

One explanation for the high incidence of occa-

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1When Alkemade is given as a reference in the discussion of associated malformations we are referring to his patients, not the cases he cites from the literature.
ional anomalies is that we may be dealing not only with a wide spectrum of expressivity of a single gene but also with different genes. These genes may include some of the ‘occasional’ anomalies as part of the range of their expressivity. Indeed, several syndromes have already been reported which may include the Rieger eye malformations. Patients with Marfan’s syndrome may have the Rieger anomaly (Wachtel, 1966). Gorlin et al. (1975) described 2 brothers with short stature, hyperextensible joints, inguinal hernia, and delayed teething. The patient of Sensenbrenner et al. (1975) had many similar features. The patients described by De Hauwere et al. (1973) had dilatation of the cerebral ventricles, hypotonia, psychomotor retardation, hyperlaxity of the joints, and hip dislocation. The children described by von Noorden and Baller (1963) and Summitt et al. (1971) may belong to the same syndrome. Alkemade (1969) described patients with ocular albinism and the Rieger eye malformations. Hales (1968) reported a case of ocular albinism and Axenfeld’s syndrome.

There must be a developmental defect of the mesenchyme which produces the iris and angle structures in the Rieger eye malformations, and it is not surprising that a variety of syndromes involving mesenchyme could include these malformations. In addition it has been pointed out by several authors (Hagedoorn, 1937; Unger, 1956) that ectoderm is probably involved, possibly neural crest (Falls, 1949).

Another possible explanation for the high incidence of occasional abnormalities is that the gene interferes with the buffering systems (Waddington, 1957) involved in developmental stability. It is possible that the mutant gene might lower the threshold for an anomaly which is already close to the borderline of normality in a particular family. An attempt was made to find in published pedigrees of patients with the syndrome of Rieger and an ‘occasional’ anomaly, a family member who had the ‘occasional’ anomaly but not the syndrome of Rieger. This, however, was unsuccessful. We suggest that a special effort be made to record every family member with congenital malformations when a patient is found to have the syndrome of Rieger.

Study of intrafamily variation may be useful in elucidating the expressivity of the gene, or genes, which produce the Rieger malformations. This review was stimulated by the study of a family (Fig. 2) referred for genetic counselling because of congenital glaucoma in a newborn infant (IV.13) with the Rieger eye malformations. Both eyes had gross mesodermal dysgenesis of the anterior chamber. There was an

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**Fig. 2** Pedigree of family with syndromes of Axenfeld and Rieger.
The Axenfeld syndrome and the Rieger syndrome

obliquely oval pupil on the right and a very prominent Schwalbe’s line. The right eye had no increase in intraocular pressure, the left eye had glaucoma with enlarged cornea and corneal oedema, but with a normal optic nerve head. On gonioscopy the left eye showed more pronounced adhesions of the mid-periphery of the iris to Schwalbe’s line, almost as a 360° band, while in the right eye these adhesions were isolated. Both eyes showed mild iris hypoplasia.

The father (III.13) had normal anterior segments and ocular pressures. The mother (III.10) had the syndrome of Axenfeld. There was a grossly prominent Schwalbe’s line which was anteriorly displaced. The mid-periphery of the iris showed intermittent isolated adhesions all around the angle. The condition was symmetrical in both eyes, and the intraocular pressure was normal. The mother was born with the secundum type of atrial septal defect. All teeth were present with the exception of the upper third molars, which is a relatively common anomaly. The mother’s sister (III.11) also had Axenfeld syndrome. She had a bilateral posterior embryotoxon and bridging of the iris processes forward across the anterior chamber angle. The intraocular pressure was normal. She had ulnar deviation of the terminal phalanges of both third digits. Her teeth were normal.

The maternal grandmother (II.5) had a prominence of Schwalbe’s line on the temporal side of both eyes, and normal teeth.

Other interesting intrafamily variations have been shown. Pearce and Kerr (1965) describe a family in which a woman whose son and father both had Rieger’s malformation, had fine iris strands only, that is there was no posterior embryotoxon or hypoplastic iris. One affected member of the family described by Wolkowicz et al. (1971) had only mild iridal hypoplasia. A 7-year-old boy (Burian et al., 1954) with inherited Rieger’s anomaly had iris hypoplasia and posterior embryotoxon but no iris strands. Crawford (1967) reported a family consisting of a mother and 2 affected sons. The sons had dental anomalies but the mother’s teeth were normal.

In conclusion, we have shown that the Rieger eye malformations may be part of several different syndromes, that the expressivity of the gene has a wide range, and that there is a high chance of having associated malformations.

We would like to express our gratitude to Dr Leonard Pinsky for critical review of the manuscript.

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J Med Genet 1978 15: 30-34
doi: 10.1136/jmg.15.1.30

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