*Am. J. Hum. Genet. 65:728–734, 1999*

# The Gene for Leukoencephalopathy with Vanishing White Matter Is Located on Chromosome 3q27

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## Summary

**Leukoencephalopathy with vanishing white matter (VWM) is an autosomal recessive disorder with normal early development and, usually, childhood-onset neurological deterioration. At present, diagnosis of VWM is based on clinical examination and the results of repeat magnetic resonance imaging and magnetic resonance spectroscopy, which show that, with time, increasing amounts of the cerebral white matter vanish and are replaced by cerebrospinal fluid. We have performed a genome linkage screening of a panel of 19 families of different ethnic origins. Significant linkage to chromosome 3q27 was observed in a 7-cM interval between markers D3S3730 and D3S3592, with a maximum multipoint LOD score of 5.1 calculated from the entire data set. The results of genealogical studies have suggested that seven parents in four Dutch families with VWM may have inherited an allele for the disease from a common ancestor who lived at least eight generations ago. Analysis of these families provided further evidence for the localization of the gene for VWM to 3q27. The patients shared a haplotype spanning 5 cM between markers D3S1618 and D3S3592. In one family of a different ethnic background, the patient had, in the same region, homozygosity for 13 consecutive markers spanning at least 12 cM, suggesting consanguinity between the parents. A healthy sibling of this patient had the same homozygous haplotype, which suggests that the healthy sibling is presymptomatic for the disease.**

Received March 25, 1999; accepted for publication July 7, 1999; electronically published August 10, 1999.

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0002-9297/1999/6503-0018$02.00

## Introduction

A new disease entity among leukoencephalopathies of unknown origin has recently been defined on the basis of a characteristic clinical course and the findings of magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) (Hanefeld et al. 1993; Schiffmann et al. 1994; Tedeschi et al. 1995; van der Knaap et al. 1997, 1998). The condition is variously referred to as "childhood ataxia with central hypomyelination" (Schiffmann et al. 1994) and "leukoencephalopathy with vanishing white matter" (VWM; MIM 603896) (van der Knaap et al. 1997). The initial development of the patient is normal or close to normal. The onset of neurological deterioration usually occurs in late infancy or early childhood (Hanefeld et al. 1993; Schiffmann et al. 1994; van der Knaap et al. 1997), but juvenile- and even adult-onset cases have been described (van der Knaap et al. 1998). The neurological signs of VWM include progressive cerebellar ataxia, spasticity, variably present optic atrophy, and relatively preserved mental abilities. The course of the disease is chronic progressive, and, in most patients, additional episodes of rapid deterioration occur after febrile infection or minor trauma to the head. MRI findings have shown a diffuse abnormality of the cerebral white matter from the presymptomatic stage onward (van der Knaap et al. 1997, 1998). The results of both MRI and MRS have provided evidence that, in time, increasing amounts of the abnormal white matter vanish and are replaced by cerebrospinal fluid. Autopsy findings have confirmed the presence of white-matter rarefaction and cystic degeneration (van der Knaap et al. 1997, 1998).

Family data have indicated that VWM has an autosomal recessive inheritance with age-dependent penetrance. We performed a genomewide analysis to determine the genetic linkage between VWM and polymorphic microsatellite markers. The data for analysis were gathered from 19 families from diverse populations. Two patients were the result of consanguineous matings, and there were five multiplex fam-

ilies that each included two patients. The search strategy involved genomewide screening of a limited number of patients. Resulting candidate regions for the gene were analyzed, with the use of closely spaced markers, in all the families. The gene for VWM was assigned to chromosome 3q27, and there was no evidence for locus heterogeneity.

## Patients and Methods

### *Patients*

The diagnosis of VWM was confirmed in all patients by expert examination of clinical data and MRI scans (by M.S.v.d.K.). The criteria for the diagnosis of VWM have been described in detail elsewhere (van der Knaap et al. 1997, 1998). After consent was obtained both from the patients' parents (and, if possible, the patients) and from the medical ethics committee of Free University Hospital, Amsterdam, samples of DNA were collected from a panel of 19 informative families, including 5 families from The Netherlands, 7 white families from the United States, 2 families from Canada, and 1 family each from the United Kingdom, Italy, Portugal, Turkey, and Germany. The panel contained five multiplex families. In two other families, in which the parents were consanguineous, the inbreeding coefficients for the patients were .25 and .03. The remaining families all included a single patient with one or two healthy siblings. Altogether, the study comprised 23 patients and 18 healthy siblings was gathered. The parents of one multiplex family were examined by use of MRI and were found to be unaffected. None of the parents had neurological signs of VWM.

### *Genotyping*

A genomewide scan incorporating 358 markers from the Marshfield screening set, version 6.0 (Center for Medical Genetics, 1998), was performed on five patients from three families (fig. 1). These patients included one affected child of a consanguineous mating (vwm18) and two pairs of affected brothers (vwm32-vwm33 and vwm36-vwm37). The average spacing of the marker set was 10.9 cM. We scored a marker as being positive when at least two of the three families met our first-level screening criterion. The criterion for the patient from consanguineous parents was homozygosity, and the criterion for the affected sib-pairs was sharing. When two adjacent markers were positive, the region was also analyzed in the three remaining multiplex families (fig. 1). Regions that were indicative of linkage in at least four of the six families were finally characterized, by use of closely spaced markers from the Centre d'Étude du Polymorphisme Humain (CEPH) linkage map (Dib et al. 1996), in all 19 families.

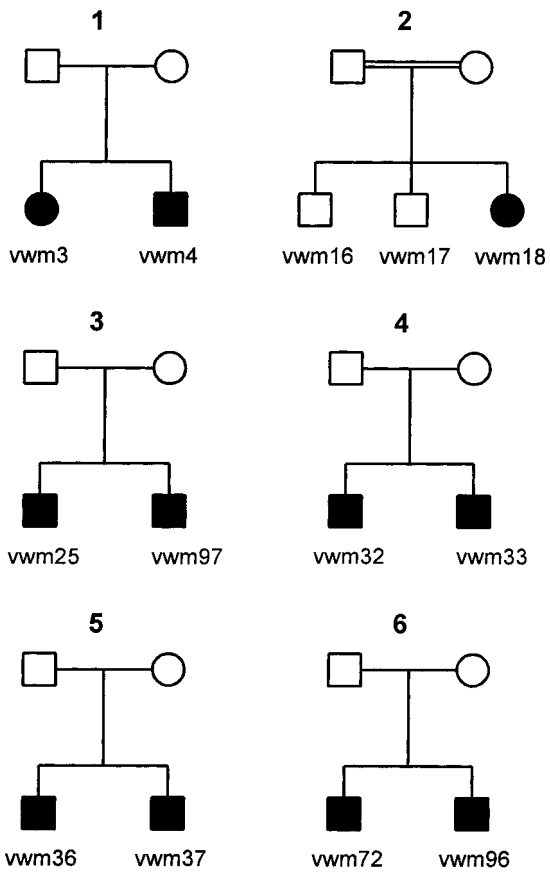


**Figure 1** Pedigrees of informative families with VWM. Families 1 and 4 are from The Netherlands, families 3, 5, and 6 are from the United States, and family 2 is of Mediterranean origin. The parents of family 2 are first cousins once removed. The patients from families 2, 4, and 5 were included in the genomewide linkage analysis. All individuals were included in the second round of analysis of the resulting candidate regions. For these six families, the estimated maximum two-point LOD score was 4.7.

The marker alleles in individual samples of DNA were analyzed, by use of PCR of the polymorphic microsatellite region, with oligonucleotide primers that were labeled with the fluorophores 6-FAM, HEX, or TET. PCR was performed in a volume of 10 $\mu$l with 50 ng genomic DNA; 10 pmol of each primer; 200 $\mu$M each of dATP, dGTP, dCTP, and dTTP; 0.4 U *Taq* DNA polymerase; 20 mM Tris-HCl pH 8.5; 50 mM KCl; 1.5 mM $MgCl_2$; 0.005% Tween-20; and 0.005% Nonidet P40. The initial denaturation step was done at 95°C for 3 min, then 30 cycles at 95°C for 30 s, 55°C for 30 s, and 72°C for 30 s. The final reaction step, which was performed in a GeneAmp 9600 thermocycler (Perkin-Elmer), was done at 72°C for 30 min. The PCR-product lengths were determined by use of automatic instrumentation (Perkin-Elmer ABI Prism 310 Genetic Analyzer). DNA obtained from CEPH individual 134702 was analyzed and was

considered the standard for DNA-fragment lengths (Dib et al. 1996).

### *Statistical Analysis of Linkage*

Multipoint LOD scores were calculated, for 14 markers on chromosome 3, with the MAPMAKER/HOMOZ computer program (Kruglyak et al. 1995); a recessive mode of inheritance with no phenocopies and with complete penetrance in homozygous individuals was assumed. Allele frequencies for the markers were calculated from the available family material. In the analysis, the order of and distances between markers were as follows: D3S3715–2 cM–[D3S3511, D3S3730]–1 cM–[D3S3699, D3S3662, D3S3603]–2 cM–D3S1618–2 cM–[D3S3583, D3S3578, D3S3609]–3 cM–[D3S3592, D3S1617]–3 cM–D3S3570–3 cM–D3S3686. Since the exact age-at-onset distribution of VWM is not known and since it may vary both within and between families, the extent to which the data on the patients' clinically unaffected siblings should contribute to the calculation of LOD scores was uncertain. Therefore, an additional multipoint LOD-score analysis was done; this additional analysis, in which a very low penetrance was assumed for homozygous affected individuals (.001), can be regarded as an "affecteds-only" analysis.

## Results

A genomewide search for the VWM gene was performed in two affected sib pairs and in a patient from a consanguineous marriage (fig. 1). The results of the genomewide scan are displayed in figure 2. Thirteen sets of markers fulfilled our criteria for sharing and/or homozygosity at the first stage of the screen (fig. 2). These genomic regions were investigated in the three additional multiplex families. Regions for which the results remained indicative of linkage in at least four of the families were analyzed with closely spaced markers. In these families, evidence for the location of a gene for VWM at chromosome 3q27 was obtained with the use of marker D3S3578 (two-point LOD score 3.6; recombination frequency, 0%). We further analyzed the remaining families, and the most informative haplotypes are displayed in figure 3. The recombinants in the multiplex families were indicative of a region between markers D3S3730 and D3S3592 as being the most likely location of the gene for VWM. Results for all but one family were consistent with localization of the gene to chromosome 3q27. In the family whose results were inconsistent with this finding, a healthy adult sibling displayed, for the region, a genotype that was identical to that in the index patient (fig. 3, vwm44 and vwm46).

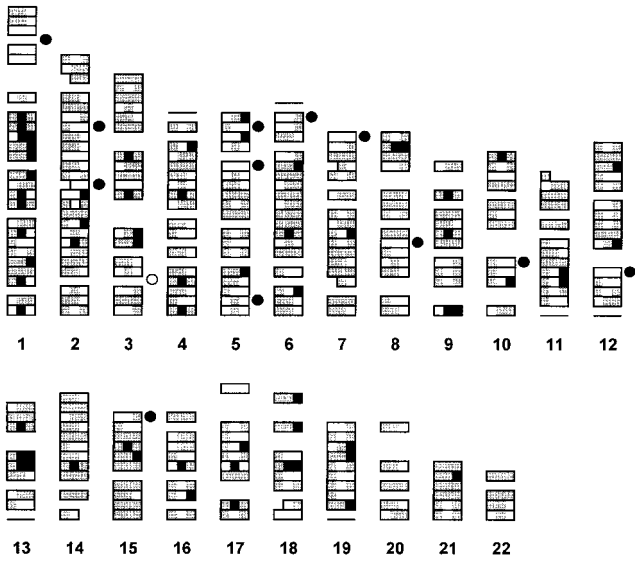


**Figure 2** Results of the first stage of the genomewide scan for linkage of polymorphic microsatellite markers to the phenotype of VWM. The blocks represent the results for the ordered markers of the genomewide set on the numbered chromosomes. The left segment of a block indicates the result of the marker with genomic DNA from patient vwm18, who has consanguineous parents. An unblackened, unshaded segment indicates homozygosity of the marker, and a gray-shaded segment indicates heterozygosity. The middle and right segments indicate the results in affected sib-pairs vwm32-vwm33 and vwm36-vwm37, respectively. An unblackened, unshaded segment in these areas means that the siblings have the same allelotypes, a gray-shaded segment means that they differ in one allele, and a blackened segment indicates that they have no allele in common. Lines indicate the relative positions of the telomeres. Open spaces represent markers that failed to produce results. Circles indicate regions with a possible location of a gene for VWM, on the basis of results from at least two families, for two or more adjacent markers. The unblackened circle denotes the region of chromosome 3 that showed significant linkage after analysis of all families. The corresponding markers, D3S2427 and D3S2398, are 20 cM apart from each other.

Both the patient and the healthy sibling were homozygous for 13 consecutive markers in the critical region of chromosome 3.

Multipoint analysis, done with the use of information obtained only from affected individuals, provided a maximum multipoint LOD score of 5.1 for a broad region between markers D3S3730 and D3S3592 (fig 4). When analysis was done with an assumption of complete penetrance, the maximum multipoint LOD score reached 3.8 in this region (fig. 4).

### *Narrowing the Region for VWM, on the Basis of Haplotype Sharing in Dutch Families*

Genealogical evaluation of seven generations indicated that the ancestors of seven parental lineages of four Dutch families with six VWM patients lived in the

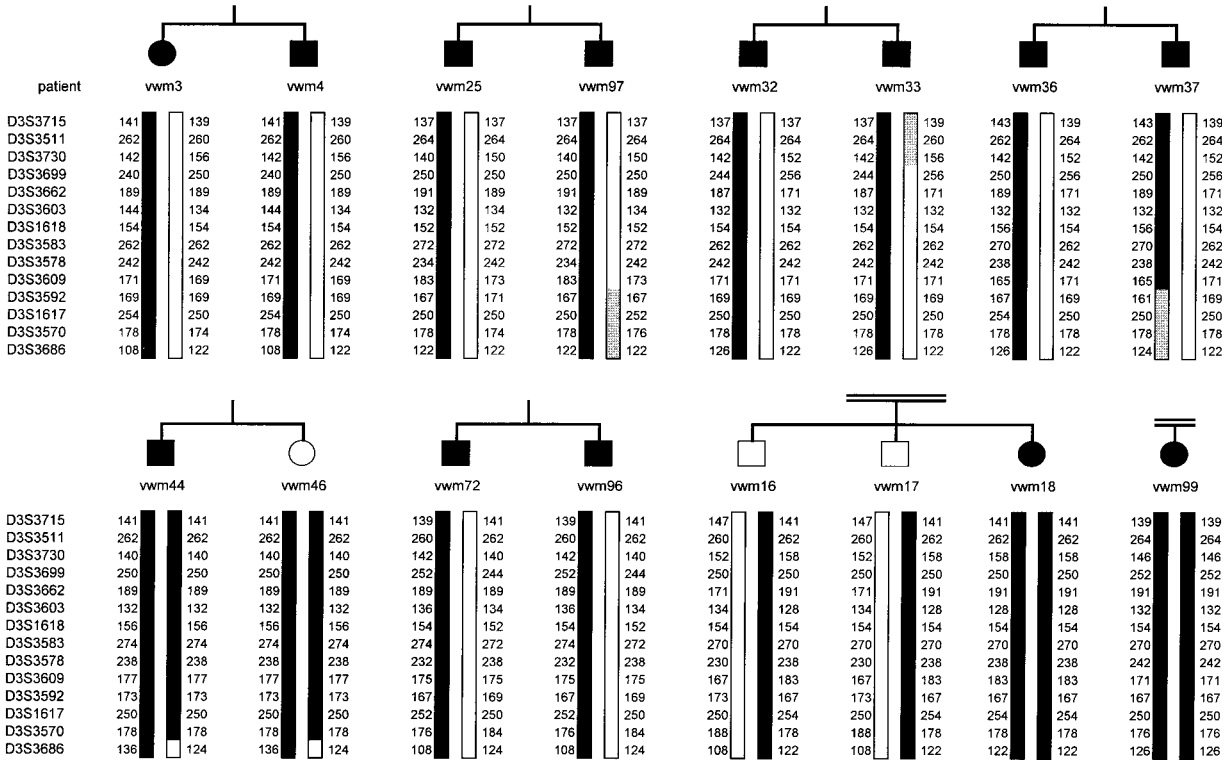


**Figure 3** Informative haplotypes from chromosome-region 3q27 in families with VWM. The haplotypes are based on the genotypes of the parents. Alleles for markers of the listed loci are given as PCR-product lengths. Gray-shaded bars indicate the positions of recombination events.

same rural area, around the city of Z., in the eastern part of The Netherlands. This geographic clustering strongly suggested that (1) a mutant allele was introduced, by a common ancestor of these families, into the area of Z. and (2) the patients in these families are homozygous for the same allele and for the surrounding genomic region. Patients vwm3, vwm4, vwm32, vwm33, and vwm90, who are from three of these families, were all indeed homozygous for the same haplotype of five markers between loci D3S1618 and D3S3592, with the exception that patients vwm3 and vwm4 inherited allele 169 at D3S3609 (fig. 5). The 6th patient, vwm98, had a single copy of the haplotype, except in the case of the allele at D3S1618. This haplotype was inherited from the patient's mother, whose ancestors lived near Z. One copy of the common haplotype is also shared by the affected sib-pair vwm36-vwm37 and by patient vwm80 from the United States (fig. 5). The results of this study indicated that the gene for VWM is located in the region between markers D3S1618 and D3S1617. The aforementioned results, when combined, show that the location for the gene for VWM can be narrowed to a 5-cM region between markers D3S1618 and D3S3592.

## Discussion

We have assigned the gene for VWM to chromosome 3q27, by use of a strategy that included a genomewide search in a limited number of patients. The patients included one individual whose parents were first cousins once removed. Homozygous genomic regions that are identical, on the basis of descent from a single ancestor of this patient, are expected to span a genetic distance of ~25 cM (Te Meerman et al. 1995). The DNA material further consisted of samples from two affected sib-pairs. Genomic regions shared by siblings are generally >25 cM. The polymorphic marker set that we used has an average spacing of 10.9 cM. Our decision to apply a relatively loose criterion (results consistent for linkage, in two of three families, for two adjacent markers,) at the first level of the screen proved to be of great value. If we had applied the more strict criterion that the findings in all three families should be consistent with linkage, the currently implicated region would not have been identified. The two markers that directed us to the current location for the gene for VWM span 20 cM, and only the findings in the patient who had consanguineous

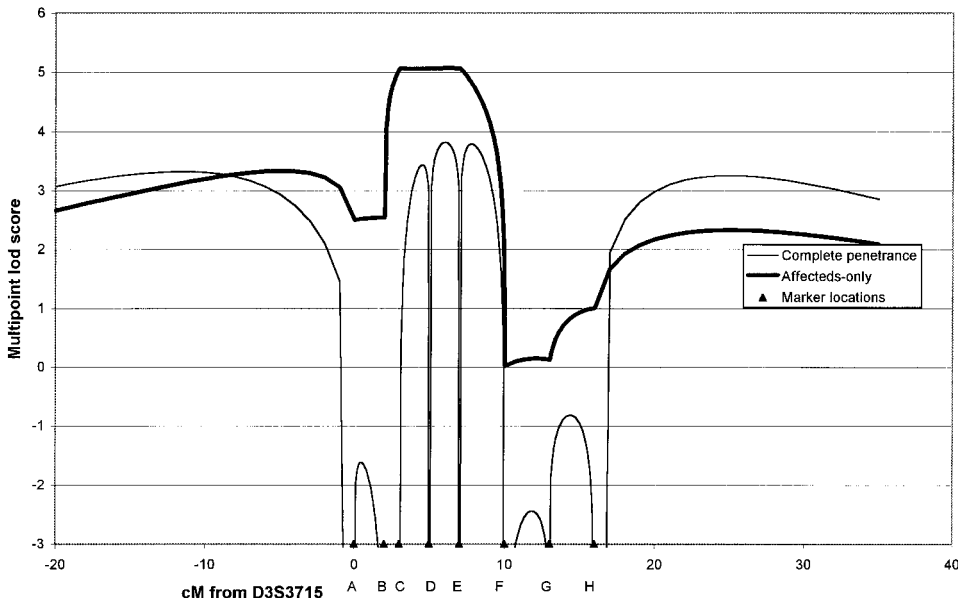


**Figure 4** Multipoint LOD scores for linkage of VWM to chromosome 3q27. LOD scores were calculated, by use of the MAPMAKER/HOMOZ computer program, from the data for 19 families with VWM. The LOD scores were calculated (see the Statistical Analysis of Linkage section of the text), with an assumption of either complete penetrance or a penetrance of .001 for homozygous affected individuals. Capital letters indicate the position of markers. A = D3S3715, B = D3S3511-D3S3730, C = D3S3699-D3S3662-D3S3603, D = D3S1618, E = D3S3583-D3S3578-D3S3609, F = D3S3592-D3S1617, G = D3S3570, and H = D3S3686.

parents indicated linkage with both markers (fig. 2). Results for each of the two affected sib-pairs suggested linkage with only one of the two markers. Conclusive evidence for the assignment of the gene for VWM to chromosome 3, between loci D3S1618 and D3S3592, came from the analysis of the complete panel of 19 families.

Only one family had results that were in apparent conflict with this localization. In this family, which did not have known consanguinity, a patient and a healthy adult sibling are identical and homozygous for the critical region. Given that the frequency of the disease allele must be very low, we suggest that (1) as a result of distant consanguinity between the parents, the patient in this family is homozygous, by descent, for a mutation in the gene for VWM on chromosome 3q27 and (2) the healthy sibling is presymptomatic. As described elsewhere, similar phenotypic variation has been seen in an affected individual and in the individual's presymptomatic adult sibling who had MRI findings typical for VWM (van der Knaap et al. 1998). We could not evaluate this apparently healthy sibling by use of MRI, because of ethical considerations. This single unaffected individual with the at-risk genotype provides the explanation for the observed differences between the regular multipoint LOD-score analysis (maximum, 3.8) and the affecteds-only analysis (maximum, 5.1). Our results confirm the autosomal recessive mode of inheritance of the disease and suggest that a single locus is involved in the etiology of VWM.

Genealogical studies indicated that a single ancestor introduced the gene for the disease in four Dutch pedigrees. A common haplotype for the critical region of chromosome 3q27 was identified in the corresponding patients, thereby confirming the assignment of the gene for VWM. The observed haplotype sharing is particularly striking, since the constituting alleles of markers D3S3583, D3S3578, D3S3609, and D3S3592 have a combined frequency of only 1.3/10 000. In patients vwm3 and vwm4, allele 169 at marker D3S3609 may have been mutated from allele 171 somewhere in the ancestral lineage. D3S3609 is flanked by markers that are in agreement with the common haplotype, and the mutation would have involved only a single dinucleotide repeat. However, the order of markers D3S3583, D3S3578, and D3S3609 is not known. If D3S3609 is flanked by D3S1618, then D3S1618 would be the only marker proximal to D3S3609 that conforms to the common haplotype in patients vwm3 and vwm4. In such a case, the deviation from the common haplotype at D3S3609 could very well be the result of a recombination event.

Interestingly, the patients who are homozygous for the haplotype have considerable phenotypic variation (van

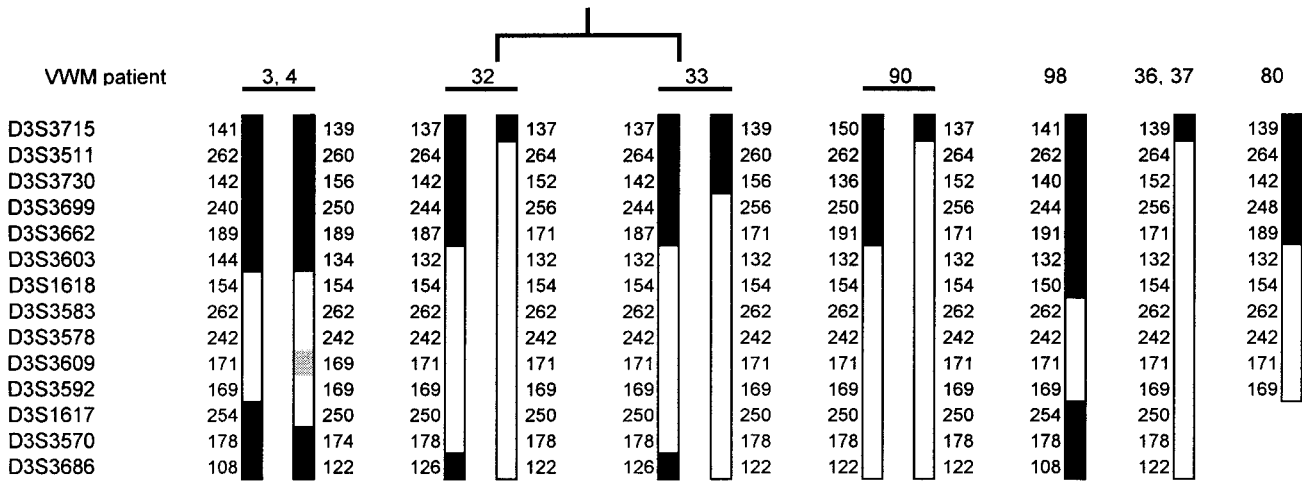


**Figure 5** Haplotypes shared by Dutch patients who are geographically linked to a rural area in the eastern part of The Netherlands. The common haplotype was also found in two VWM families from the USA who were of unknown ancestry (patients vwm36-vwm37 and vwm80). Unblackened, unshaded bars indicate the common genomic regions in at least three families. The gray-shaded block indicates allele 169 of marker D3S3609, which may have been mutated from allele 171 in the ancestral lineage of patients vwm3 and vwm4.

der Knaap et al. 1998). Patient vwm90 had a severe phenotype associated with early-onset and rapidly progressive neurological deterioration. Patients vwm3, vwm4, and vwm33 had an intermediate phenotype characterized by onset later in childhood and slower neurological deterioration. Patient vwm32 had diagnostic MRI and MRS findings but remains clinically presymptomatic at the age of 24 years. Apparently, other genetic or environmental factors influence the course of the disease.

A recently described gene that codes for oligodendrocyte-specific protein (OSP) was localized, by use of FISH, to the region where the gene for VWM is located (Bronstein et al. 1996*a*). The OSP gene was originally identified by cDNA cloning of mRNAs that are specific for the CNS (Bronstein et al. 1996*b*). On the basis of amino-acid-sequence comparison, the predicted structure, and the expression pattern, it was suggested that OSP is a transmembrane protein that is composed of CNS myelin and is similar to PMP22 of the peripheral nervous system. Mutations in PMP22 are correlated with demyelinating peripheral neuropathies, including Charcot-Marie-Tooth disease type 1A, hereditary neuropathy with liability to pressure palsies, and Déjérine-Sottas syndrome (Roa et al. 1993*a;* Roa et al. 1993*b;* Nicholson et al. 1994). OSP is abundant, like PMP22, and comprises 7% of the myelin protein in the CNS (Bronstein et al. 1997). We considered OSP to be a good candidate gene for involvement in VWM. We therefore studied the location of the OSP gene in detail, by means of radiation hybrid mapping with the Genebridge 4 panel (The International RH Mapping Consortium, 1998) (Walter et al. 1994). The OSP gene maps between loci D3S1564 and D3S3725 (data not shown), a region that is ~12 cM proximal to the critical region that we identified for the gene for VWM; this finding excludes OSP as the gene responsible for VWM.

At least 30 expressed-sequence tags (ESTs) have been assigned, by radiation hybrid mapping with the Genebridge 4 panel (The International RH Mapping Consortium, 1998), to the chromosome-3 interval that includes the gene for VWM. In this area, the resolution of this panel is insufficient to align these ESTs with the polymorphic microsatellite markers of the critical region for VWM. Known proteins that are encoded in the region include diacylglycerol kinase gamma (DAGK3), the transcription-regulator B-cell lymphoma protein 6 (BCL6), the chloride-channel protein ClC-2, the protein tyrosine kinase receptor HEK2 and enoyl-CoA:hydratase 3-hydroxyacyl-CoA dehydrogenase (the peroxisomal bifunctional protein EHHADH). Patients with EHHADH deficiency have been described. The clinical symptoms of this deficiency are dominated by neurological abnormalities. Demyelination of the cerebral white matter occurs (Watkins et al. 1989; Wanders et al. 1990). Our group of patients with VWM did not, however, exhibit the typical clinical history and metabolic changes that accompany EHHADH deficiency (van der Knaap et al. 1997). Nonetheless, we cannot rule out the possibility that specific mutations in the EHHADH gene cause the distinct clinical features of VWM. Interestingly, four different ESTs, which, apparently, are specifically expressed in the brain, have been localized in the ge-

nomic interval. These ESTs are NIB1365 (WI-13413); A004N34, which is weakly similar to DAGK3; stsN34433; and WI-13612. We suggest that the corresponding genes are prime candidates for involvement in VWM.

## Acknowledgments

We thank G. Pals, Ph.D., of the Department for Human Genetics, Free University, Amsterdam, The Netherlands, for providing the genomewide marker set. For referral of families with VWM, we acknowledge Drs. H. Stroink, Rotterdam; F. J. M. Gabreëls and J. J. Rotteveel, Nijmegen, The Netherlands; P. G. Barth, Amsterdam; J. F. de Rijk van Andel, Breda, The Netherlands; R. Surtees, E. Llewellyn, and C. de Sousa, London; J. T. R. Clarke, A. Feigenbaum, and S. Blaser, Toronto; E. Franzoni, Bologna; E. Gut, Allensbach, Germany; and M. S. Scher, Cleveland. Dr. J. M. Powers, Rochester, NY, is acknowledged for sending brain tissue. Tissue specimens obtained from the National Neurological Research Specimen Bank, Veterans Administration Medical Center, Wadsworth Division, Los Angeles, which is sponsored by the National Institute of Neurological Disorders and Stroke/National Institute of Mental Health, the National Multiple Sclerosis Society, the Hereditary Disease Foundation, and the Veterans Health Services and Research Administration, Department of Veterans Affairs.

## Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

Center for Medical Genetics, Marshfield Medical Research Foundation, http://www.marshmed.org/genetics (for the genomewide marker set)

Centre d'Étude du Polymorphisme Humain, http://www.cephb.fr (for the CEPH-Généthon integrated genetic map and for distances between chromosome-3q27 markers)

The International RH Mapping Consortium, National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/genemap99 (for mapped genes and for ESTs)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim (for VWM [MIM 603896])

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