Graefe's Arch Clin Exp Ophthalmol (1999)
237:387–393

CLINICAL INVESTIGATION

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Wagner vitreoretinal degeneration with genetic linkage refinement on chromosome 5q13-q14

Received: 30 June 1998
Revised version received: 5 October 1998
Accepted: 6 October 1998

Partially presented at the joint 20th Meeting of the Club Jules Gonin and 29th Annual Scientific Session of the Retina Society, Bern, Switzerland, 9–13 September 1996

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Abstract ● Background: It has been previously described that Wagner disease is linked to chromosome 5q13-q14. This study was carried out to describe the ophthalmological aspects and report the results of genetic linkage analysis in a large pedigree affected by Wagner disease.
● Methods: Fourty members of one same family agreed to be examined. ● Results: Twenty patients presented vitreoretinal degeneration in both eyes without any extra-ocular abnormalities. In young patients, visual acuity was usually normal after correction of frequent mild myopia. Presenile cataracts progressed by the third decade and required removal for visual rehabilitation. The primary disorder involved an abnormal vitreous. A few avascular vitreous bands were usually the only optical feature in the mostly empty vitreous cavity. A circumferential vitreous condensation formed in contact with the retina on many spots. Less common retinal findings included retinal detachment, abnormal retinal pigmentation, progressive atrophy of the RPE simulating choroideremia and lattice degeneration. Genetic analysis revealed a highly significant linkage (lod score >5.0) between the disease and 10 markers of the chromosome 5q13-q14 region. Two recombination events allowed us to refine the linked interval to 20 cM between the D5S650 and D5S618 markers.
● Conclusion: Ophthalmological aspects of Wagner's disease appear to progress with age. Regular ophthalmological examination is important for detecting retinal abnormalities. The gene involved in Wagner's disease lies in a 20 cM interval on chromosome 5q13-q14.

Introduction

Hereditary vitreoretinopathies are characterized by an abnormal-looking vitreous gel and associated retinal changes. Hans Wagner, in 1938, described an inherited vitreoretinal disease in a Swiss family [24]. This family was regularly followed up [2, 17], and the last clinical analysis was carried out by Graemiger et al. [12]. Features of this disease included autosomal dominant inheritance, vitreous pathology characterized by an almost empty vitreous cavity with avascular membranes, strands and veils, lattice degeneration of the retina, chorioretinal atrophy with loss of pigment epithelium, pre-senile cataracts and mild myopia. The disease could manifest from early childhood and showed a progressive clinical course.

Wagner disease shares some clinical features with Stickler syndrome [22]. These two diseases were long

considered to be the same entity presenting variable evolution and severity. However, there is an ophthalmological distinction: rhegmatogenous retinal detachments are less common (15%) in patients with Wagner disease [12] but occur in approximately 50% of patients with Stickler syndrome [14]. Another feature differentiating Stickler from Wagner disease is the progressive retinal changes, including atrophy of the retinal pigment epithelium and choriocapillaris. Electrophysiological and psychophysical examinations also help in this discrimination [12]. Moreover, unlike Stickler syndrome, there are no known systemic manifestations of Wagner disease.

Furthermore, molecular genetic studies have enabled the two diseases to be distinguished by virtue of a linkage on the long arm of chromosome 5q13-14 in the case of Wagner disease [5]. Mutations occur in the *COL2A1* gene on chromosome 12 in about two thirds of cases of Stickler syndrome [1, 3, 10, 25], whereas mutations in the *COL11A1* gene (chromosome 1p21) have been reported in other families [20, 21].

Accurate studies on large families suffering from Wagner disease are quite rare. The purpose of the present study is to analyze the clinical features and to identify the chromosome location of the gene involved in a single large French family affected with Wagner disease.

Materials and methods

Patients

The patients studied belong to a single large pedigree (Fig. 1). Of the 47 members of the pedigree who could be traced, five had died, 40 could be examined. All persons gave their informed consent prior to their inclusion in the study, and all procedures were performed according to the Declaration of Helsinki. A thorough medical history was obtained, with specific questions about retinal detachment, glaucoma, myopia, arthralgia or arthropathy, cleft lip or palate, hearing loss, cardiovascular abnormalities or other medical conditions. Otorhinolaryngological and orthopedic evaluations were performed to evaluate abnormalities of the palate, oropharynx, long bones and joints. All individuals underwent complete eye examination by the same ophthalmologist (J.C.Z.), including best corrected visual acuity, slit-lamp biomicroscopy, applanation tonometry, and dilated fundus examination. Particular attention was given to examination of vitreous morphology. In consideration of the wide clinical spectrum of Wagner disease, a patient was deemed affected by the disease if he/she had fibrillary condensations or avascular strands in an empty vitreous cavity. Electrophysiological and psychophysical tests were not performed in this family.

Genetic analysis

Thirty-nine individuals were analyzed. Genomic DNA was obtained from leukocytes [16]. The microsatellite markers were chosen from the chromosome 5 Genethon map [8], except the GT polymorphism of the human proteoglycan link gene (*CRTL1*) [13]. These markers were amplified by PCR in a 50-µl reaction mixture containing 100 ng of genomic DNA, 40 µM of each dNTP (dATP, dGTP, dCTP, dTTP), 50 mM KCl, 1.5 mM $MgCl_2$, 10 mM Tris-HCl pH 7.9 and 50 pmol of each primer. Amplification was carried out during 35 or 27 cycles of denaturation (94°C for 40 s) and annealing (55°C for 30 s). Then, a final elongation step (72°C for 2 min) was performed. Amplified products (markers: D5S2089, D5S1988, D5S424, D5S618, D5S644, D5S495) were denatured and electrophoresed on sequencing gels, transferred onto a nylon membrane and revealed with a specific (^{32}P)dCTP primer labelled using terminal deoxnucleotidyltransferase or using a peroxidase-labelled poly-AC probe detected by chemiluminescence [23]. For markers D5S672 and D5S2029, (*CRTL1*) GT repeat and D5S459 amplified products were separated on 8% or 12% nondenaturant polyacrylamide gel and stained by silver.

Linkage analysis

Two-point and multipoint lod scores were calculated using the Linkage 5.1 program package [15] and Fastlink 3.0P [6]. Mlink two-point lodscores were calculated between the disease and each marker. We assumed that the disease was transmitted as a dominant trait with a gene frequency of 1/50 000. Three liability classes were assigned: age between 5 and 15 years, 50% penetrance; age between 15 and 30 years, 75% penetrance; age over 30 years, 98% penetrance. The number of alleles was set at equal to the observed number in the family and the allele frequencies were set equal to each other.

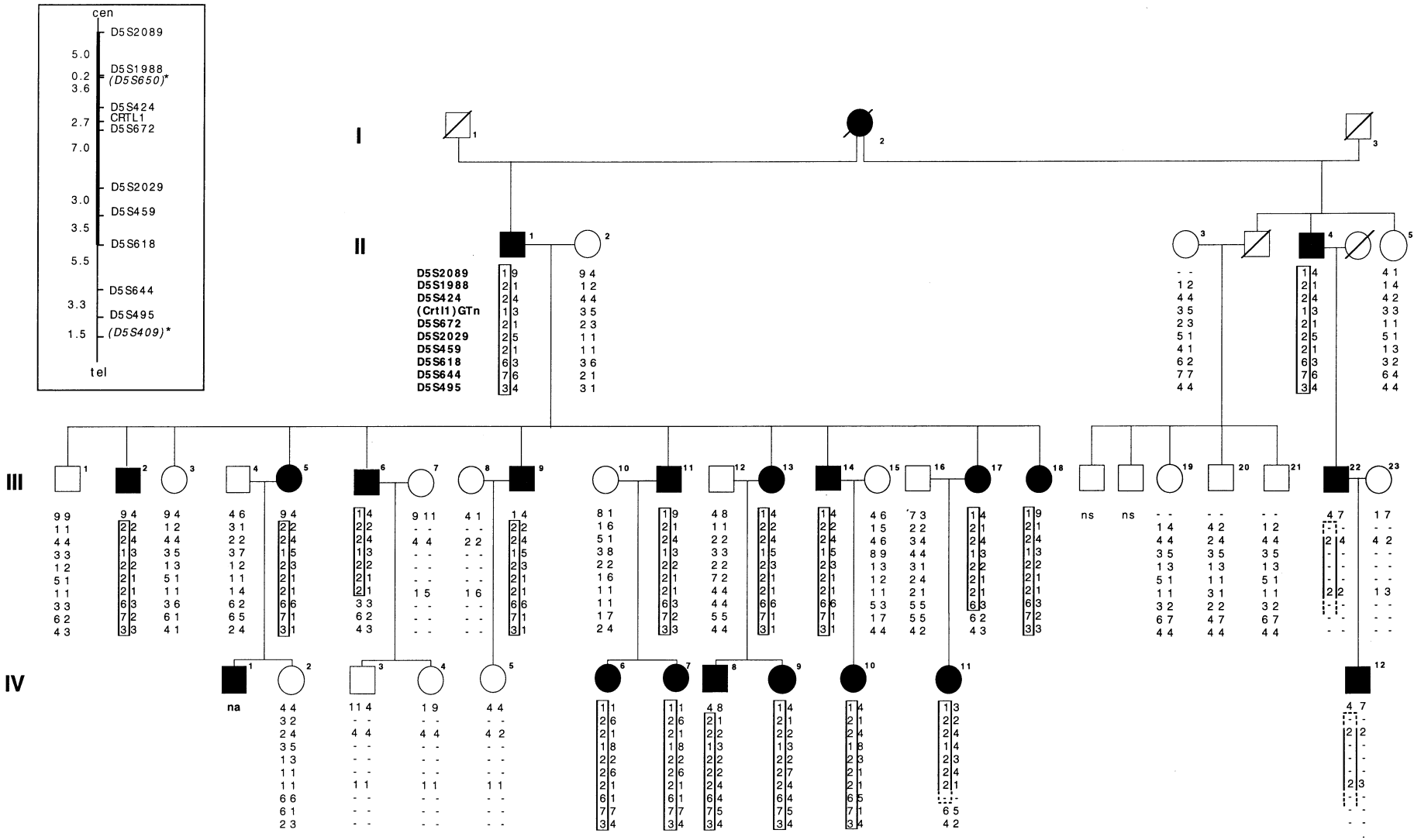
Results

Clinical findings

Of 40 members examined from the same family, 20 were identified as being affected with Wagner disease (Fig. 1). None of the remaining 22 members showed other signs suggestive of the disease, such as vitreous pathology, midperipheral chorioretinal atrophy, cataracts or retinal detachment. The age range of all members was 5–82 years (median 34 years). The mean age of affected members was 33 years, and the mean age of unaffected individuals was 36 years. Inheritance was autosomal dominant. Four consecutive generations were affected. No consanguineous marriage was reported.

Given the clinical definition of Wagner disease used in this study, vitreous pathology (peripheral avascular vitreous veils) was found in all 20 patients affected (7 of whom were younger than 15 years). This pre-retinal veil is usually located on the equator level and on average spreads over a 253°±19° circumference (Fig. 2a). In one patient, this veil was more posterior and bordered the op-

Fig. 1 Pedigree of the family and haplotype for markers on chromosome 5. *Solid symbols* Affected members, *ns* members who were not examined. The genotypes for the 10 tested markers on chromosome 5 are given below each analyzed individual. The haplotype linked to the disease is *boxed*. Only three markers (D5S2089, D5S424 and D5S459) were analyzed in the most recently investigated individuals (III-7, -8, -22, -23; IV-3, -4, -5, -12). Genotyping was not performed for individual IV-1. *Inset* Genetic distances between markers expressed in centimorgans [8]: * these two markers, not analyzed in the present family, delimit the previously reported linked interval [5]; *vertical bold line* linked interval in the present family ▶


cen
D5S2089
5.0
D5S1988
0.2
(D5S650)*
3.6
D5S424
CRTL1
2.7
D5S672
7.0
D5S2029
3.0
D5S459
3.5
D5S618
5.5
D5S644
3.3
D5S495
1.5
(D5S409)*
tel
I
II
III
IV
D5S2089
D5S1988
D5S424
(Crtl1)GTn
D5S672
D5S2029
D5S459
D5S618
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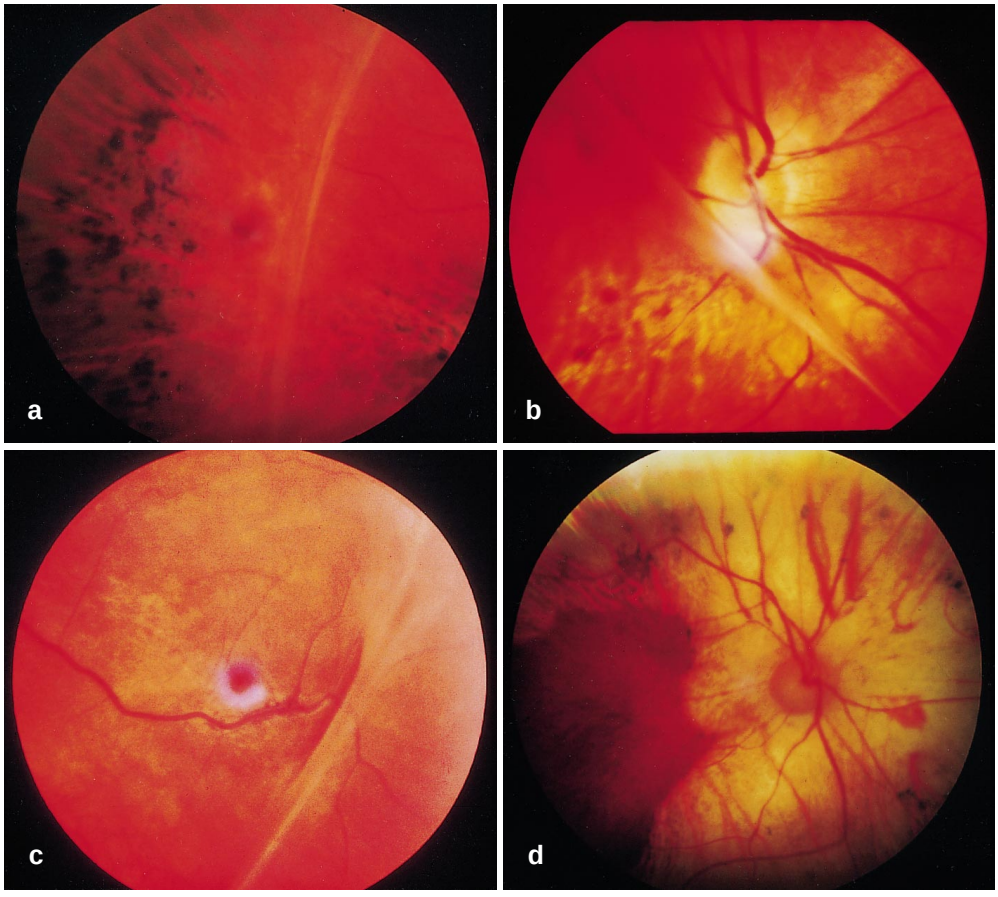

Fig. 2a–d Colour fundus photographs of affected patients. **a** Fundus photograph of a 44-year-old affected man (case III-9) shows annular preretinal vitreous condensation in the mid-peripheral retina. Pigment clumping is also noted in the periphery. **b** In this 45-year-old man (case III-6), the vitreous condensation bordered the optic nerve on the nasal side. **c** A 33-year-old affected woman (case III-18) with vitreoretinal adhesion and small tractional retinal detachment. **d** An 82-year-old man (case II-1) with advanced chorioretinal atrophy, mimicking choroideremia. Visual acuity was 20/100

Table 1 Prevalence of various features of Wagner disease

Feature	Age (years)				
	<30 No. of eyes (%)	30–40 No. of eyes (%)	41–50 No. of eyes (%)	51–60 No. of eyes (%)	>60 No. of eyes (%)
VA >20/100	12 (30)	8 (20)	6 (15)	0 (0)	0 (0)
VA ≤20/100	2 (5)	4 (10)	4 (10)	0 (0)	4 (10)
Cataract surgery	1 (2.5)	14 (35)	4 (10)	0 (0)	0 (0)
No cataract surgery	15 (37,5)	4 (10)	2 (5)	0 (0)	0 (0)
Tractional RD	0 (0)	2 (5)	1 (2.5)	0 (0)	0 (0)
Rhegmatogenous RD	2 (5)	1 (2.5)	0 (0)	0 (0)	0 (0)

VA: visual acuity, *RD:* retinal detachment

tic nerve on the nasal side (case III-6) (Fig. 2b). None of our patients showed posterior vitreous detachments or synchysis scintillans.

Chorioretinal changes are represented by a peripheral alteration of the pigmentary epithelium (7 patients, mean age 43 years), lattice degeneration (6 patients, mean age 45 years), and chorioretinal atrophy involving the retinal periphery and the posterior pole (2 patients, mean age 63 years) (Fig. 2c). Prophylactic photocoagulation was performed for retinal breaks without detachment (4 patients, mean age 43 years).

Rhegmatogenous retinal detachment had previously occurred in 3 patients (cases III-14, IV-8 and IV-12) at the age of 7, 11 and 30 years respectively (Table 1). Retinal detachment was due to flap tears and/or atrophic holes; the retina could be reattached by conventional scleral buckling procedures. In one eye, surgery was unsuccessful with consecutive amaurosis.

Table 2 Cataract surgery in 20 patients affected by Wagner disease

	Number of patients (%)	Mean age in years (range)
No cataract surgery	9 (45%)	19 (7–44)
Cataract extraction one eye	3 (15%)	28 (10–38)
Cataract extraction two eyes	8 (40%)	52 (39–82)

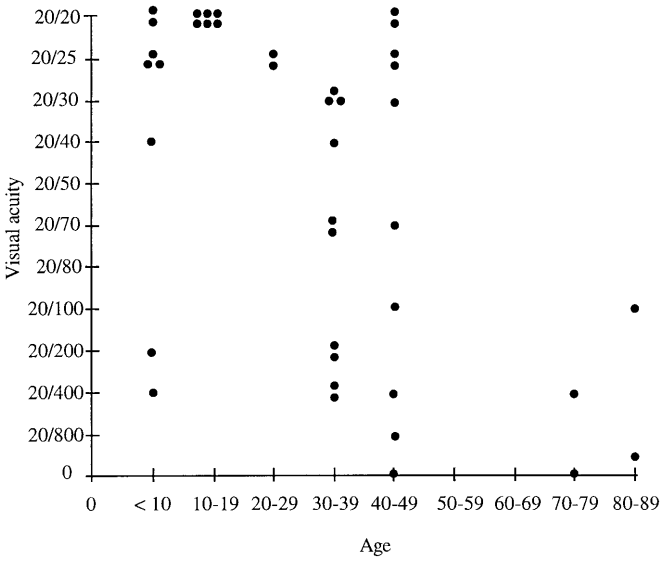

Fig. 3 Visual acuity at last examination (20 patients, 40 eyes)

Slight peripheral tractional detachment was observed in 3 patients (cases III-6, III-13 and III-14, at the age of 36, 36 and 45 years respectively) and seemed to be due to contraction of peripheral vitreoretinal adhesions (Fig. 2d).

Cataracts were observed and removed in 11 patients (55%). The surgery was bilateral in 8 patients. The mean age at surgery was 33 years (range 7–46 years) (Table 2).

No primary chronic open-angle glaucoma was observed. The few ocular hypertension cases were encountered in aphakic eyes only.

Refraction was performed in all 20 patients. We took into account the refraction before the appearance of a cataract in the patients that were operated on. The mean refraction was –5.75 diopters. Five patients (25%) presented severe myopia greater than –6 diopters. Visual acuity was usually normal in young patients and severely reduced in older patients (Fig. 3).

Linkage and refinement of the linked region on chromosome 5

On the basis of the results published by Brown et al. [5], who demonstrated that the involved locus in Wagner disease maps to 5q13-q14 between D5S650 and D5S409 markers, we investigated 10 markers spanning this interval in the family presented here (Fig. 1). A significant linkage was found with positive lod scores for a broad region (Table 3). The maximum two-point lod score was 5.6 (θ=0) for marker (*CRTL1*) GT repeat and the maximum multipoint lod score was 5.8 (θ=0) for markers D5S2029, (*CRTL1*) GT repeat and D5S459. Five recombinants were found with the most centrometric marker D5S2089, placing the disease gene telomeric to this marker. Two other key recombinants were identified: in patient III-17, a recombination was found between markers D5S644 and D5S618, and in patient III-6 a recombination occurred between D5S618 and D5S459. These two recombinants placed the disease locus centromeric to the D5S618 marker. Thus, our results indicate that the gene involved in Wagner disease is localized in a 20 cM region between D5S650 and D5S618.

Discussion

The common element in vitreoretinal heredodegeneration is undoubtedly the vitreous degeneration. In Wagner disease, the vitreous usually shows a liquefaction associated with veiling [2, 12, 17, 24]. We found this vitreous abnormality in 20 patients from a French family suffering from Wagner disease. These alterations of the vitreous gel can occur very early, and we observed them in a 7-year-old girl (case IV-10). Initially they were modifications of the vitreous structure which looked like an optically empty vitreous cavity. Secondarily an annular peripheral preretinal vitreous condensation can be seen which seems to be the hallmark of the disease. On average, this condensation spreads over three quarters of the eye circumference. A careful and frequent survey of the fundus is therefore indispensable because this vitreous ring shows strong

Table 3 Two-point lodscores between the disease and chromosome 5 markers. The most recently investigated individuals (III-7,-8,-22,-23; IV-3,-4,-5,-12) were not included in the two-point linkage analysis.

	Recombination fraction (θ)						
	θ=0	θ=0.01	θ=0.05	θ=0.1	θ=0.2	θ=0.3	θ=0.4
D5S2089	–4.600	–1.234	0.697	1.344	1.613	1.360	0.796
D5S1988	3.405	3.337	3.057	2.695	1.929	1.123	0.351
D5S424	4.785	4.712	4.415	4.031	3.192	2.222	1.083
(*CRTL1*)GTn	5.623	5.529	5.144	4.641	3.548	2.327	0.981
D5S672	4.664	4.584	4.255	3.824	2.892	1.854	0.722
D5S2029	5.495	5.405	5.036	4.554	3.507	2.337	1.046
D5S459	5.457	5.368	4.999	4.518	3.471	2.301	1.011
D5S618	–5.474	0.826	1.313	1.337	1.041	0.579	0.132
D5S644	–4.931	1.410	2.475	2.641	2.297	1.593	0.703
D5S495	–6.035	0.318	1.466	1.730	1.576	1.062	0.386

links with the retina. Effectively, in our series, three patients (15%) had a localized tractional retinal detachment which occurred much later (mean age 39 years) than the rhegmatogenous retinal detachment (mean age 16 years). The fact that the rhegmatogenous retinal detachment can occur very early justifies a yearly examination of the eye fundus from the age of 10 years. Retinal abnormalities within this group are more diversified and not particularly specific, which raises the question of differential diagnosis. A strong retinal pigmentation could suggest Goldmann-Favre's disease [9, 11]; temporal vitreoretinal tractions can also suggest family exudative vitreoretinopathy [7]. Electroretinography and angiography can help to establish accurate diagnosis (in the present family, electrophysiological and psychophysical data are not available). The examination of the whole family appears to be the most useful to make a good diagnosis.

Lattice degeneration needs no prophylactic treatment. A retinal break or hole, however, necessitates treatment by laser photocoagulation, because patients suffering from Wagner disease show an increased risk of rhegmatogenic detachment [12]. In fact, in our series, three patients (15%) presented a rhegmatogenous retinal detachment. The surgical treatment was conventional and required no intraocular surgery. In contrast, the risk of retinal detachment is about 50% in Stickler syndrome and in erosive vitreoretinopathy [4, 22].

Expressivity of Wagner disease is age dependent, and a progressive clinical course is well known for these patients [12]. It is true that in most cases, visual acuity and the lens are normal until the age of 30 years. Then cataract develops almost inexorably and all patients must undergo operation, on average at the age of 33 years. A few patients with severe myopia were operated by intracapsular extraction without any implant. We observed a regressive macular edema after intracapsular cataract extraction (case III-13). We never found any neovascular glaucoma or iris neovascularization after surgery, contrary to what is reported in the literature [12]. The best technique at present seems to be phacoemulsification with an implant in the capsular bag. Retaining the posterior capsule reduces vitreous mobility and consequently the pathological vitreoretinal tractions.

We never found any isolated ocular hypertension. In fact, the few cases of ocular hypertension observed were associated with aphakia. The usual description, given by Wagner, indicates only a rather moderate myopia. In our series, however, we found five patients (25%; cases II-1, III-13, III-14, IV-7 and IV-10) who had severe myopia of more than –6 diopters, necessitating regular examination of the fundus. Visual acuity progressively decreased with age. It can be seen that, before the age of 30 years, visual acuity was normal in most cases. Between the ages of 30 and 50 years, 65% of eyes presented visual acuity greater than 20/100. After the age of 50 years, visual acuity decreased and only 25% of the eyes had better than 20/100. This seems to be related to the extent and progression of chorioretinal degeneration illustrated by ERG degradation [12].

The various elements described in this family of 40 members enable us to confirm the clinical data for Wagner disease [2, 12, 17, 24].

In the present family, genetic linkage showed that the location of the gene responsible for Wagner disease was similar to that previously reported by Brown et al. [5] in a Wagner family and in an erosive vitreoretinopathy family. Two recombinants allowed us to refine the linked region to 20 cM. The cartilage link protein gene (*CRTL1*) and chondroitin sulfate proteoglycan 2 (*CSPG2*) were proposed as candidate genes [5]. In the mouse chromosome 13 syntenic region, the *Cspg2* gene lies close to the *Ccnb-1* gene (1.5 cM) and the *Hexb* gene (3 cM). In humans, the *CCNB* homologue gene is located outside the linked interval, whereas the *HEXB* homologue gene remains inside. Thus, the *CSPG2* gene cannot be excluded on the basis of our mapping data. However, as the *CSPG2* gene is expressed in various tissues (brain, tail, lung, spleen, heart, muscle and skin) [18, 19], it would be difficult to explain how an alteration in the *CSPG2* gene would only affect the vitreous. The *CRTL1* gene also remains in the linked interval. Brown et al. [5] reported that they analyzed 75% of the corresponding cDNA by SSCP and found no abnormality. At the present time, we have no strong arguments for other genes mapped in the human linked region or in the mouse syntenic region which could be good candidates. Despite the fact that the clinical aspect is different, the disease in an erosive vitreoretinopathy family is also linked to chromosome 5 [4, 5]. However, it is not yet possible to say whether these two diseases stem from different mutations in one single gene or from mutations in two different but tightly linked genes.

To sum up, this study demonstrates that different ophthalmological aspects of Wagner's vitreoretinal degeneration can be present. The vitreous abnormality is a very typical peripheral condensation. The other findings are extremely variable and appear to progress with time. In fact, visual acuity, usually normal in young patients, is severely diminished in older patients. Moreover, regular ophthalmological examination is very important for detecting retinal abnormalities and ensuring early prophylactic treatment. Genetic linkage reduces the chromosome location on the long arm of chromosome 5 to an interval of 20 cM. In the future, linkage analysis should help to find the molecular origin of this vitreoretinopathy and provide new insight into the pathogenesis of vitreous disease.

Acknowledgements This work was supported in part by the Association Française contre les Myopathies, the Centre National de la Recherche Scientifique (CNRS UMR5534), the Hospices Civils de Lyon, the Université Claude Bernard Lyon I and Chauvin Laboratory (Montpellier, France). We thank the members of the family for their participation. We also thank Jocelyne Kaplan, PhD, for constructive discussions and Marie C. Babron, RI, for her help in linkage analysis. Finally, we thank Serge Balter for photographic assistance (Médiathèque, Université Claude Bernard Lyon I).

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