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Genetic Linkage of Wagner Disease and Erosive Vitreoretinopathy to Chromosome 5q13-14

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Background: Wagner disease and erosive vitreoretinopathy are potentially blinding autosomal dominant diseases that share some similarities with Stickler syndrome. However, both disorders have associated retinal pigment epithelial changes, poor night vision, visual field defects, and abnormal electroretinographic findings, which are not found in families with *COL2A1*-associated Stickler syndrome. In addition, rhegmatogenous retinal detachments are uncommon in Wagner disease but occur in approximately 50% of patients with either Stickler syndrome or erosive vitreoretinopathy.

Objectives: To identify the chromosomal location of the genes involved in Wagner disease and erosive vitreoretinopathy and to distinguish these conditions genetically from Stickler syndrome.

Methods: Fifteen affected members of a family affected with erosive vitreoretinopathy and 24 affected descendants of the pedigree described by Wagner were genotyped with a set of short tandem repeat polymorphisms distributed across the genome.

Results: Significant linkage was observed in each family between the disease phenotype and markers that map to chromosome 5q13-14. The highest lod score for the family affected with erosive vitreoretinopathy was 4.2 and was obtained with marker *GATA3H06* (θ=0). The highest lod score for the family affected with Wagner disease was 5.8 and was obtained with marker *D5S815* (θ=0). A candidate gene (cartilage link protein) that is known to lie near the linked interval was screened for mutations, but none was found in either family.

Conclusions: These data suggest that erosive vitreoretinopathy and Wagner disease are allelic disorders and demonstrate that they are genetically distinct from *COL2A1*-associated Stickler syndrome.

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HEREDITARY vitreoretinopathies are potentially blinding inherited disorders characterized by an abnormal-appearing vitreous gel and associated retinal changes. Four of these disorders, Stickler syndrome,[1,2] Wagner disease,[3,4] erosive vitreoretinopathy,[5] and Goldmann-Favre syndrome,[6] exhibit marked syneresis of the vitreous gel. Stickler syndrome is the most common of these disorders and has been shown to be caused by mutations in the *COL2A1* gene on chromosome 12.[7-9] Wagner disease and erosive vitreoretinopathy share some clinical features with Stickler syndrome, but both have associated retinal pigment epithelial (RPE) changes, difficulties with night vision, visual field defects, and abnormal electroretinographic findings, which are not found in families with *COL2A1*-associated Stickler syndrome. Rhegmatogenous retinal detachments are uncommon in patients with Wagner disease but occur in approximately 50% of patients with Stickler syndrome or erosive vitreoretinopathy. Unlike Stickler syndrome, there are no known systemic manifestations of Wagner disease or erosive vitreoretinopathy.

The disorders described by Wagner[3] and Stickler et al[1] are frequently confused with one another. Stickler described an autosomal dominant condition with pronounced vitreous syneresis similar to that described in the Wagner pedigree. However, Stickler's patients had a higher degree of myopia, and 50% had retinal detachments. Orofacial, skeletal, and auditory abnormalities are found in almost all patients with Stickler syndrome but are not present in patients with Wagner disease. Despite these differences, over 20 publications on "Wagner syndrome" or "Wagner-Stickler syndrome" have been pub-

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METHODS

GENOTYPING

After obtaining informed consent, blood samples were obtained from 39 affected family members and 15 informative spouses. DNA was prepared from whole blood using a nonorganic procedure.[10] A screening panel of over 200 short tandem repeat polymorphisms, distributed across the autosomal genome, was selected from those characterized by the Cooperative Human Linkage Center (CHLC), Iowa City, Iowa; Généthon, Evry, France; or the published literature. The majority of the markers used were *GATA* tetranucleotide repeats obtained through the CHLC. Oligonucleotide primers flanking each short tandem repeat polymorphism were synthesized using standard phosphoramidite chemistry (Model 391 DNA synthesizer, Applied Biosystems, Foster City, Calif).

Thirty nanograms of each patient's DNA was used as a template in an 8.35-μL polymerase chain reaction mixture containing the following: 1.25 μL of buffer solution consisting of TRIS hydrochloride (100 mmol/L, pH 8.8), potassium chloride (500 mmol/L), magnesium chloride (15 mmol/L), and gelatin (0.01% wt/vol); 200 μm each of deoxycytidine triphosphate, deoxyadenosine triphosphate, deoxyguanosine triphosphate, and deoxythymidine triphosphate; 1 pmol of each primer; and 0.25 U of *Taq* polymerase (Perkin-Elmer Cetus, Norwalk, Conn). Samples were incubated in a DNA thermocycler (Omnigene, Woodbridge, NJ) for 35 cycles at 94°C for 30 seconds, 50°C for 30 seconds, and 72°C for 30 seconds. After amplification, 5 μL of stop solution (95% formamide; sodium hydroxide, 10 mmol/L; 0.05% bromophenol blue; and 0.05% xylene cyanol) was added to each sample. The samples were then denatured and electrophoresed on 6% polyacrylamide gels at 60 W for about 3 hours. Following electrophoresis, gels were silver stained as previously described.[11,12] Permanent records were created of all gels with EDF film (Eastman Kodak Co, Rochester, NY).

SINGLE-STRAND CONFORMATION POLYMORPHISM ANALYSIS

Single-strand conformation polymorphism analysis was used to screen the majority of the coding sequences of the *CRTL1* gene for the presence of mutations in affected individuals from both families. Polymerase chain reaction primer sequences were chosen from the published *CRTL1* sequence[13,14] (**Table 1**). Each exon was amplified in 8.35 μL of polymerase chain reaction mixture using the same reaction mixture as that used for genotyping (above). Samples were incubated in the DNA thermocycler for 35 cycles at 94°C for 30 seconds, 58°C for 30 seconds, and 72°C for 30 seconds. Following amplification, 5 μL of stop solution was added to each well. Samples were denatured and electrophoresed on fan-cooled nondenaturing 6% polyacrylamide gels (5% glycerol; TRIS hydrochloride, 45 mmol/L (pH 8.0); boric acid, 45 mmol/L; and ethylenediaminetetraacetic acid [EDTA], 0.5 mmol/L) at 20 W for approximately 4 hours at room temperature. Following electrophoresis, gels were silver stained as described above.

LINKAGE ANALYSIS

Linkage analysis was performed using the LINKAGE program package (version 5.1).[15] The MLINK routine was used for the pairwise analysis. For the data given in **Table 2**, the allele frequencies were assumed to be equal for each marker. The reference genetic maps used for the analysis were obtained from Murray et al[16] and the CHLC. The CHLC map was generated using version 2.5 of combined CEPH data (Center d'Etudes du Polymorphisme Humain, Evry). (These data are available on request from CEPH or electronically at FTP.CHLC.ORG or via Gopher server at Gopher.CHLC.ORG.)

lished in the genetic and ophthalmic literature over the past 30 years, each of which suggests that Wagner disease and Stickler syndrome are synonymous or are part of a continuum. The purpose of this study was to use genetic linkage analysis to identify the chromosomal location of the genes involved in Wagner disease and erosive vitreoretinopathy and to determine whether these conditions could be genetically distinguished from one another or from Stickler syndrome.

RESULTS

CLINICAL FINDINGS

Twenty-six family members of the erosive vitreoretinopathy pedigree originally reported by Brown and coworkers[5] were studied (**Figure 1**, left). All were at a 50% risk of having the disease because of a known affected parent or sibling. Fifteen of these patients were found to have marked vitreous syneresis and other typical findings of erosive vitreoretinopathy. A constant finding in affected patients was a translucence or erosion of the RPE that allowed clear visualization of the choroidal vessels. In severely affected patients, the RPE was denuded in a geographic, scalloped pattern at the equator. Late in the course of the disease, some patients had profound RPE atrophy and pigment clumping similar to retinitis pigmentosa or choroideremia (**Figure 2**). Vitreous syneresis was seen in all affected patients as pronounced vitreous sheets, veils, and ropes. Often, vitreous traction was observed at the border between erosive lesions

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and normal-appearing RPE. Eleven affected patients (73%) had rhegmatogenous retinal detachments, five of which were bilateral. Only two affected patients over the age of 10 years had completely attached retinas. As in Stickler syndrome, the retinal breaks were often posterior and difficult to repair. Visual acuity was reduced to light perception or worse in six (20%) of the 30 affected eyes.

Sixty living descendants of the original pedigree described by Wagner[3] were also available for study. Fifty-two were at a 50% risk of having the disease because of a known affected parent or sibling (Figure 1, right). Twenty-eight were believed to have unmistakable characteristics of Wagner dis-

ease, which included at least the presence of syneretic vitreous and RPE abnormalities. Five patients (18%) had suffered a rhegmatogenous retinal detachment in one of their eyes. An additional 11 patients (39%) were found to have bilateral peripheral tractional retinal detachments without retinal breaks. Only three (5%) of the 56 affected eyes had visual acuities of light perception or worse.

LINKAGE RESULTS

Blood samples were available from 15 affected patients and eight informative spouses from the family affected with erosive vitreoretinopathy and from 24 affected patients and seven informative spouses from the family affected with Wagner disease. The first phase of the linkage strategy was to determine whether erosive vitreoretinopathy could be allelic with Stickler syndrome and to confirm Francomano and coworkers'[17] exclusion of Wagner disease at this locus. Linkage analysis with markers within and flanking the *COL2A1* gene on chromosome 12 revealed multiple recombinations between these markers and the disease phenotype in both families, thus excluding this gene as the site of the disease-causing mutations in these diseases. Because Wagner disease and erosive vitreoretinopathy are both associated with changes in the vitreous and the retina, the second phase of the study was to examine a group of candidate loci, including the genes that encode collagen type IX[18] as well as five autosomal loci previously associated with retinitis pigmentosa.[19-25] Each of these loci was excluded in both families.

The last phase of the study was genome-wide linkage analysis using a panel of short tandem repeat polymorphisms. Linkage of erosive vitreoretinopathy to 5q was first suspected when all 15 affected individuals were found to share an allele of marker *D5S107*. Additional chromosome 5 markers were tested, and significant linkage was discovered between the disease and three other polymorphisms (Table 2). The highest lod score was 4.2, which was obtained with marker *GATA3H06* (θ=0). The family affected with Wagner disease was then genotyped with markers at this locus, and significant linkage was demonstrated with 10 different markers (Table 2). The highest lod score for this family was 5.8 and was obtained with marker *D5S815* (θ=0). Combining the lod scores from the two families resulted in 14 markers with lod scores greater than 3.0. For 12 of these linked markers, the allele associated with the affected phenotype in the family with erosive vitreoretinopathy was different from that in the family with Wagner disease (Table 2).

Figure 3 summarizes the recombination events that were detected in both families between the disease locus and various chromosome 5 markers. The two flanking markers are *D5S650* (centromeric) and *D5S409* (telomeric). The interval delimited by these markers is approximately 35 centimorgans in size.

There are two genes known to exist near the linked interval whose products have functions compatible with potential involvement in both erosive vitreoretinopathy and Wagner disease. *CRTL1* encodes cartilage link protein, which is a 42- to 49-kd protein that stabilizes the interaction between hyaluronic acid and a proteoglycan known as aggrecan.[26] *CSPG2* encodes a 263-kd protein that forms the protein core of chondroitin sulfate proteoglycan.[27]

The *CRTL1* gene has been mapped with fluorescent in situ hybridization to 5q13-14.[28] A short tandem repeat polymorphism exists within the *CRTL1* gene,[29] and genotyping of this marker in the two families revealed no affected recombinants (combined lod score, 7.5; θ=0). Although no intron sequence data have been published for the *CRTL1* gene, the cDNA sequence and positions of the introns are known.[13,14] These data were used to develop a single-strand conformation polymorphism assay that spans 77% of the coding sequence (Table 1). No mutations were detected in either family using this assay.

No intragenic polymorphisms have been found in the *CSPG2* gene, and its precise location on 5q is not known. The structure of the *CSPG2* gene is even less well-characterized than that of *CRTL1*, and, as a result, mutation analysis of this gene was not performed.

Table 1. Primer Sequences for *CRTL1* Assay*

Exon	Primers	Nucleotide Positions
1	5′ GGCTGTAATTAGGGGATTTGG 3′	4-24
	5′ GGAGTTCGGATGCTCTCAAG 3′	254-273
2	5′ TGAAGAAGATTCTTTGGGCTAT 3′	290-311
	5′ TTGGATGTGAATAGCTCTGTCA 3′	293-414
3A	5′ AGAAAATGGCCCCCATCTAC 3′	417-436
	5′ GGAAACAAAAACATCCACTTCC 3′	495-606
3B	5′ GTGGACCAAGCTAACTTCGG 3′	555-574
	5′ TAAGTCCAGTGCTACCACA 3′	765-783
4A	5′ TGGTATTCCCTTACTTTCCACG 3′	791-812
	5′ AGGCGTCGTACAGCTGGTC 3′	950-969
4B	5′ GACCAGCTGTACGACGCCT 3′	889-907
	5′ AAAAACGGCCATTGAAATTG 3′	1080-1099
5	5′ CCCCACCAAACTGACCTATG 3′	1113-1132
	5′ AAACTAGTGCGCTCTAAGGGC 3′	1385-1405

**Primers chosen from sequence data of Dudhia and coworkers[13,14]; nucleotide positions correspond to GenBank file X 78076.*

Table 2. Two-Point Linkage Data

	Linked Alleles*		Lod Score (Θ)	
Marker	Erosive Vitreo-retinopathy	Wagner Disease	Erosive Vitreo-retinopathy	Wagner Disease
ATA3F07	4/7	5/7	1.6	4.6
CRTL1	6/7	3/6	2.2	5.3
D5S428	4/6	2/5	2.6	5.5
D5S488	4/4	3/3	0.5	3.6
D5S644	1/8	5/5	3.7	3.8
D5S811	5/12	4/7	2.7	2.1 (.05)
D5S815	2/8	7/8	3.2	5.8
GATA3G10	3/4	2/4	2.8	2.8
GATA23G12	2/4	1/5	2.8	2.3 (.09)
GATA26H09	3/6	6/6	1.4 (.07)	2.9 (.05)
GATA3H06	2/4	5/6	4.2	4.3
GATA61B11	3/4	3/4	1.8	3.5 (.04)
GATA61C02	3/5	3/4	2.0	3.3
GATA69H12	2/7	1/6	3.4	4.6

**The first number of the pair is the allele that is most commonly linked to the disease (1=greatest number of repeats). The numbering system is consistent between the two families. The second number of the pair is the total number of alleles observed in the individual family.*

†Θ at which the highest lod score occurred is given in parentheses if not zero.

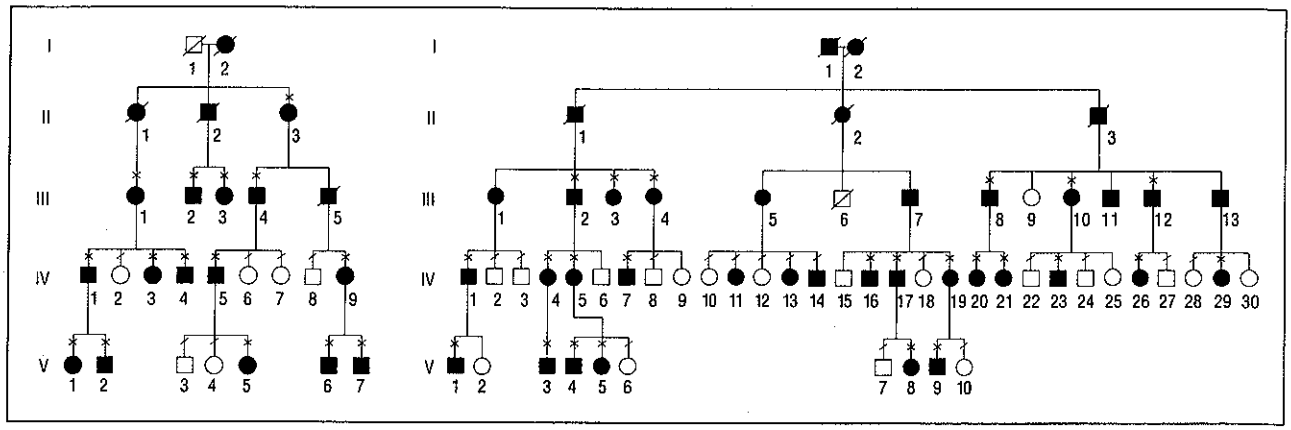

Figure 1. *Pedigree drawings of the families affected with erosive vitreoretinopathy (left) and Wagner disease (right). Clinically affected individuals are shown with solid symbols; unaffected individuals are shown with open symbols; and shaded symbols indicate unknown diagnoses. Patients who were examined and whose DNA was genotyped for linkage analysis are shown with an X above their symbol, examined patients from whom samples were not available or whose samples were not included in the linkage analysis are marked with a slash above their symbol, and deceased patients are marked with a slash through their symbol. Squares indicate males; circles, females. Spouses have been omitted for clarity.*

Figure 2. *Erosive vitreoretinopathy. Photograph of the retina of the right eye of patient III-1 (Figure 1, left) at 54 years of age. The visual acuity is 20/1500. The retinal vessels are attenuated, and the retinal pigment epithelium is atrophic, revealing the underlying choroidal vessels. Scattered bone-spicule–like pigmentation can also be seen.*

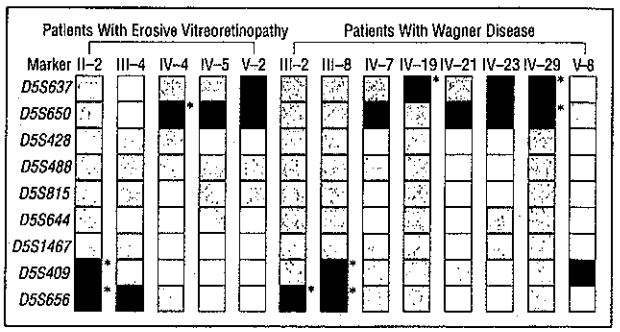

Figure 3. *Analysis of recombinant individuals. Each vertical bar corresponds to a clinically affected individual whose genotype reveals a recombination event in the interval bounded by markers* D5S637 *(centromeric) and* D5S409 *(telomeric). The order of the markers shown on the left was obtained from the Cooperative Human Linkage Center (Iowa City, Iowa) framework map (see "Methods" section). A solid box indicates that during the meiosis that gave rise to the individual, an informative recombination event occurred between the marker and the disease gene; an open box, the meiosis is informative (at least with respect to the affected parent) and no recombination occurred between the disease gene and the marker; a shaded box, the meiosis is uninformative at that marker; asterisk, the assignment of the solid box to the left required the consideration of the affected haplotype elsewhere in the pedigree or the genotypes of affected sibs or descendants. In these cases, choices between multiple possibilities were made to minimize the total number of recombination events required to explain the data. The data summarized in this figure demonstrate that the disease-causing mutations lie within the interval bounded by* D5S409 *and* D5S650.

COMMENT

In 1938, Wagner[3] described a Swiss family with myopia, early cataract formation, liquefaction of the vitreous, retinal vascular changes, and RPE changes. He termed the disease "degeneratio hyaloideo-retinalis hereditaria." This family has subsequently been studied by Böhringer et al,[30] Ricci,[31] and Maumenee et al.[4] Prior to the recent reexamination of the Wagner pedigree (R.A.G. and E.P.M., unpublished data, 1994), only one patient with Wagner disease had ever been found to have a rhegmatogenous retinal detachment.

In 1993, Korkko and colleagues[32] described a glycine-to-aspartate substitution in the *COL2A1* gene in a family who they believed had a disease "similar to the original family described by Wagner." Their article describes only three patients, all of whom had retinal detachments and none of whom had the RPE changes found in erosive vitreoretinopathy and Wagner disease. In addition, radiographic examinations were not performed. We believe that the findings in this family are more compatible with Stickler syndrome than with Wagner disease.

In 1994, Brown et al[5] described a new entity known as erosive vitreoretinopathy. It has a much higher incidence of rhegmatogenous retinal detachments and a poorer visual prognosis than Wagner disease. Both can be clinically distinguished from Stickler syndrome by the absence of systemic findings such as cleft lip or palate, joint pains, and radiographic abnormalities.

This study shows that both Wagner disease and erosive vitreoretinopathy are genetically distinct from Stickler syndrome and are caused by mutations in a 35-centimorgan region of the long arm of chromosome 5. The disparity between the alleles linked to the affected phenotypes in the two families with the majority of the

linked markers (Table 2) suggests that the disease-causing mutation in each family arose independently. Thus, the different clinical features in these two diseases could stem from different mutations in a single gene or from mutations in two different but tightly linked genes.

Among the genes known to map to the long arm of chromosome 5 are two (*CRTL1* and *CSPG2*) whose products (cartilage link protein and chondroitin sulfate proteoglycan core protein) contribute significantly to the structure of the extracellular matrixes of cartilage and vascularized connective tissue, respectively. In the chicken, *CRTL1* has been shown to be expressed in a variety of noncartilaginous tissues, including the eye.[33,34] The expression of *CRTL1* and *CSPG2* in the human eye has not, to our knowledge, been investigated. *CRTL1* and *CSPG2* have some homologous domains and may have arisen from a common ancestral gene.[27] It is therefore possible that other undiscovered members of this gene family also reside on 5q.[27] The present study cannot exclude either *CRTL1* or *CSPG2* from potential involvement in erosive vitreoretinopathy or Wagner disease.

In summary, this study demonstrates that the mutations that cause Wagner disease and erosive vitreoretinopathy are linked to markers on the long arm of chromosome 5. In the future, the combination of mutation analysis of the *COL2A1* gene and linkage analysis with chromosome 5 markers should allow the correct molecular cause of vitreoretinopathy to be determined in many families. The eventual identification of the specific disease-causing mutations in these families is likely to provide significant new insight into the structure of the vitreous and retina, and it is hoped that this information will also provide new insight into the pathogenesis of many forms of human retinal detachment.

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