

# A Novel Hereditary Developmental Vitreoretinopathy with Multiple Ocular Abnormalities Localizing to a 5-cM Region of Chromosome 5q13-q14

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**Background:** To undertake a clinical and molecular analysis of a previously unpublished kindred with a phenotypically distinct vitreoretinopathy characterized by associated ocular developmental abnormalities.

**Design:** Family genetic study.

**Participants:** A total of 23 members, both affected and unaffected, of 1 kindred with vitreoretinopathy.

**Method:** Individuals within the kindred were examined clinically and blood samples taken for DNA analysis. Genetic analysis was performed for the proximal region of chromosome 5q by means of polymerase chain reaction (PCR).

**Main Outcome Measures:** Detection of vitreoretinopathy and associated abnormalities.

**Results:** This novel, hereditary vitreoretinopathy, showing the classic features of vitreous pathology and early-onset retinal detachments, was associated with a variety of ocular developmental abnormalities, including posterior embryotoxon, congenital glaucoma, iris hypoplasia, congenital cataract, ectopia lentis, microphthalmia, and persistent hyperplastic primary vitreous. There were no associated systemic features. Genetic mapping with markers from the proximal region of 5q13-q14 showed linkage to a 5-cM region between the markers D5S626 and D5S2103.

**Conclusions:** The 5-cM region is within that implicated in the etiology of both Wagner and erosive vitreoretinopathies. This suggests that this novel condition may be allelic, refines the genetic mapping for vitreoretinopathies that map to 5q13-q14, and implicates a gene important not only in vitreous production but also in early ocular development. *Ophthalmology* 1999;106:2074-2081

The autosomal dominant vitreoretinopathies are characterized by abnormal vitreous development, a predisposition to myopia, and an increased risk of rhegmatogenous retinal detachment. The group includes conditions without extraocular features (e.g., Wagner syndrome MIM#143200)<sup>1</sup> and those associated with extraocular features such as deafness, cleft palate, and micrognathia (e.g., Stickler syndrome, MIM#108300).<sup>2</sup> To date, only the Stickler-type vitreoretinopathies have been characterized at the genetic level; the majority of pedigrees show mutations in genes encoding collagen macromolecules (COL2A1, COL11A1), which are important in the biogenesis and maintenance of extracellular matrices in the vitreous gel,

cartilage, and other tissues.<sup>3,4</sup> Those vitreoretinopathies described to date without systemic features have been mapped to a 35-cM region of chromosome 5q13-q14.<sup>5</sup>

With the exception of cataract, which is seen in both Stickler and Wagner syndromes, abnormalities of the anterior segment of the eye are not generally associated with vitreoretinopathy.<sup>6</sup> Here, a family with, until now, an undescribed autosomal dominant vitreoretinopathy manifests a range of coexisting pathologies in the eye. These include microphthalmia, persistent hyperplastic primary vitreous, congenital cataract, anterior segment dysgenesis, and congenital glaucoma and implicate the protein underlying the condition not only in vitreoretinal pathology but also in early ocular development.

Genetic analysis performed on this family with markers from the proximal region of 5q13-q14 shows linkage to a 5-cM region flanked by the markers D5S626 and D5S2103 (i.e., within that implicated in the etiology of both Wagner and erosive vitreoretinopathies).<sup>5</sup>

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## Methods

### Clinical Details

Members of the family W2, which has not been reported previously, were ascertained on the basis of a family history strongly

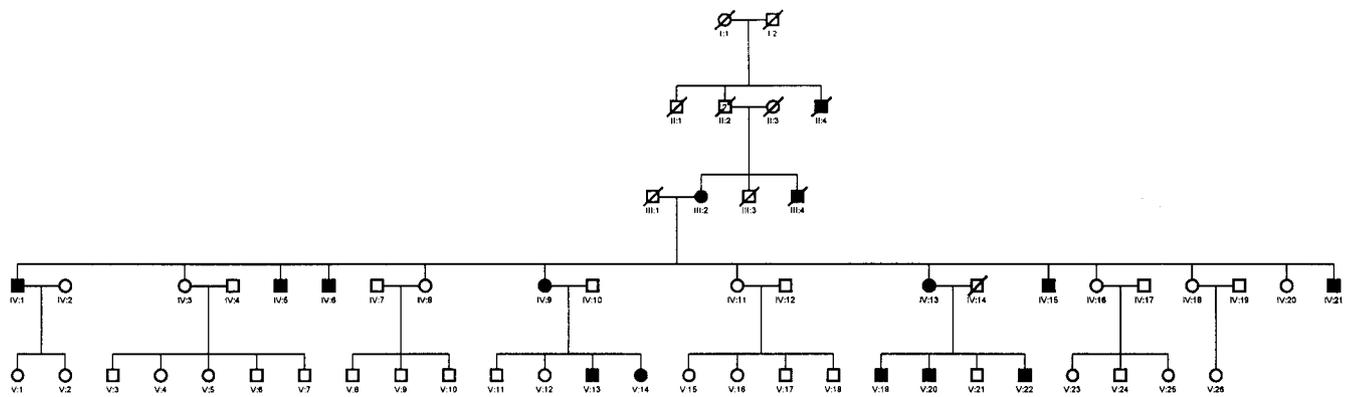


Figure 1. Pedigree of family W2.

suggestive of inherited vitreoretinopathy (Fig 1) and according to guidelines approved by the North–West Region Ethics Committee. A thorough medical history was obtained, and examinations were performed seeking evidence of arthropathy, cleft palate, hearing loss, cardiovascular abnormalities, or other medical conditions. Where possible, previous ophthalmic records were scrutinized, and family members underwent a complete eye examination, including slit-lamp biomicroscopy, applanation tonometry, and dilated fundus examination. Blood samples were obtained, and DNA was extracted using conventional methods.

### Polymerase Chain Reaction Genotyping

Microsatellite markers D5S1962, D5S626, CRTL1, D5S2094, D5S644, and D5S2103 were polymerase chain reaction amplified with the primers described elsewhere.<sup>7,8</sup> Microsatellite markers D5S1962, D5S626, CRTL1, D5S2094, D5S644, and D5S2103 were PCR amplified with the primers described elsewhere.<sup>7,8</sup> Standard PCR reactions were performed using 100 ng genomic DNA in a 20  $\mu$ l reaction volume containing 3.7 mM MgCl<sub>2</sub>, 67 mM tris–Cl [pH8], 166 mM (NH<sub>4</sub>)<sub>2</sub>SO<sub>4</sub>, 0.17 mg/ml BSA, 3 mM each dinucleotide triphosphate, 10 pmols of each primer and 0.1 iu of *Taq* polymerase (Gibco BRL). The samples were heated to 94°C for 5 minutes (denaturation). The samples were processed through the following conditions: 94° C for 50 seconds, 57° C for 50 seconds, 72° C for 50 seconds for 30 cycles, then finally heated to 72° C for 5 minutes. The amplified products were extracted with chloroform, run on an 8% polyacrylamide gel, and silver stained according to standard methods.

### Linkage Analysis

Linkage analysis was performed using the MLINK program and the genetic distances given by Dib et al.<sup>7</sup>

## Results

### Clinical Manifestations in Family W2

The family consisted of four affected generations (Fig 1) and, although the status (affected/unaffected) of one deceased individual (II-2, an obligate carrier) is unknown, there is nevertheless evidence for male–male transmission (II-2 to III-4) in prior generations, consistent with autosomal dominant inheritance. There was no evidence of consanguinity nor, in any family members

(affected or unaffected), of arthropathy, cleft palate, hearing loss, cardiovascular abnormalities, or other familial medical conditions.

All 13 affected patients had been diagnosed as such in the first decade of life; all 6 of these with a documented examination within the first 6 months of life showed signs of the disorder at that stage. The majority of affected individuals were severely visually handicapped. All affected adults had been registered blind, four with light perception only in one eye or no light perception in either eye. In generation V, two individuals (V-13 and V-14) who are 15 and 12 years of age, respectively, retain visual acuity of 6/18 and 6/24 in their better eye, respectively.

The range of ocular manifestations, both recorded in the past and confirmed at ascertainment, is summarized in Table 1. Developmental abnormalities included defects of organogenesis (microphthalmia) as well as anterior segment development (buphthalmos, iris hypoplasia, posterior embryotoxon) and lenticular development (cataract, lens subluxation; Figs 2A, B). A comprehensive and systematic evaluation of all eyes according to predetermined criteria was obviated by changes arising as a consequence of buphthalmos or by degenerative features (including phthisis bulbi) that had developed as a secondary consequence of retinal detachment where this had been untreated or unsuccessfully repaired. The lenticular opacities observed in two younger family members were heterogeneous in form: V-13 had multiple, bilateral wedge-shaped opacities (Fig 2B) similar to those seen in Stickler syndrome, while V-14 had bilateral opacities that were progressive and lamellar in distribution.

The condition carried classic features of an inherited vitreoretinopathy. Several patients showed the characteristic “optically empty” appearance of the vitreous gel; in other patients, fibrillary condensations were visible in the vitreous cavity as were abnormal vitreoretinal adhesions, particularly in the midperipheral and peripheral retina. Of the 13 affected individuals, 8 had a clear history of sudden reduction of vision secondary to retinal detachment in 1 or both eyes. Of the four detachments (in three patients) treated recently in our institution (V-13, V-14 [bilateral], and IV-21), the detachments were secondary to small atrophic retinal holes within peripheral degenerative latticelike patches or to tractional tears following posterior vitreous detachment and abnormal vitreous adhesion to focal areas of chorioretinal scarring. The retinas reattached with conventional scleral buckling or with closed intraocular microsurgery with gas tamponade or both. Before the detachments, the retinal appearance had been within normal limits (Fig 3A); pigmentary changes beneath the reattached retina represented pigment fallout from cryotherapy (Fig 3B) or reflected the chronicity of detachment (Fig 3C).

Table 1. Ocular Findings in Affected

Patient No.	Age (yrs)	Age at Onset	Associated Ocular Features	Age (yrs) of Retinal Detachment
III-2	72	<9 yrs	Childhood cataracts RE ectopia lentis	None documented
IV-1	48	Birth	Congenital cataracts RE childhood glaucoma	None documented
IV-5	46	Birth	RE childhood glaucoma	LE 20
IV-6	44	Birth	Blind LE in childhood Congenital cataracts	None documented
IV-9	42	Birth	Congenital cataracts Nystagmus	RE 11 LE 30
IV-13	38	Birth	Congenital cataracts	RE 34 LE None documented
IV-15	37	Birth	Congenital cataracts Blind RE from birth	RE None documented LE 13
IV-21	30	Birth	Congenital cataracts Bilateral ectopia lentis	RE 29 LE 14
V-13	15	Birth	RE microphthalmia Wedge-shaped cortical cataracts	RE None documented LE 9
V-14	12	2 mos	RE posterior embryotoxon Bilateral iris hypoplasia Congenital cataracts	RE 10 LE 7
V-19	20	<1 yr	RE microphthalmia RE persistent hyperplastic primary vitreous	RE None documented LE 10
V-20	14	Birth	RE congenital glaucoma, ectopia lentis, and posterior embryotoxon LE iris hypoplasia	None documented
V-22	12	Birth	Bilateral congenital glaucoma Bilateral posterior embryotoxon	RE 12 days LE None documented

VA = visual acuity; CF = count fingers; PL = perception of light; NPL = no perception of light; RD = retinal detachment; RE = right eye; LE = left eye.

The right eye of patient V-13 showed widespread intraretinal pigment migration in a circumscribed distribution (i.e., classic features of spontaneous retinal reattachment) (Fig 4A). These changes were first observed when she was 6 months of age and were therefore suggestive of congenital retinal detachment. At 12 days of age, the right eye of V-22 was also noted to have scattered pigmentation of attached retina and a healthy optic disc; the presence of a shallow accumulation of subretinal fluid in the extreme periphery again suggested that these retinal changes were the result of a congenital retinal detachment and spontaneous reattachment. Patient IV-1 showed a pale fundal appearance with evidence of intraretinal pigment migration in his remaining (left) eye when examined at 48 years of age (Fig 4B); the optic disc remained healthy and was not atrophic. He too had an area of subretinal fluid accumulation in the extreme superotemporal periphery. This, together with sparing of the superonasal periphery from pigmentary changes, is suggestive of spontaneous reattachment of a chronic detachment.

### Linkage Analysis in Family W2

On the basis of accepted criteria, exclusion was obtained for all candidate regions tested with the exception of the proximal region of chromosome 5q. Linkage was confirmed and the highest Lod score obtained, assuming penetrance to be 100%, ( $Z_{max} = 5.41$ ,  $\theta = 0$ ), was with the marker D5S2094 (Table 2). In view of the severe consequences and early

onset, a patient's normal ophthalmic examination, particularly with biomicroscopically normal vitreous architecture, at the age of 15 years was considered to be consistent with unaffected status.

Haplotype analysis revealed three multiply, informative recombination events in individuals IV-5, IV-20, and V-11, which define a critical region of interest of approximately 5-cM (Fig 5), placing the gene between the markers D5S626 and D5S2103. If it is assumed that the disease-linked haplotype is seen in individuals IV-1, IV-6, IV-21, V-13, V-14, V-19, and V-20, then a recombinant distal to D5S2103 in affected male IV-5 places this marker as the distal flanking marker of the disorder. A second distal recombination event in the unaffected individual IV-20 was seen just proximal to D5S644, which lies approximately 5 cM distal to D5S2103. Finally, in individual V-11, a recombination proximal to D5S2094 places DXS626 as the proximal flanking marker of the disease. V-11 is an unaffected 15-year-old male with no signs or symptoms of the disease and defines a proximal boundary for the critical region. The region flanked by the two markers is approximately 5 cM (Fig 6).

Analysis with the intragenic marker within the link protein (CRTL1) gene showed that affected female III-2 was uninformative (Fig 5). However, IV-9, the mother of the unaffected male V-11, was informative and showed that

## Individuals in Family W2

Retinal Status at Ascertainment	VA at Ascertainment	Other Comments
RE Attached LE no view RE Enucleated	RVA 2/36 LVA NPL RVA —	RE Widespread chorioretinal atrophy/retinal pigmentation LE Rubeotic phthisis with band keratopathy LE Pseudophakic, widespread intraretinal pigmentation sparing nasal periphery; healthy disc (see Fig. 4b)
LE Attached RE No view LE No view RE Attached LE No view RE No view LE Enucleated RE Attached LE Attached RE Attached LE Total RD RE Attached	LVA 2/36 RVA NPL LVA NPL RVA PL LVA NPL RVA NPL LVA — RVA 2/36 LVA 6/60 RVA PL LVA NPL RVA 1/60	RE Staphylomata, band keratopathy, nuclear sclerosis LE Phthisis RE Abnormal retinal pigmentation Nystagmus RE Phthisis LE Enucleated for secondary glaucoma Bilateral chorioretinal atrophy and retinal pigmentation RE Widespread chorioretinal atrophy/retinal pigmentation LE Phthisis RE Retinal detachment from tears related to focal chorioretinal scars: successful lensectomy, vitrectomy and gas
LE Total RD RE Attached LE Attached	LVA PL RVA 6/36 LVA 6/24	RE Abnormal retinal pigment seen at 6 mos (Fig. 4a) LE Rhegmatogenous detachment: successfully treated by buckle to tiny superotemporal break (Fig. 3c)
RE Attached	RVA 6/36	RE Rhegmatogenous detachment: successfully treated by buckle to close small temporal hole
LE Attached	LVA 6/18	LE Rhegmatogenous detachment: 2 operations (buckle followed by vitrectomy) for superotemporal break (Fig. 3a,b)
RE Not known LE Partially attached beneath silicone oil	RVA PL LVA CF	RE Blind from birth LE Traumatic lens subluxation and retinal detachment with preexisting high myopia.
RE Not known	RVA PL	BE Widespread retinal pigmentation noted at 6 mos and confirmed in LE at ascertainment
LE Attached RE No view	LVA 6/60 RVA PL	RE Superior localized detachment noted (12 days and 13 mos of age) with scattered pigment across remaining (attached) retina
LE Attached	LVA 2/60	LE Extensive chorioretinal degeneration with normal disc noted at birth; remains unchanged

CRTL1 is not recombinant and lies distal to the proximal boundary. Physical mapping information, as well as our own data (unpublished), places CRTL1 between D5S626 and D5S2103, which is within the critical region identified.

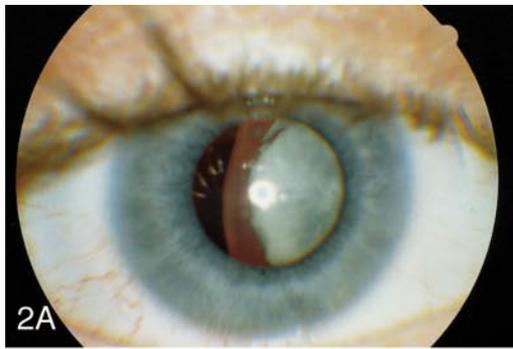
## Discussion

The inherited vitreoretinopathies show a narrow range of ocular abnormalities that are mainly confined to the posterior segment of the eye.<sup>9</sup> With the exception of cataract formation, abnormalities of the anterior segment are uncommon. A characteristic wedge-shaped, segmental cortical cataract is seen in approximately 40% of patients with Stickler syndrome,<sup>10</sup> cataract that increases with age is seen in Wagner syndrome,<sup>6</sup> and nasal lens “coloboma” with subluxation has once been reported in Stickler–Marshall syndrome.<sup>11</sup> In addition, there are reports of congenital glaucoma in occasional patients within families with vitreoretinopathy (including one patient from the extensive pedigree originally described by Wagner).<sup>6,12</sup> The family W2 presented here thus shows a unique form of vitreoretinopathy,

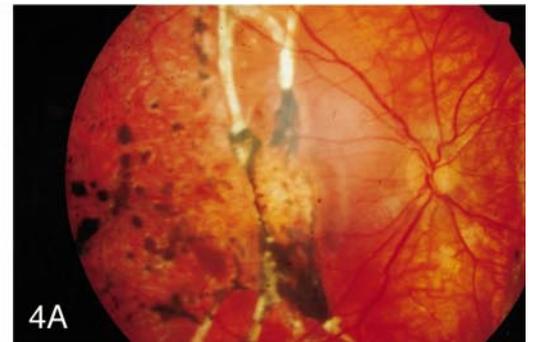
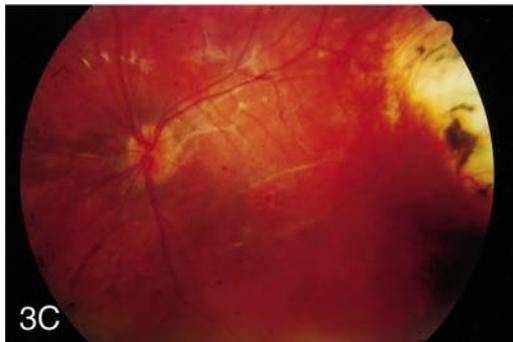
which we have termed a “developmental vitreoretinopathy” since it is consistently associated with other ocular defects. Such defects include abnormalities of ocular organogenesis (microphthalmia) as well as of early embryonic vitreous development (persistent hyperplastic primary vitreous), anterior segment development (posterior embryotoxon, iris hypoplasia, congenital glaucoma), and lenticular development (early-onset cataract and lens subluxation). Interestingly, although a range of various types of cataract was seen within the family, these included a patient (V-13) with multiple wedge-shaped cortical opacities identical to those seen in Stickler syndrome, suggesting a common pathogenic mechanism.

The primary vitreous is a vascular structure, the development of which is intimately associated with lens, zonule, and iris development. It is replaced during the second and third trimesters by the secondary (or adult) vitreous.<sup>13</sup> The findings presented here suggest that a disturbance of early vitreous development can have severe consequences for generalized ocular development. An alternative explanation may be that the defects represent abnormalities of a protein in which expression extends beyond the vitreous and pos-

**Figure 2.** Clinical features of developmental vitreoretinopathy (I): Lens. **A**, nasal subluxation of cataractous lens, patient IV-21, 32 years of age. **B**, wedge-shaped lens opacities, patient V-13, 13 years of age.



**Figure 3.** Clinical features post-acute rhegmatogenous retinal detachment, family W2. **A**, retina, left eye of patient V-14 at 7 years of age; acute temporal macula-off retinal detachment. **B**, retina, left eye of patient V-14 at 11 years of age; retina surgically reattached. Pigmentation visible between macula and disc represents "pigment fallout." **C**, retina, left eye of patient V-13 at 14 years of age; surgically reattached retina with oblique subretinal strands, indicating the chronicity of detachment. Temporal depigmentation after retinopexy.



**Figure 4.** Retinal features secondary to spontaneous reattachment of longstanding retinal detachment. **A**, retina, right eye of patient V-13 at 9 years of age, spontaneously reattached congenital retinal detachment, vertical white subretinal strands, and well-delineated intraretinal pigment migration and clumping temporally. Identical findings were visible at first examination at 6 months of age. **B**, montage of retina, left eye of patient IV-1 at 48 years of age; thinning of pigment epithelium and intraretinal pigment migration. The disc is pink. An area of nasal retina without pigmentary changes and well-demarcated from the abnormal retina is not seen. In the superotemporal periphery, a region of vitreous debris overlying a small, presumed residual, collection of subretinal fluid suggested that the pigmented retina represents spontaneous reattachment of a previous retinal detachment. There was no history of sudden alteration of vision. **C**, retina, left eye of unrelated patient (RB) shown as a control for comparison with **B**. This patient had a fully documented history of spontaneous reattachment of a rhegmatogenous detachment. In common with **B**, pigment epithelial attenuation, intraretinal pigment migration, and clumping are seen. The disc remains healthy pink, surrounded by a grayish peripapillary retinal cuff.

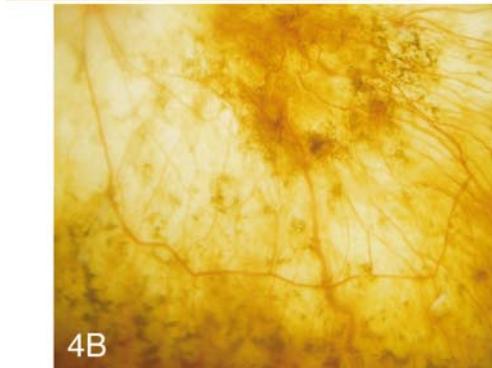
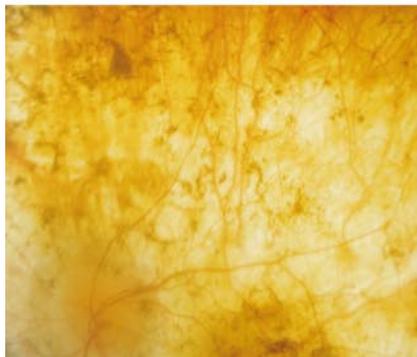


Table 2. Results of Two-point Linkage Analysis between the Disease Gene and Markers from 5q14.3

Marker	LOD Score for Family W2 at $\theta =$								$Z_{max}$	$\theta_{Max}$
	0	0.01	0.05	0.1	0.2	0.3	0.4			
D5S1962		3.33	3.71	3.59	2.97	2.11	1.03	3.71	0.05	
D5S626		2.74	3.15	3.08	2.57	1.81	0.87	3.15	0.05	
D5S2094	5.41	5.33	4.99	4.54	3.57	2.47	1.20	5.41	0	
CRTL1	2.10	2.07	1.95	1.78	1.42	1.02	0.55	2.10	0	
D5S2103		2.33	2.84	2.85	2.45	1.76	0.86	2.85	0.1	
D5S644		1.64	2.71	2.98	2.55	1.88	0.94	2.98	0.1	

terior segment. A precedent for the latter hypothesis is the demonstration of changes in scleral and anterior segment architecture in mice with mutations in the Type-II collagen gene.<sup>14,15</sup>

Previous observations of both Wagner syndrome and erosive vitreoretinopathy<sup>6,16</sup> have demonstrated progressive chorioretinal degeneration with RPE thinning and an associated reduction in retinal function affecting, in particular, scotopic ERGs. Because this has been shown in both conditions in the absence of retinal detachment, this represents strong evidence of a primary dystrophic process occurring within the retina. By contrast, most individuals in family W2 in whom there was prominent subretinal or intraretinal pigment migration had a history of, or circumstantial evidence for, prior retinal detachment. In patient V-13, for example, fundus examination revealed subretinal strands in addition to a peripheral anulus of intraretinal pigment migration (Fig 4A), while in IV-1 (Fig 4B) and V-22, the widespread chorioretinal disturbance was associated with a normal, healthy optic disc and a small area of (presumed residual) peripheral subretinal fluid accumulation. The findings in these eyes were indicative of spontaneous reattachment of a chronic retinal detachment (an example from a clinically well-documented and unrelated patient is seen in Fig 4C).<sup>17,18</sup> V-22 and V-14 were already fully expressed at

6 days and 6 months of age, respectively. The pigmentary changes of these features in individuals IV-6, IV-15, and V-20 (also evident by age 6 months) possibly suggest an analogous mechanism of early visual loss in these individuals as well. When combined with other evidence of early disruption of vitreous development, these changes suggest that here, and potentially in other inherited vitreoretinopathies, the dystrophic appearance of the retina, even when bilateral, can be secondary to early (even prenatal) vitreoretinal disturbance.

Previous studies have shown that Wagner syndrome and erosive vitreoretinopathy map to a 35-cM region of chromosome 5q13-q14.<sup>5</sup> Our results suggest linkage of the vitreoretinopathy in family W2 to the same region with refined mapping to a 5-cM region defined by the polymorphic markers D5S626 and D5S2103. A potential caveat must remain: the results assume full penetrance of the condition since individual V-11 is unaffected. He is 15 years of age and shows no signs or symptoms of the condition, including no biomicroscopic abnormality of vitreous architecture. By contrast, all six affected individuals who had been examined by the age of 6 months had shown clear signs of the condition, even at that stage.

There has been considerable debate over the clinical distinction between the Wagner and Stickler syn-

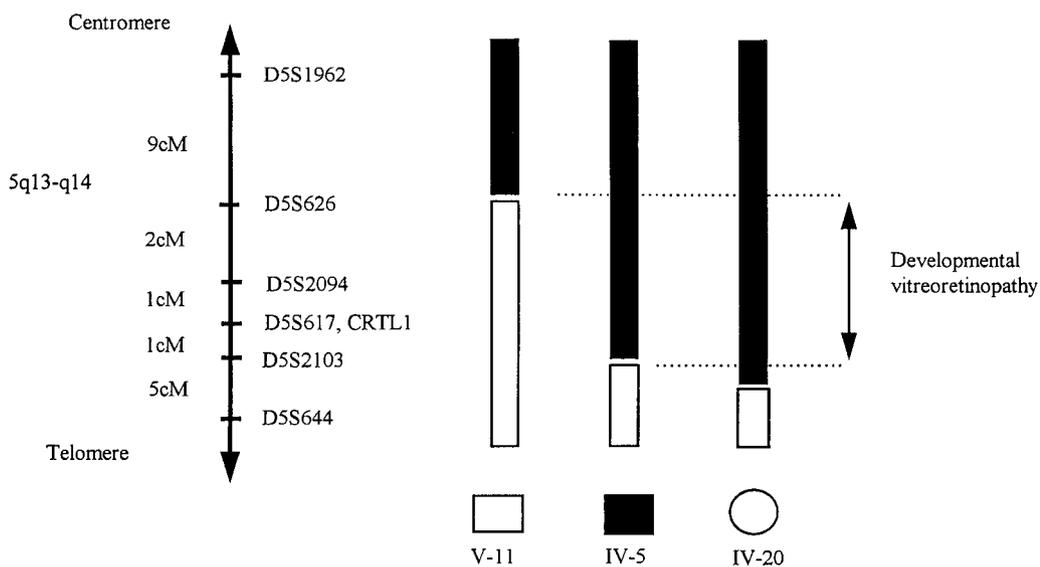
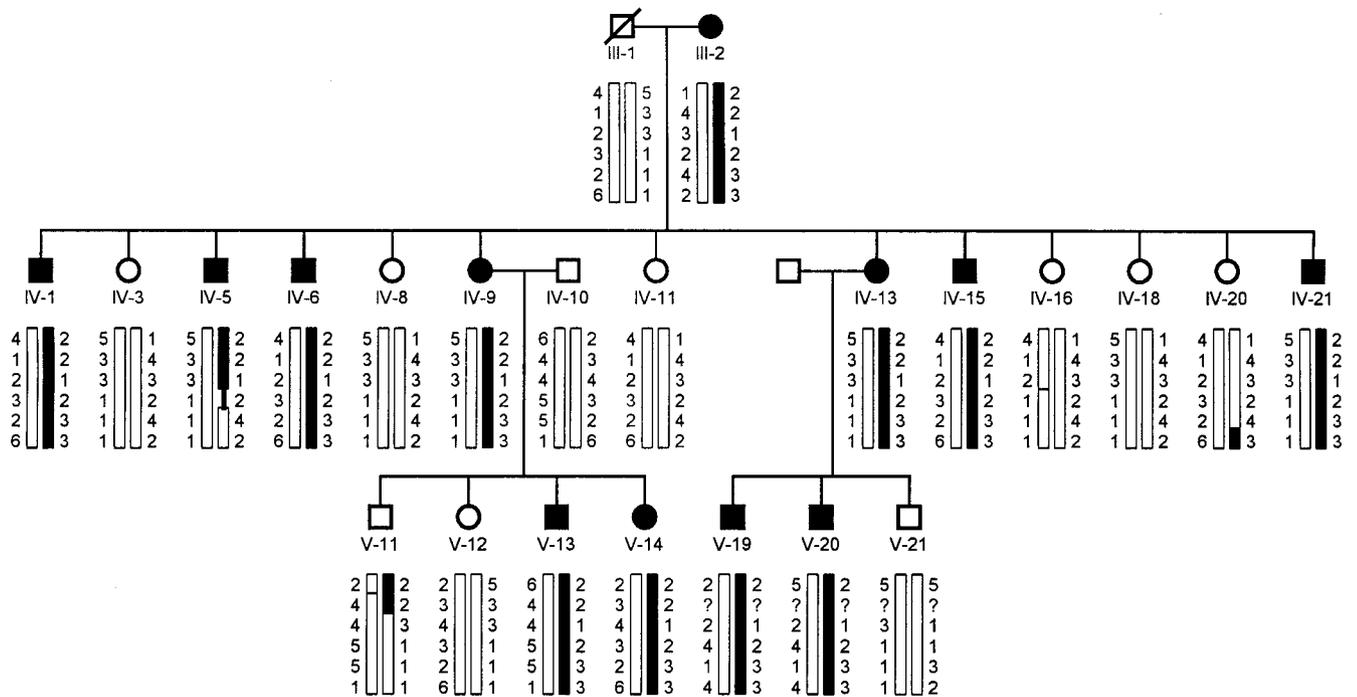


Figure 5. Chromosome 5q14.3 haplotype analysis. Haplotype analysis illustrating recombination events between the developmental vitreoretinopathy gene and the microsatellite markers from chromosome 5q14.3. Proximally, unaffected individual V-11 has a recombination event between markers D5S626 and D5S2094, a distance of approximately 2 cM. Distally, affected individual IV-5 has a recombination distally between D5S2103 and D5S617. Unaffected individual IV-20 also has a recombination distally between markers D5S2103 and D5S644. The disease gene lies in a region of less than 5 cM between markers D5S626 and D5S2103.



**Figure 6.** Haplotype analysis of developmental vitreoretinopathy. Haplotypes refer to markers D5S1962, D5S626, D5S2094, CRTL1, D5S2103, and D5S644 from top to bottom. Dark bar represents the presumed affected chromosome.

dromes.<sup>2,19-21</sup> It is now generally accepted that they are distinguished on the basis of the presence (Stickler) or absence (Wagner) of extraocular sequelae. Molecular investigations back this up since, to date, all families linked to chromosome 5q13-q14 have had no extraocular manifestations. Wagner syndrome, erosive vitreoretinopathy, and the developmental vitreoretinopathy presented here are all linked to this region, suggesting that there is a range of mutations of a single gene that lies at 5q14.3, and their effects form part of a spectrum. The spectrum of effects appears to be sufficient to allow the recognition of distinctions between clinical phenotypes within families, although formal delineation of such conditions will require characterization of the gene underlying the condition and elucidation of its structure. However, the possibility does remain that these conditions are distinct and are in fact caused by mutations at separate, but closely linked, loci.

Brown et al<sup>5</sup> identified two possible candidate loci for the vitreoretinopathies: cartilage link protein (CRTL1) and versican (CSPG2). Both have been mapped cytogenetically to 5q13-q14.<sup>22,23</sup> From the current genetic and physical map of the region, the markers D5S620 and DXS428 flank the CRTL1 gene, which therefore lies in the same 5-cM region. In addition, haplotype analysis with the intragenic microsatellite within the CRTL1 gene confirms that the CRTL1 locus is placed distal to this recombination point in individual V-11, thereby confirming its localization on genetic grounds within the critical region. We have shown that the gene lies in the same YAC clones as CRTL1.<sup>24</sup> Both of these extracellular matrix components bind hyaluronan and recently have been identified in the vitreous.<sup>25</sup> They repre-

sent excellent candidates for a condition that is characterized by a developmental vitreous abnormality. The data presented here will contribute toward a positional cloning approach to the identification of the gene underlying vitreoretinopathies, which map to the region of chromosome 5q.

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