Genetic heterogeneity in Rieger eye malformation

E Legius, C E M de Die-Smulders, F Verbraak, H Habex, R Decorte, P Marynen, J P Fryns, J J Cassiman

Abstract

A three generation family with Rieger eye malformation sequence is described. No other abnormalities were present apart from the eye malformation. Linkage to EGF and D4S193 localised in 4q25 was excluded and this indicates that Rieger eye malformation is genetically different from typical Rieger syndrome with teeth and umbilical anomalies.

(*J Med Genet* 1994;31:340-341)

Department of
Clinical Genetics,
Maastricht, The
Netherlands
C E M de Die-Smulders

Netherlands
Ophthalmic Research
Institute, Amsterdam,
The Netherlands
F Verbraak

Centre for Human
Genetics, University
of Leuven, Campus
Gasthuisberg, O&N6,
Herestraat 49, B-3000
Leuven, Belgium
E Legius
H Habex
R Decorte
P Marynen
J P Fryns
J J Cassiman

Correspondence to
Professor Cassiman.

Received 18 June 1993
Revised version accepted for
publication 13 October 1993

Rieger syndrome (RS) is an autosomal dominant disorder affecting cleavage of the anterior segment of the eye (Rieger eye malformation sequence) as well as the development of teeth and midfacial structures.¹ This results in iris hypoplasia, strands running from the iris to the posterior surface of the cornea, posterior embryotoxon, glaucoma in 50% of patients, hypodontia, abnormal teeth, and midfacial hypoplasia. Redundant periumbilical skin is also an important feature.

Until recently the chromosomal localisation of RS was uncertain. Probable linkage of anterior segment mesenchymal dysgenesis to the MNS blood group on 4q has been reported.² Five patients with small deletions in the 4q23-26 region and Rieger syndrome have been identified,³⁻⁷ and more recently definite linkage to markers from the same chromosomal region was reported in three Rieger syndrome families.⁸ A maximum lod score of 4.36

was obtained for D4S193 at 0% recombination. RS has also been linked to the epidermal growth factor (EGF) locus, and although a recombinant was identified EGF remains a candidate gene for RS.

In an attempt to confirm these linkage data we performed molecular studies on 19 members of a three generation Dutch family (figure) with typical Rieger eye malformation sequence, hypertelorism, and maxillary hypoplasia. All members were carefully examined clinically and ophthalmologically. Anomalies of the anterior chamber of the eye were present in all patients. Expression was variable, ranging from iris hypoplasia, iris strands, and uncomplicated glaucoma arising at adult age to congenital buphthalmos. No teeth anomalies or umbilical changes were present in affected persons.

Using the polymerase chain reaction (PCR), two short tandem repeat polymorphisms on chromosome 4q, EGF⁸ and D4S193,⁹ were amplified from genomic DNA. The results are summarised in the figure. It is clear from these data that neither of the two markers segregate with the disease in this large family.

Statistical analysis of the data is shown in the table, and a region of 9 cM was identified on both sides of each of the two markers with a lod score lower than -2, excluding linkage to this region in this family. Lowering the value of the penetrance only extended the region with a two point lod score lower than -2. These data exclude linkage to the same region that showed strong linkage to RS in previously reported families. This may indicate that Rieger eye malformation with maxillary hypoplasia and hypertelorism but without teeth or umbilical anomalies is genetically different from typical RS with hypodontia or umbilical abnormalities or both. Heterogeneity in this type of eye malformation has to be taken into account in genetic counselling, especially if definite linkage to markers on 4q cannot be established within the family examined.

Various other chromosomal abnormalities have been reported in association with a Rieger-type of eye anomaly^{13,14} and are candidate regions for other forms of dominantly inherited Rieger eye malformation sequences, with or without hypodontia.

This investigation was supported by a grant "Geconcerteerde Acties - Ministerie voor Onderwijs" from the Belgian Government and by a grant from the Interuniversity Network for Fundamental Research (IUAP, 1991-1995) from the Belgian government. Peter Marynen is an "Onderzoekseider" of the "Nationaal Fonds voor Wetenschappelijk Onderzoek", Belgium.

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Pedigree of the three generation family with Rieger eye malformation syndrome. The upper marker underneath each subject represents the tetranucleotide repeat polymorphism in EGF, the lower marker is a dinucleotide repeat at D4S193. For each short tandem repeat one of the PCR primers was conjugated with fluorescein isothiocyanate (FITC), and PCR fragments were separated by electrophoresis on an automated sequencing device (ALF Pharmacia).

Two point lod scores between RS and EGF and D4S193 at different recombination fractions. Data were analysed using MLINK from the LINKAGE package,¹⁰ with a penetrance of 1 for RS. Since all subjects in this three generation family were completely typed we could assume the same allele frequency for the different alleles^{11,12} (an exact allele frequency for these markers is not available). Linkage of RS to each of the two short tandem repeat markers is excluded, but on the other hand both markers segregated perfectly with each other, and a maximum two point lod score of 3.9 was obtained between EGF and D4S193 at 0 recombination.

θ	0.010	0.020	0.030	0.040	0.050	0.060	0.070	0.080	0.090
EGF	-5.614	-4.431	-3.749	-3.272	-2.907	-2.613	-2.369	-2.160	-1.979
D4S193	-5.614	-4.431	-3.749	-3.272	-2.907	-2.613	-2.369	-2.160	-1.979

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