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A Familial Alzheimer's Disease Locus on Chromosome I

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The Volga German kindreds are a group of seven related families with autosomal dominant early-onset Alzheimer's disease (AD). Linkage to known AD-related loci on chromosomes 21 and 14 has been excluded. Significant evidence for linkage to AD in these families was obtained with D1S479 and there was also positive evidence for linkage with other markers in the region. A 112–base pair allele of D1S479 co-segregated with the disease in five of seven families, which is consistent with a common genetic founder. This study demonstrates the presence of an AD locus on chromosome 1q31–42.

Alzheimer's disease (AD) is genetically heterogeneous and complex. As AD is common in the elderly (*1*), the clustering of cases in a family may occur by chance, representing either non-allelic, genetic heterogeneity or etiologic heterogeneity (with genetic and non-genetic cases co-existing in the same kindred). In addition, the clinical diagnosis of AD is confounded by other dementing diseases, particularly those common in the elderly. Mutations in the amyloid precursor protein (APP) gene on chromosome 21 cause early-onset (<65 years) autosomal dominant AD (*2*). Mutations in a gene AD3 on chromosome 14 also result in early-onset autosomal dominant AD (*3*). For late-onset AD, the APOE ϵ4 allele elevates risk for AD, possibly by reducing the age of onset, whereas the ϵ2 allele may be protective (*4–7*). Gene-gene interactions may also occur in AD; the age of onset of AD caused by the APP Val^{717} mutation may be modified by APOE genotypes (*8*).

The known AD loci do not account for all cases of AD. In the Volga German (VG) kindreds (*9*), as in several other families (*10*) in which AD appears to be inherited as an autosomal dominant trait, the known AD loci have been excluded (*3, 10–14*). The VG families are a group of related kindreds with AD onset age means ranging from 50.2 to 64.8 years (Table 1). German immigrants in Russia, they remained culturally distinct and did not intermarry with the surrounding population (*9*). Numerous affected subjects in these families have been characterized, both clinically and neuropathologically (*9*) and at least one affected subject from each family has had autopsy confirmation of the diagnosis of AD. Except for the relatively early age of onset, AD in the VG is clinically and pathologically indistinguishable from typical AD.

The locus responsible for AD in the VG kindreds does not cosegregate with markers at the APP locus, and no mutations have been detected in the APP gene (*11*). The AD3 locus on chromosome 14 has been excluded by linkage analysis (*3, 12, 13*). APOE is unlikely to be the major locus for AD in these families as linkage analysis with a highly informative short tandem repeat polymorphism (STRP) in the APOCII locus, located within 30 kb of ApoE, yields negative linkage results under a number of different models (*14*). Although APOE ϵ4 allele frequency in affected VG subjects is elevated relative to Caucasian controls (0.33 versus 0.15), the ϵ4 frequency in VG spouses is also elevated (0.28) suggesting that the frequency of ϵ4 may be high in the VG population (*14, 15*). The APOE genotype does not appear to influence the age of onset in these kindreds (*15*).

DNA was prepared from lymphoblastoid cell lines from 139 individuals in the VG families, including 37 affected subjects. When suggestive evidence for linkage was found, autopsy-derived tissue, either frozen or embedded in paraffin, was used to prepare DNA from eight additional affected subjects for whom no other tissue was available. Markers on all chromosomes were genotyped (*16*) and analyzed by the logarithm of the likelihood ratio for linkage (lod score) method (*17*). For the genome screen, evidence for linkage was evaluated under the assumption of autosomal dominant inheritance with age-dependent penetrance and a 0% sporadic rate. Lod scores were also computed by a low (1%) penetrance model, which makes no assumption about the disease status of at-risk individuals and thus serves as a check that information about linkage was based primarily from the affected individuals (in whom the genotype at the disease locus is more accurately known compared to that of at-risk subjects). Published marker allele frequencies (*18*) were used unless critical allele frequencies were significantly lower than those estimated in the VG, in which case frequencies based on

Table 1. VG kindreds used for linkage analysis. Families were evaluated as described (*9*).

Family	Affected (*n*)	Autopsied (*n*)	Sampled (*n*)†		Mean age of onset ± SD, (*n*), range
			Affecteds	Total	
H	8	3	4 (2)	4	59.5 ± 3.9 (6) 56–68
HB	23	5*	6 (2)	30	60.8 ± 7.1 (22) 54–75
HD	19	2	6	20	59.6 ± 10.3 (17) 46–82
KS	14	3	8 (1)	29	64.8 ± 5.4 (13) 55–71
R	20	5	9 (3)	37	50.2 ± 7.3 (17) 40–67
W	4	2	2	4	52.8 ± 4.5 (4) 48–58
WFL	6	2	2	15	63.8 ± 7.6 (6) 55–76
Totals	94	22	37 (8)	139	58.7 ± 8.9 (85) 40–82

*Includes one unaffected subject autopsied. †Numbers in parentheses indicates DNA samples obtained from autopsy material, either as paraffin blocks or frozen brain.

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all subjects in the VG pedigrees (affecteds, at-risk, and spouses) were used. This conservative approach was taken during screening as underestimation of the frequency of an allele co-segregating with the disease can cause false positive evidence for linkage (*19*). However, this approach will underestimate lod scores if the true allele frequency is lower than assumed. In this study, 162 markers were genotyped (*16*). Among these were 70 STRP markers with heterozygosity values mostly >0.70, spaced ≥20 cM apart.

Initial suggestive lod scores for chromosome 1 were obtained for markers D1S103, for which the peak lod score (Z_{max}) was 1.79 when the maximum likelihood estimate of the recombination fraction) ($\hat{\theta}$) was 0.10) and D1S249 (Z_{max} = 1.76, $\hat{\theta}$ = 0.20; Table 2), which are separated by approximately 26 cM (*20*). Subsequently, 21 other markers in this region spanning 55 cM were analyzed (Table 2). When the conservative screening analysis conditions were used, significant evidence for linkage ($Z_{max} \geq 3.0$) was obtained with D1S479 (Z_{max} = 4.40, $\hat{\theta}$ = 0.11); this lod score was similar to that predicted by earlier power analyses (*21*). Most of the evidence for linkage comes from families HB and R, with positive lod scores also observed for families H, W, and HD (Table 3). Other markers in the region also gave positive though non-significant lod scores (for example, D1S439, Z_{max} = 2.82, $\hat{\theta}$ = 0.17; D1S320, Z_{max} = 1.87, $\hat{\theta}$ = 0.19; D1S103, Z_{max} = 2.40, $\hat{\theta}$ = 0.08; Table 2).

In the VG pedigrees, genotypes are not available from many deceased individuals who connect sampled subjects (for example, all individuals in generations I–III in Fig. 1). Because of this missing data problem, marker allele frequencies can influence linkage analysis results. For most of the markers used, allele frequencies in the VG families were similar to those from controls. However, for D1S479, the 112-bp allele, which segregated with AD in most of the subjects in five of the families (H, HB, HD, R, and W), was substantially more frequent in the affected subjects compared to in controls (0.32 in affected subjects, 0.18 in all VG subjects, and 0.04 in controls) (*22*). Such an increase in frequency for a closely linked marker allele is expected, as sampling of multiplex families is likely to result in over-representation of one or more specific alleles in affected and at-risk subjects, but not in spouses who should be representative of the sampled population. This is especially true in the case of a founder effect, in which the same allele is expected to segregate with the disease in most of the families. This hypothesis is supported by the fact that 112-bp allele of D1S479 has a frequency of 0.03 in the VG spouses, a frequency similar to that observed in controls (0.04). Thus, the allele frequencies from the controls and the VG spouses may more accurately reflect the appropriate D1S479 allele frequencies for use in lod score computations. When control frequencies were used for the 112-bp D1S479 allele, the maximum lod score for D1S479 increased from Z_{max} = 4.40 ($\hat{\theta}$ = 0.11) to Z_{max} = 6.29 ($\hat{\theta}$ = 0.10) (Table 3).

Linkage analysis can be confounded by the presence of phenocopies (non-AD dementia cases or AD caused by something other than the major gene segregating in these families). As the onset ages for AD in the VG families extend up to 82 years (Table 1), and because late-onset AD is common, some of the late-onset cases may be "sporadic" AD or phenocopies. To correct for this possibility, lod scores were calculated (*12, 17*) by a genetic model in which we assume that as the age of onset of a subject increases, the probability that the individual represents a phenocopy increases (*23*). Despite the fact that in the absence of true phenocopies this model reduces the power to detect linkage (*24*) for all markers analyzed, the lod scores increased (*25*). These results support the hypothesis that at least some AD cases in these families are phenocopies.

Haplotypes were constructed for the R family with the 23 markers spanning approximately 55 cM of chromosome 1 (Fig. 1). A common haplotype between D1S238 and D1S235 was observed in all but one of the affected subjects (IV-1, Fig. 1). This individual did not share the disease haplotype across the entire region, had an age of onset of 67 years which is greater than 2 standard deviations above the family mean, and had an ε4/ε4 genotype at the APOE locus. Thus this

Table 2. Lod scores for linkage of FAD to chromosome 1 markers. Genotypes were performed by conventional methods (*16*). All genotypes for D1S479 were determined in duplicate. For markers D1S439, D1S479, and D1S225 genotypes were determined for eight samples from affected subjects either derived from either paraffin blocks or frozen brain material (not all samples amplified with all markers). Other markers genotyped that are not shown are D1S238, D1S422, D1S412, D1S306, D1S310, D1S245, D1S205, D1S425, D1S217, D1S229, D1S227, D1S320, D1S213, D1S251, D1S103, D1S459, D1S446, and D1S235. Lod scores were computed with the assumption of age-dependent penetrance (*17*).

Locus	Het.†	Recombination fraction (θ)						
		0.001	0.05	0.10	0.15	0.20	0.30	0.40
D1S249	0.87	−9.76	−1.12	0.65	1.44	1.76	1.60	0.81
D1S237	0.76	−4.77	−1.88	−0.76	−0.13	0.20	0.36	0.20
D1S479*	0.80	−0.05	3.91	4.39	4.25	3.81	2.50	0.99
D1S439	0.80	−5.59	1.05	2.36	2.78	2.76	1.97	0.73
D1S225	0.79	−10.44	−2.62	−0.48	0.60	1.12	1.16	0.52

*Lod scores were computed with published allele frequencies (*17*) except for D1S479. For this marker, the allele frequency for the 112-bp allele was derived from the VG subjects as a group. †Het., heterozygosity.

Table 3. Family lod scores for linkage of AD to D1S479. For the D1S479 112-bp allele, lod scores were computed with either the frequency from the VG group or from controls. For the H, HB, and R families, maximum lod scores were obtained with D1S479. No marker was positive for the WFL family under any condition. Under the low (1%) penetrance model, Z_{max} values were 3.27 ($\hat{\theta}$ = 0.08) and 1.49 ($\hat{\theta}$ = 0.12) for the control and VG allele frequencies, respectively.

Family	Frequency (112-bp allele)	Recombination fraction (θ)						
		0.001	0.05	0.10	0.15	0.20	0.30	0.40
H	VG	0.45	0.36	0.28	0.21	0.15	0.06	0.01
	Control	0.90	0.78	0.66	0.54	0.42	0.21	0.06
HB	VG	1.67	1.78	1.71	1.54	1.33	0.80	0.26
	Control	2.38	2.47	2.37	2.18	1.93	1.31	0.59
HD	VG	−1.84	−0.45	−0.22	−0.12	−0.08	−0.05	−0.02
	Control	−1.30	0.07	0.28	0.34	0.32	0.19	0.07
KS	VG	−1.57	−0.28	−0.06	0.03	0.05	0.03	0.00
	Control	−1.57	−0.28	−0.06	0.03	0.05	0.03	0.00
R	VG	1.07	2.32	2.49	2.40	2.19	1.55	0.70
	Control	1.46	2.69	2.84	2.73	2.48	1.76	0.83
W	VG	0.67	0.59	0.50	0.42	0.34	0.18	0.05
	Control	0.67	0.59	0.50	0.42	0.34	0.18	0.05
WFL	VG	−0.50	−0.41	−0.32	−0.24	−0.17	−0.07	−0.02
	Control	−0.49	−0.40	−0.31	−0.24	−0.17	−0.07	−0.02
Totals	VG	−0.05	3.91	4.39	4.25	3.81	2.50	0.99
	Control	2.05	5.92	6.29	5.99	5.37	3.61	1.57

subject may be a phenocopy. In other families, definite assignment of a common disease haplotype was difficult because of missing data and will require extensive multipoint analysis (*26*). However, for D1S479, the 112-bp allele segregated with the disease in the H, HB, HD, W, and R pedigrees. In the HD family, the one affected subject who did not have the 112-bp allele, had an age of onset of 75 years and was ϵ3/ϵ4 at the APOE locus. However, age of onset alone cannot be used to unambiguously determine whether a subject is a phenocopy. In the HB family, subjects with onsets of up to 75 years shared the D1S479 112 allele with other younger affected subjects. The KS family is the only VG kindred in which no affected subject had the D1S479 112-bp allele. Analysis of this family is complicated because of the late age of onset (64.8 years) and because of the eight affected subjects three were APOE ϵ4/ϵ4 homozygotes (onset ages of 57, 58, and 67 years) and four were ϵ4 heterozygotes (onset ages 67, 68, 68, and 71 years). Thus, the KS family could be an example of genetic heterogeneity within the VG kindreds, although within-group heterogeneity tests did not detect heterogeneity (*17*). However, the finding of the same rare allele segregating with AD in most of the VG pedigrees supports the hypothesis of a common genetic founder for most of the families.

The data presented here demonstrate the presence of an AD locus at 1q31–42. Analysis of recombinants in the R family define the candidate region as between D1S225 (subjects V-1 and V-3) and D1S217 (subject IV-16) in Fig. 1, a region spanning 14 cM. Even though the VG locus may be a rare cause of AD, identification of the responsible gene will be important for understanding AD pathogenesis, just as identification of rare APP mutations has lead to a greater understanding of the role of APP processing in AD (*27*) and has resulted in the first animal model of AD (*28*).

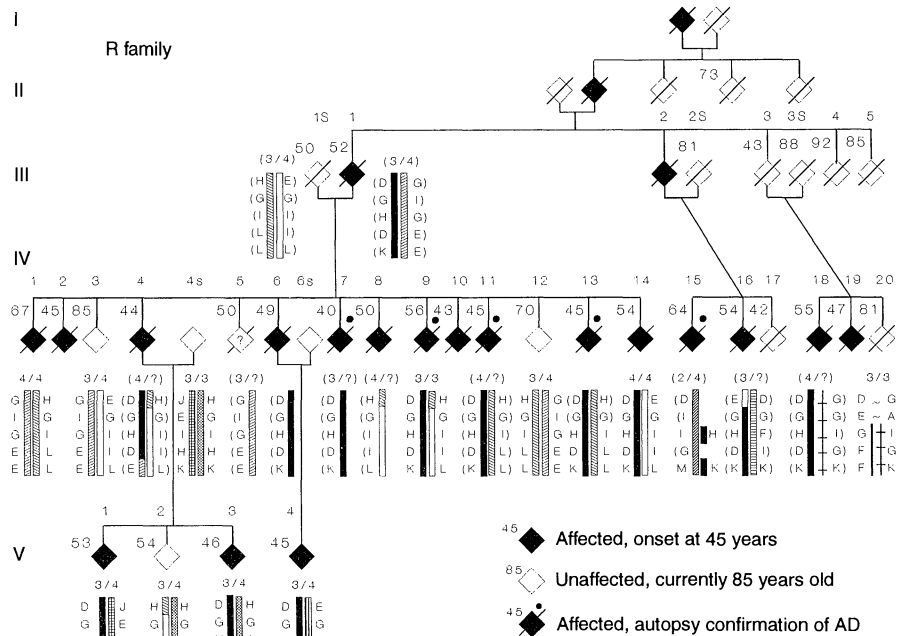

Fig. 1. Segregation of chromosome 1 markers in the R family. The bars beneath each subject represent minimum recombinant haplotypes constructed using the 23 markers from D1S238 to D1S235 (Table 2). Alleles shown, from top to bottom, are for D1S249, D1S237, D1S479, D1S439, and D1S225; size of the particular allele is represented by the letter of the alphabet. The solid bar represents the haplotype segregating with the disease. Other haplotypes are represented by bars with different hatching or marking. A partially missing bar indicates markers not genotyped (subject IV-15). A "~" symbol represents regions where the phase cannot be assigned. APOE genotypes are shown directly above the haplotypes with 2, 3, and 4 representing the ϵ2, ϵ3, and ϵ4 alleles, respectively. Recombinants were observed on the disease haplotype between D1S479/D1S439 and D1S225 in subjects V-1 and V-3, and between D1S306 and D1S310 in subject IV-18. In IV-16 there is a recombination between D1S217 and D1S237. Although this subject is D/E at D1S249, and D is the allele segregating with the disease elsewhere in the pedigree, haplotype analysis of five markers centromeric to (above) D1S249, and four markers between D1S249 and D1S237, strongly suggests that the D allele is on the haplotype IV-16 inherited from the nonaffected parent. A total of four recombinations (three on chromosomes not related to the disease) were observed between D1S249 and D1S237 in the 27 chromosomes in generation IV. The distance between these markers is 12 cM and the chance that up to four recombinants would be observed is 41%. The pedigrees have been altered to protect confidentiality and not all subjects genotyped are shown. Subject IV-5 died of pancreatic cancer and was reported demented by some family members, but not others. This subject was considered affected for the analysis. If this subject does not actually have AD (a misclassification), the Z_{max} would be higher than shown in Tables 2 and 3.

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13. D14S77 is a highly polymorphic marker closely linked to AD3. Lod scores for linkage of AD in the VG kindred to D14S77 by the age-dependent penetrance model, low-penetrance (1%) model, and phenocopy correction model (θ in parentheses), respectively were −23.04, −11.13, −11.63 (0.001); −9.90, −4.17, −6.15 (0.05); −6.1, −2.27, −3.73 (0.10); −3.81, −1.29, −2.25 (0.15); −2.34, −0.71, −1.32 (0.20); −1.37, −0.37, −0.74 (0.25); −0.74, −0.18, −0.39 (0.30); and −1.50, −0.03, −0.08 (0.40).
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16. STRP genotypes were determined by end-labeling one PCR primer with ^{32}P by means of T4 kinase. Genomic DNA (100 ng) was amplified by conventional methods and the resulting fragments resolved on polyacrylamide gels containing 8M urea and 30% formamide. APOE genotypes were determined with the restriction digest method [J. E. Hixson, D. T. Vernier, *J. Lipid Res.* **31**, 545 (1990)]. In the initial phase of this work, 15 blood markers, 22 restriction fragment length polymorphic (RFLP) markers, and 8 variable number of tandem repeat (VNTR) markers were genotyped. The remaining loci were STRP markers with polymorphism information content (PIC) values ≥ 0.6. Although markers on all chromosomes were tested, clusters of nonindependent markers in the vicinity of known AD loci were genotyped, including nine near the APP gene on chromosome 21, ten near APOE on chromosome 19, and four near the AD3 locus on chromosome 14.
17. Lod scores [N. E. Morton, *Am. J. Hum. Genet.* **7**, 277 (1955)] were calculated with the computer program LIPED [J. Ott, *ibid.* **26**, 588 (1974)] modified to handle up to 20 alleles and the capacity to handle different alleles for each family (*12*). Inheritance was assumed to be autosomal dominant with an AD gene frequency of 0.001. The family-specific penetrance curves used were constructed from the observed

mean onset age for the family, a combined standard deviation from the onset ages in all families (8.62 years), and an ultimate penetrance of 100%. For the phenocopy correction model, lod scores were determined by an age-dependent penetrance model with a phenocopy correction that assumes a cumulative normal age-of-onset function with a mean of 110 years and a standard deviation of 14 years (*12*). Possible heterogeneity was examined with the admixture test [S. E. Hodge, C. E. Anderson, K. Neiswanger, R. S. Sparkes, D. L. Rimoin, *ibid.* **35**, 1139 (1983)].

18. Unless otherwise noted, published allele frequencies are from the Genome Database.
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20. Marker order for some loci was from G. Gyapay *et al.*, *Nat. Genet.* **7**, 246 (1994); this order with centimorgan (sex-averaged) distances is D1S238–4–D1S422–4–D1S412–7–D1S306–6–D1S249–7–D1S245–1–D1S205–2–D1S425/D1S217–6–D1S229–1–D1S227–4–D1S439/D1S213/D1S479–3–D1S225–2–D1S459–2–D1S446–4–D1S235. As part of this study, additional mapping of six loci was performed with the complete CEPH mapping panel (40 families) and the computer program CRIMAP [E. R. Lander and P. Green, *Proc. Natl. Acad. Sci. U.S.A.* **84**, 2363, (1987)]; the order was D1S229–5.7–D1S320–2.6–D1S213–1–D1S479/D1S439–5.4–D1S103.
21. Initial power analysis of the families (which did not include the neuropathologic samples) indicated that with a reasonably polymorphic marker [PIC = 0.7; D. Botstein, R. L. White, M. Skolnick, R. W. Davies, *Am. J. Hum. Genet.* **32**, 314 (1980)], at $\theta = 0.05$, the mean $Z_{max} = 2.91$ with a maximum expected lod score of 7.55, and at $\theta = 0.1$, these lod scores would be 1.8 and 6.25, respectively. These lod scores are somewhat less than the 4.40 actually obtained, but as the power analysis did not assume the availability of the neuropathologic samples, such a result was expected.
22. Control allele frequencies for D1S479 were determined by allele counting. Frequencies for grandparents of members of pedigrees from the Centre d'Etude du Polymorphisme Humain (CEPH) (244 control chromosomes), all the VG subjects (affecteds, at-risk, and spouses; 254 chromosomes), affected VG subjects (74 chromosomes), and VG spouses (32 chromosomes) are respectively: 102 bp, 0.013, 0.012, 0.0, and 0.063; 104 bp, 0.029, 0.012, 0.00, and 0.031; 106 bp, 0.074, 0.055, 0.027, and 0.063; 108 bp, 0.013, 0.004, 0.0, and 0.031; 110 bp, 0.344, 0.343, 0.257, and 0.438; 112 bp, 0.041, 0.165, 0.31, and 0.031; 114 bp, 0.033, 0.055, 0.054, and 0.0; 116 bp, 0.307, 0.263, 0.243, and 0.219; 118 bp, 0.049, 0.008, 0.014, and 0.031; 120 bp, 0.066, 0.067, 0.054, and 0.094; 122 bp, 0.013, 0.004, 0.014, and 0.0; 124 bp, 0.012, 0.012, 0.027, and 0.0; 126 bp, 0.008, 0.0, 0.0, and 0.0.
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25. Lod scores computed using the phenocopy correction model for D1S479 were $Z_{max} = 4.60$ ($\hat{\theta} = 0.10$) and $Z_{max} = 6.51$ ($\hat{\theta} = 0.08$) with the VG and control allele frequency for the 112-bp allele, respectively. Under this model, the maximum D1S479 lod score for a single family, the R family, was 2.95 ($\hat{\theta} = 0.09$) using the control allele frequency for the D1S479 112-bp allele. For other markers, maximum lod scores under the phenocopy correction model were as follows: D1S227, $Z_{max} = 0.92$, $\hat{\theta} = 0.20$; D1S213, $Z_{max} = 0.27$, $\hat{\theta} = 0.20$; D1S439, $Z_{max} = 3.13$, $\hat{\theta} = 0.15$; D1S225, $Z_{max} = 1.40$, $\hat{\theta} = 0.23$; D1S459, $Z_{max} = 0.27$, $\hat{\theta} = 0.30$; D1S103, $Z_{max} = 2.58$, $\hat{\theta} = 0.06$.
26. Multipoint linkage analysis was not performed because of the extraordinary computer time necessary with traditional methods. Alternatives based on simulation methods are under development [A. Kong, N. Cox, M. Frigge, M. Irwin, *Genet. Epidemiol.* **10**, 483 (1993); S. Lin, E. Thompson, E. M. Wijsman, *IMA J. Math. Appl. Med. Biol.* **10**, 1 (1993); S. Lin, E. M. Wijsman *Am. J. Hum. Genet.* **55**, A40 (1994)]; however, such methods cannot yet accommodate age-dependent reduced penetrance, and thus cannot be used for AD linkage analysis.
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Candidate Gene for the Chromosome 1 Familial Alzheimer's Disease Locus

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A candidate gene for the chromosome 1 Alzheimer's disease (AD) locus was identified (*STM2*). The predicted amino acid sequence for *STM2* is homologous to that of the recently cloned chromosome 14 AD gene (S182). A point mutation in *STM2*, resulting in the substitution of an isoleucine for an asparagine (N141I), was identified in affected people from Volga German AD kindreds. This N141I mutation occurs at an amino acid residue that is conserved in human S182 and in the mouse S182 homolog. The presence of missense mutations in AD subjects in two highly similar genes strongly supports the hypothesis that mutations in both are pathogenic.

Alzheimer's disease is the most common cause of dementia in the elderly. The pathogenic pathway leading to neurodegeneration and AD is not well understood. However, at least some forms of the disease have a genetic etiology. For autosomal dominant, early-onset (<65 years) AD, causative mutations have been identified in the amyloid precursor protein (APP) gene on chromosome 21 (*1*), and mutations that segregate with familial AD (FAD) have been identified in S182, a strong candidate gene for the chromosome 14 AD3 locus (*2*). In addition to these major gene effects, the ε4 allele of the apolipoprotein E (APOE) gene modifies the risk of developing some forms of AD, possibly by lowering the age of onset (*3*). A third autosomal dominant locus, responsible for AD in the Volga German (VG) kindreds, has been recently localized to chromosome 1q31-42 (*4*). Identification of this locus was complicated by the overlap in the ages of onset of the affected VG subjects with late-onset AD, which is a common disease; thus, potential phenocopies, presumably a result of etiologic (genetic and nongenetic) heterogeneity, were observed among the affected VG subjects (*4*).

Nine VG families were used in this study (Fig. 1). The ancestors of these families immigrated from the Hesse region of Germany to Russia in the 1760s and subsequently to the United States at the turn of the 20th century (*5*). The families were ascertained as part of our larger genetic linkage studies because they contained multiple cases of autopsy-documented AD occurring in two or more generations. Families with both early- and late-onset AD cases were included. Detailed clinical, neuropathologic, and genetic studies of these families have been published elsewhere (*6*, *7*).

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