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.

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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. 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 periubminal 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. Five patients with small deletions in the 4q23-26 region and Rieger syndrome have been identified, and more recently definite linkage to markers from the same chromosomal region was reported in three Rieger syndrome families. 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 macrpylhoplasia. 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, EGF and D4S193, 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 and are candidate regions for other forms of dominantly inherited Rieger eye malformation sequences, with or without hypodontia.

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 fluorescent isothiocyanate (FITC), and PCR fragments were separated by electrophoresis on an automated sequencing device (ALF Pharmacia).

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Two point lod scores between RS and EGF and D4S193 at different recombination fractions. Data were analysed using MLINK from the LINKAGE package,2 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 alleles3-12 (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.

<table>
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<th>Marker</th>
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<th>0-030</th>
<th>0-040</th>
<th>0-050</th>
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<th>0-070</th>
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<td>3.749</td>
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<td>2.907</td>
<td>2.613</td>
<td>2.369</td>
<td>2.160</td>
<td>1.979</td>
</tr>
<tr>
<td>D4S193</td>
<td>5.614</td>
<td>4.431</td>
<td>3.749</td>
<td>3.272</td>
<td>2.907</td>
<td>2.613</td>
<td>2.369</td>
<td>2.160</td>
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</tr>
</tbody>
</table>

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