Stargardt’s disease is not allelic to the genes for neuronal ceroid lipofuscinoses

Sylvie Gerber, Sylvie Odent, Anne Postel-Vinay, Nicolas Janin, Jean-Louis Dufier, Arnold Munnich, Jean Frezal, Josseline Kaplan

Abstract
Stargardt’s disease is an autosomal recessive condition characterised by a rapid and bilateral loss of central vision at around 7 to 12 years, with typical changes in the macular and perimacular region. It is one of the most frequent causes of macular degeneration in childhood and accounts for 7% of all retinal dystrophies. Considering that inclusions of lipofuscin-like substances are observed in retinal pigmentary cells of patients with Stargardt’s disease on the one hand, and that the early symptoms of neuronal ceroid lipofuscinoses (CLN3) are suggestive of Stargardt’s disease on the other hand (age of loss of visual acuity, appearance of the fundus), we decided to test allelism of Stargardt’s disease with the infantile (CLN1) and juvenile forms of neuronal ceroid lipofuscinoses (CLN3), which map to chromosomes 1p32 and 16p12-p11 respectively. Using highly informative microsatellite DNA markers in eight multiplex families, we were able to exclude Stargardt’s disease from the vicinity of the CLN1 and CLN3 loci. These results strongly reject the hypothesis of allelism of Stargardt’s disease with the neuronal forms of ceroid lipofuscinosis.

Patients
Twenty four affected persons and 42 relatives belonging to eight multiplex families (fig 1) were recruited in France. The minimal diagnostic criteria were: (1) sudden loss of visual acuity between 7 and 12 years of age; (2) ophthalmoscopic evidence for alteration of the macula; (3) normal appearance of the peripheral retina and normal calibre of retinal vessels with no pigmented bone spicules; (4) typical visual field showing a central scotoma; (5) fluorescein angiography showing the “dark choroid” effect; (6) abnormal colour vision showing hypochromia (4); (7) finally, normal or abnormal photopic ERG. The minimum criteria for inclusion in the study were families with at least two affected children of either sex born to healthy parents.

Results and discussion
Hypervariable microsatellites linked to the CLN1 and CLN3 gene loci on chromosomes 1 and 16 were recruited in French families. We tested allelism of Stargardt’s disease with the infantile (CLN1) and juvenile forms of neuronal ceroid lipofuscinoses (CLN3), which map to chromosomes 1p32 and 16p12-p11 respectively, especially as the early symptoms of CLN3 are suggestive of Stargardt’s disease (age of loss of visual acuity, appearance of the fundus). Here, we show that Stargardt’s disease is not linked to either locus.

Figure 1 Families with Stargardt’s disease.
Pairwise lod scores between Stargardt's disease gene and markers on chromosomes 1p32 and 16p12-16cen

<table>
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<th>Probe</th>
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<th>0-05</th>
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<th>0-2</th>
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<td>D1S255</td>
<td>-x</td>
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<td>D1S232</td>
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<tr>
<td>AFM12oxd4</td>
<td>D1S209</td>
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<td>-4.58</td>
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<td>-0.27</td>
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<tr>
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<td>D16S410</td>
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</table>

1p32 and 16p12 respectively were chosen from the Genethon linkage map on the basis of their informativeness, at an average genetic distance of θ = 0·1 (table). The orders:

and

were previously established by analysis of CEPH reference families (J Weissenbach, personal communication). Genotyping was carried out as previously described and linkage analysis was performed using the MLINK and LINKMAP options of the 5.1 version of the LINKAGE program. Negative lod score values with probes AFM260zg5, AFM159ye9, and AFM120xd4 at loci D1S255, D1S232, and D1S209 were obtained for each family and the combined families, excluding the Stargardt gene from close proximity to the CLN1 gene on chromosome 1p32 (table). Multipoint analysis excluded the Stargardt gene from a large area (64·3 cM) including the CLN1 locus on the short arm of chromosome 1p (fig 2A). Similarly, negative lod score values were obtained with probes AFM159yb6, AFM049xd2, AFM025yg9, and AFM161wl1 at loci D16S410, D16S403, D16S401, and D16S409 respectively, excluding the disease gene from the vicinity of the CLN3 gene (table, fig 2B).

The present study excludes the Stargardt gene from close proximity to the CLN1 and CLN3 genes in eight informative families and strongly rejects the hypothesis of allelism of Stargardt's disease with the neuronal forms of ceroid lipofuscinoses.

We are grateful to Jean Weissenbach and Alain Vignal from Genethon for helpful discussion and preliminary information on unpublished polymorphic DNA markers. We thank Monique Poussette for her help in preparing this manuscript. This study was supported by Association Francaise contre les Myopathies (AFM), Association Francaise Retinitis Pigmentosa (ARFP), and Institut Electrique Sainte.