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Alzheimer Disease: Evidence for Susceptibility Loci on Chromosomes 6 and 14

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SUMMARY

We report the transmission of *HLA* haplotypes and *Gm* allotypes in 97 members of a single kindred containing 257 individuals, 45 of whom were determined by clinical examination, autopsy, or historical data to have had Alzheimer disease (AD). Extensive inbreeding suggests that more than one gene may contribute to susceptibility to AD in this family, despite the apparent vertical transmission of illness. The distribution of *HLA* haplotypes and of *Gm* allotypes to affected and unaffected siblings is consistent with the possibility that genes in the *HLA* region of chromosome 6 and perhaps also in the *Gm* region of chromosome 14 are determinants of susceptibility. Further studies are needed to investigate whether susceptibility to AD may result from an interaction between (immune response?) genes on these two chromosomes.

INTRODUCTION

Alzheimer disease (AD) is the most common form of chronic, progressive, irreversible dementia. Clinical diagnosis is made principally by exclusion of other causes of dementia, with onset, by convention, before age 65. The disorder does, however, have characteristic histopathologic features, such as senile plaques and neurofibrillary tangles in the cerebral cortex. In some cases, AD is familial; in others, it appears to be sporadic [1].

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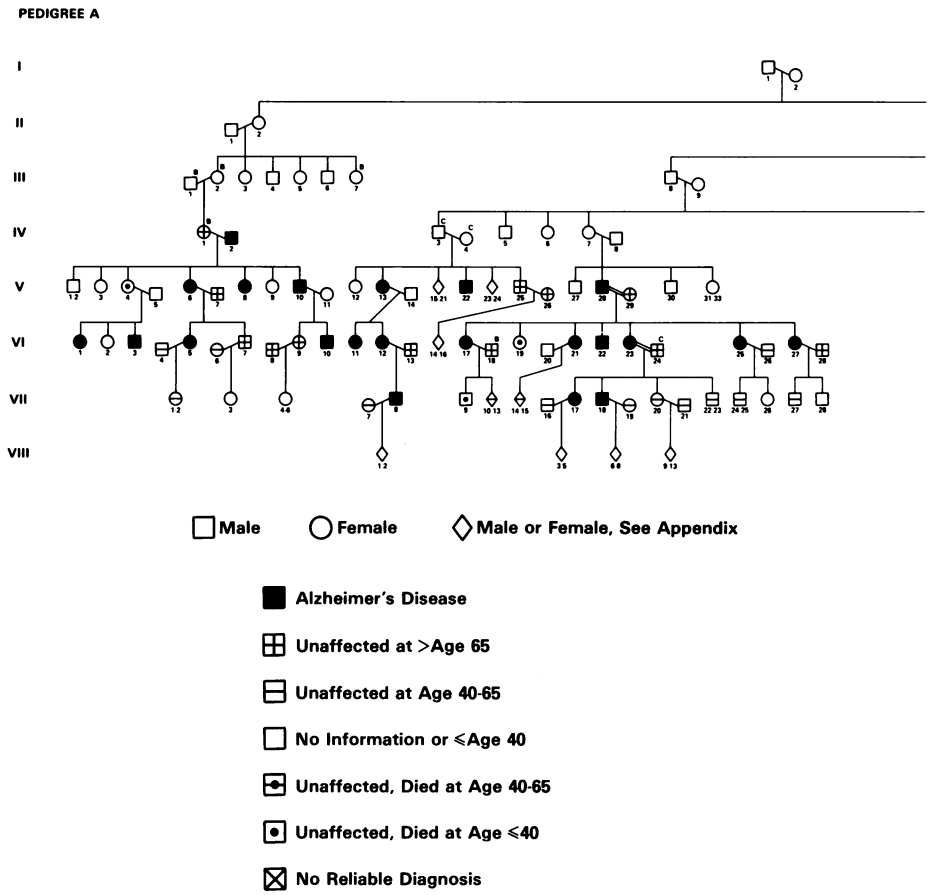

FIG. 1.—Pedigree A: kindred D155, a family with AD. Additional details including clinical and genetic marker data are listed in an appendix* and in table 1. Other relationships of individuals designated B or C are shown in figure 2.

Studies of an association between HLA antigens and Alzheimer dementia have reported different results [2], although one study does demonstrate a highly significant association between HLA-B7 and the sporadic form [3]. This observation, taken together with limited data on the pattern of distribution of *HLA* haplotypes in sibships with familial AD, suggests that genes in the *HLA* region of chromosome 6 contribute to susceptibility to this disease [2].

We report here a detailed genetic study of a large kindred with a "dominantly" transmitted form of AD. On the basis of a complex pattern of inbreeding and of

* See NAPS document no. 04081 for 8 pages of supplementary material, including pedigree number, sex, year of birth, year of death, age at onset, age at death, whether examined, whether a blood sample was obtained, *HLA* haplotypes and *Gm* and *Km* phenotypes. Order from NAPS, % Microfiche Publications, P.O. Box 3513, Grand Central Station, New York, NY 10163. Remit in advance in U.S. funds only $7.75 for photocopies or $4.00 for microfiche. Outside the U.S. and Canada, add postage of $4.50 for the first 20 pages and $1.00 for each 10 pages of material thereafter. $1.50 for microfiche postage.

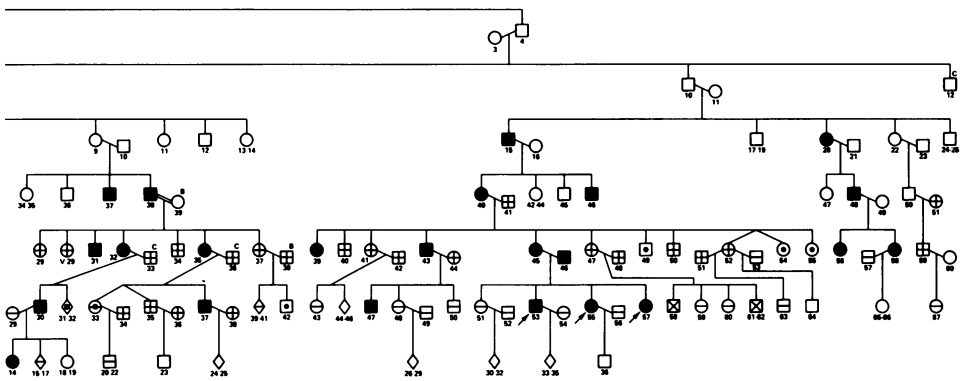

FIG. 1.—Continued

the occurrence and duration of illness in members of this pedigree, we hypothesize that at least two genes contribute to susceptibility to this disorder. The pattern of transmission of *HLA* haplotypes and immunoglobulin (*Gm*) allotypes is consistent with the possibility that genes at loci linked to *HLA* on chromosome 6 and to *Gm* on chromosome 14 may be determinants of susceptibility to AD.

SUBJECTS AND METHODS

Three siblings (VII-53, -55, and -57, pedigree A of kindred D155, fig. 1) were referred to the National Institute of Mental Health (NIMH) for Alzheimer dementia. The history of the family and the results of clinical and laboratory evaluation of 51 family members and of the neuropathological examination of four deceased affected relatives are described by Nee et al. [4]. The diagnostic criteria used for AD included: (1) insidious onset of memory disorder, intellectual dysfunction and disintegration of social interaction and personal habits, (2) a gradually progressive course of failure in the above functions for a minimum of 12 months, (3) exclusion of known reversible causes of dementia, and (4) the absence of stroke-like neurological episodes or deficits. Clinical phenotypes were determined in Bethesda independently of genetic marker typing in Rochester.

Blood samples on 97 family members were collected by venipuncture into vacutainers containing acid citrate dextrose (N.I.H. formulation A). The *HLA-A*, *-B*, and *-C* loci were typed within 36 hrs using fluorescein diacetate [5] and ethidium bromide [6] in the microlymphocytotoxicity test. Properdin factor B (Bf) and glyoxalase (GLO) typing were performed as described by Alper et al. [7] and Lamm et al. [8]. The red cell antigens A, B, C, c, D, E, e, Fy^a, Fy^b, M, N, S, s, K, Kp^a, Jk^a, and P, and the immunoglobulin specificities Gm a, x, f, bl + b0, g, and Km 1 were typed by standard techniques. Chromosome 6 haplotypes—that is, the specific combination of alleles at the *HLA-A*, *HLA-C*, *HLA-B*, *Bf*, and *GLO* loci—were constructed for each family member on the basis of the phenotypes of that individual's parents or offspring. Haplotypes of individuals not available for typing were inferred, when possible, from the types of collateral relatives.

Analyses of the linkage relations between AD and the genetic marker loci *HLA*, *Gm*, and *Km* were performed using the computer program LINKAS [9]. For purposes of this analysis, we assumed dominant inheritance of AD and used age-specific affection rates calculated from an age-at-onset distribution derived from data in the pedigree.

RESULTS AND DISCUSSION

Pedigree Analysis

Both parents of the index cases (VII-53, -55, and -57, pedigree A, fig. 1) were determined on historical grounds to have had dementia. The mother (VI-45) died in 1961 at age 62 after a 4-year illness. The father died in 1969 at approximately age 74 after a dementing illness lasting about 5 years. Limited historical information could be obtained for the relatives of the father, but there was no evidence of dementia in his father (died age 80), his mother (died about age 65), or his seven siblings. Three living nephews of the father, ages 54, 55, and 64, were reported to be well.

A summary of clinical and genetic data on most of the 255 ancestors, descendants, and collateral relatives of the affected mother shown in pedigree A (fig. 1) is listed in an appendix which has been filed with the National Auxiliary Publication Service.* There are, in addition to this woman and her three affected offspring, 40 relatives of the mother affected with Alzheimer disease. For most of these, the diagnosis has been made on historical grounds. However, nine living affected individuals (VI-10, VI-58, VII-8, VII-18, VII-47, and VIII-14, in addition to the three index probands) have been examined and confirmed to have AD; four individuals (VI-3, VII-8, VII-17, and VII-37) had autopsy diagnoses of AD [4].

Casual inspection of pedigree A suggests autosomal inheritance. However, three features of the inheritance pattern suggest the possibility that more than one gene, either alleles or genes at more than one locus, may contribute to the development of AD in this family. First, there is extensive inbreeding among the parents of some affected individuals. Second, there is a higher frequency of illness among the offspring of the consanguineous matings as compared with other matings in this pedigree. Third, the duration of illness is more alike among closely related individuals than among more distantly related family members. These features are considered below.

Dominant inheritance. Three characteristics of fully penetrant, dominant inheritance of AD are apparent in pedigree A: (1) the absence of skipped generations, (2) a near 50:50 segregation ratio for affected and unaffected offspring of affected individuals, and (3) direct descent from a single ancestor (with one possible exception). First, the one instance of a skipped generation involved a woman, V-4, who died at age 35, well before the age at risk. There are no instances of affected offspring from two well parents, both of whom had entered the age at risk and were examined or reliably reported to have been well. For three examined individuals, VII-58, VII-61, and VII-62, a reliable diagnosis could not be made. Second, in the 13 nuclear families with one affected parent and a well spouse who survived to over age 50, there are, among the offspring who lived to greater than age 40, 18 affected and 21 unaffected. Two other affected individuals survived to unknown age and four individuals are of unknown status or age. In the six

* See NAPS document no 04081 for 8 pages of supplementary material, including pedigree number, sex, year of birth, year of death, age at onset, age at death, whether examined, whether a blood sample was obtained, *HLA* haplotypes and *Gm* and *Km* phenotypes. See footnote page 444 for more information.

nuclear families with one affected parent and a spouse of unknown status, there were 11 affected offspring, five unaffected offspring, and five offspring of unknown status. Third, each affected relative of VI-45 is related by direct descent through the two individuals in generation I with the apparent exception of IV-2. This man died in 1886 at age 47 and was reliably reported to have been affected. His wife, IV-1, died at age 94 and did not have AD. No information on the parents of IV-2 was available. However, his name, prior to a change of surname, was identical with that of II-4. Since the surname is fairly uncommon, it seems likely that IV-2 is somehow related to I-1, perhaps through one of the known male lines of descent.

Inbreeding. The possibility that IV-2 may be related to I-1 strengthens the argument for dominant inheritance of a rare gene. However, the fact that his unaffected wife, IV-1, is a known direct descendant of I-1 hints that inbreeding may be relevant to the pattern of inheritance. Inquiry about the ancestry of the 25 spouses of presumed transmitters of the AD gene yielded some information about 14 of them. Eight of the spouses were related, either through pedigree A or through pedigrees B or C (fig. 2). Relatives of III-1 are shown in pedigree B. One of the brothers of III-1 married III-7, a sister of the wife of III-1. III-7 and her husband were the parents of V-39 (an unaffected parent of affected offspring). Thus, not only was V-39 a first cousin of IV-1 but also a second cousin once removed of her affected husband, V-38. One unaffected daughter of these two (V-29) was the spouse of her father's affected cousin, V-28. The only unaffected person among the seven offspring of this latter, highly consanguineous union was one who died in 1918 at age 21. One of these six affected offspring, VI-23, also had affected offspring. Her spouse, VI-24, was a grandson of III-12 (see also pedigree C, fig. 2). The wife of III-12 was a sister of IV-4. These two were aunts to VI-33 and VI-36, the well spouses of affected individuals with affected offspring. Of the six remaining spouses, V-49 was a sibling of VI-42. V-41 had a paternal grandfather with the same uncommon surname as his mother-in-law, IV-16. Three (IV-8, V-11, and VI-44) could be traced back only to parents.

The evidence for extensive consanguinity among the unaffected spouses suggests the possibility that multiple factors with additive effects rather than only a single

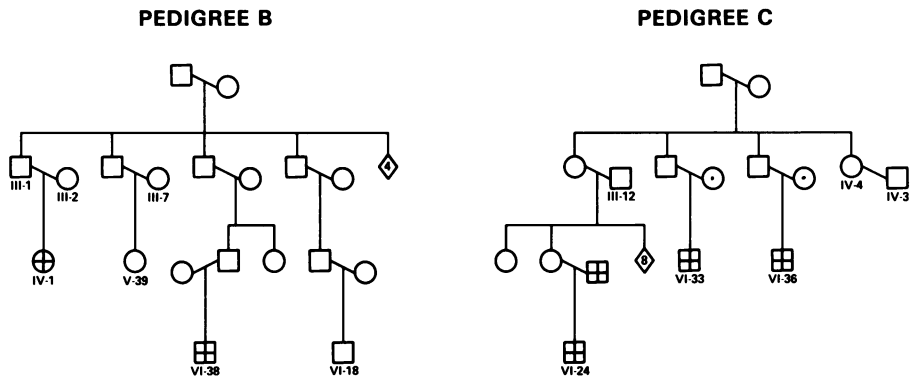

FIG. 2.—Pedigrees B and C. The numbered individuals are shown in pedigree A, figure 1

dominant gene may determine susceptibility to AD in this kindred. Bias inherent in a retrospective family study makes segregation analysis extremely crude. It may be of interest, however, that in two sections of the pedigree (V-28 and V-38) in which all offspring had passed through the age of risk, nine out of 13 were affected. The high incidence of AD in sibships in which there is parental consanguinity is also consistent with an additive multigenic effect.

Onset and duration of illness. In this family, the decrease in life expectancy from AD is about 15 years. Among the 35 affected individuals who had died, the age at death could be determined for 28. That age ranged from 44 to 71 with a mean of 59.6. In contrast, the ages at death of the spouses of AD patients who had died, determined for 12 out of 18 such spouses, ranged from 57 to 94 (mean 72.4). Three ancestral individuals (III-10, IV-3, and IV-7) who would have transmitted AD, assuming dominant inheritance, died at ages 62, 61, and 55. The ages at death of the spouses of these three were 71, 81, and 61. Among the 34 unaffected siblings of AD patients, ages at death were available on 10. For the eight of these who had died at greater than age 40, the range was from 68 to 95 (mean 78.4).

An age at onset could be determined for 22 of the 44 affected individuals: it ranged from 40 to 66 years with a mean of 53.0. In 14 individuals in whom both age at onset and age at death could be determined, the duration of illness was from 3 to 13 years (mean 7.6 years). Nine of the individuals were descendants of III-8, and five were descendants of III-10. The former had an estimated range of duration from 6 to 13 years (mean 9.4), and the latter from 3 to 6 years (mean 4.2). The apparent absence of AD in the ancestors of VI-46, the father of the probands, plus the fact that the onset of his disease at about age 69 was outside the range of onset of illness in his wife's relatives (40–66 years) suggests that his dementia may have had a different etiology from that of his spouse. Alternatively, the difference in duration of illness in two major sections of pedigree A (descendants of III-8 and descendants of III-10) plus the later age at onset of illness in VI-46 may indicate the importance of modifying genes on the course of illness.

In conclusion, direct descent from a common ancestor through all generations and an overall 50:50 segregation ratio suggest autosomal inheritance of a major gene for AD. However, extensive inbreeding among the parents of affected individuals, the evidence favoring a more similar course of illness among closely related family members than among more distantly related individuals, and the possibility that there is a higher incidence of illness among the offspring of consanguineous matings all suggest that more than one gene may contribute to the development of disease in this family.

Relation between AD and HLA

The *HLA* haplotypes of the nine living affected individuals plus five additional affected individuals for whom complete *HLA* haplotypes could be inferred from the types of relatives are shown in table 1. The HLA-B7 antigen, associated with sporadic AD [3], occurred only once. Two individuals (VII-30 and VII-37) share the same combination of haplotypes, but among the 28 haplotypes in the 14

TABLE 1

HLA, BF, GLO, GM, AND KM TYPES OF AFFECTED INDIVIDUALS IN PEDIGREE A

Pedigree no.	Sex	HLA haplotypes	Km 1	Gm
Living:				
VI-10 ...	M	A2 C3 B17 S 2/A9 C6 B18 F[1] 2	+	ag
VI-58 ...	F	A24 B17 S 1/A3 B7 S 1	−	fb
VII-8	M	A3 B12 F 1/A2 B14 F 2	+	fb
VII-18 ...	M	A26 B12 F 2/A1 B8 S 1	+	fb
VII-47 ...	M	A2 B12 S 2/A1 B8 S 2	+	fb
VII-53 ...	M	A28 C4 B35 S 2/A2 C3 B15 S 1	−	fb
VII-55 ...	F	A28 C4 B35 S 2/A1 C6 B17 S 2	+	afb
VII-57 ...	F	A2 B12 S 2/A2 C3 B15 S 1	+	afb
VIII-14 ...	F	A26 C6 B12 S 1/A30 C6 B13 S 2	−	fb
Dead:*				
VI-23 ...	F	A1 B8 S 1/A24 C2 B12 S 1	...	...
VI-25 ...	F	A1 B8 S 1/A2 C3 B17 S 2	...	...
VI-43 ...	M	A2 B12 S 2/A2 C3 B15 S 1	...	...
VII-30 ...	M	A1 B8 S /A30 C6 B13 S	...	...
VII-37 ...	M	A1 B8 S 2/A30 C6 B13 S 2	...	...

* HLA haplotypes inferred from types of relatives.

individuals, there are at least 14 different haplotypes even considering only the small section of chromosome delimited by the *HLA-C*, *HLA-B*, and *Bf* loci. Since the recombination frequency between *HLA-C* and *Bf* is only about 1/2% [10], it is unlikely that a single dominantly expressed susceptibility gene within this region could be the sole determinant accounting for the transmission of AD in this kindred.

This conclusion is further illustrated by an analysis for linkage between *HLA* and an "AD locus," under the assumption of dominant inheritance of AD and taking into account age-specific affection rates. The maximum lod scores ($\hat{z}$), corresponding recombination fraction ($\hat{\theta}$), and lod scores at $\theta = .05, .1, .2, .3,$ and .4 are shown in table 2 for two separate analyses, using different sections of the pedigree. The first analysis includes descendants of V-40, for which there is no evidence for linkage between *HLA* and the postulated AD locus. (The lod scores were calculated under the assumption that the VI-46 does not have the inherited form of AD segregating in this pedigree. Eliminating his offspring approximately halves the lod scores, yielding a maximum score of 0.003 at $\theta = .42$.) Thus, in this part of the pedigree, we confirm the exclusion of close linkage to *HLA*, as was previously reported in a different kindred [11] using the same model of transmission.

The second analysis includes the descendants of V-38 and V-28, giving account to the fact that they are first cousins. The peak lod score is 0.66 at 9% recombination (table 2). If the relationship between V-38 and V-28 is ignored, the maximum lod score for this section of the pedigree becomes 1.52 at zero recombination. The parts of the pedigree yielding positive lod scores between the postulated AD locus and *HLA* are those in which inbreeding is prominent: the first cousins, V-28 and V-38, are related to a greater or lesser degree to their spouses, and indeed their spouses are related as mother and daughter. Other inbreeding occurs within this section of the pedigree (cf., figs. 1 and 2). The two affected individuals who

TABLE 2

LOD SCORES FOR THE LINKAGE RELATIONSHIPS BETWEEN A LOCUS FOR AD, ASSUMING DOMINANT INHERITANCE, AND *HLA*, *Gm* AND *Km* IN PEDIGREE A

MARKER	RECOMBINATION FRACTION, θ =						
	.05	.1	.2	.3	.4	$\hat{z}$	$\hat{\theta}$
HLA:							
Descendants of V-40	−1.54	−0.95	−0.40	−0.15	−0.03	0	0.50
Descendants of V-38 and V-28	0.60	0.66	0.51	0.27	0.07	0.66	0.09
Km	−1.19	−0.86	−0.41	−0.16	−0.04	0	0.50
Gm	1.17	0.99	0.66	0.34	0.10	1.37	0

share *both HLA* haplotypes (VII-30 and VII-37) are first cousins through their affected mothers and second cousins through their unaffected fathers. Other coincidences in the transmission of the same *HLA* haplotype to affected cousins through their unaffected parent strongly hint that *HLA*-linked genes contribute to susceptibility to AD, giving the effect, in the highly inbred section of the kindred, of tight linkage between AD and *HLA*, under the model of dominant transmission.

Either pair of *HLA* haplotypes that can be deduced for the parents (VI-45 and VI-46) of the proband sibship from their offspring (A28 C4 B35 S 2/A2 C-B12 S 2 and A2 C3 B15 S 1/A1 C6 B17 S 1) are, curiously, compatible with the two sets of haplotypes in the mother's parents (V-40 and V-41), as deduced from the mother's siblings. (There was no evidence for inbreeding between VI-45 and VI-46.) This improbable occurrence happened in the only family in which both parents had AD; it could explain why two of their affected offspring (VII-55 and VII-57) might be completely discordant for *HLA* haplotypes.

Relation to Km and Gm

The light chain immunoglobulin allotype, Km 1, has a Caucasian gene frequency of .10 [12], giving it an antigen frequency of .19. It occurred three times in 16 unrelated spouses, but at a much higher frequency in the descendants of I-1. Linkage analysis, nevertheless, does not suggest a relationship between *Km* and susceptibility to AD (table 2).

The tested Gm specificities, Glm (a, x, f) and G3m (g and b0 + b1), usually occur in Caucasians in three common haplotypes, fb, ag, and axg, with population frequencies of approximately .776, .175, and .045 [12]. Gm phenotypes in the nine living affected individuals include one ag, two afb, and six fb. The two individuals, VII-55 and VII-57, who are phenotype afb, must, from the phenotypes of their two sibs, be heterozygotes for the fb haplotype and Glm a (with or without b). The one individual who does not have an fb haplotype is VI-10, a member of the part of the pedigree in which transmission of AD is least clearly related to ancestors of the three probands.

The part of the pedigree most informative for segregation of Gm is the family of the probands. The genotypes of their parents must have been ag/fb and a-/fb. The ag/fb genotype is more likely to have belonged to the mother since two of her sibs, VI-41 and VI-52, have ag/fb genotypes and a third sib, VI-47, must have had an ag haplotype. In the proband sibship, the three affected offspring received the fb haplotype from whichever parent did, in fact, have the ag/fb genotype; the unaffected offspring received the ag haplotype from this parent.

Taking the population frequency of the fb, ag, and axg haplotypes (determined from spouses) as .67, .23, and .10, respectively, the results of linkage analysis are consistent with the transmission of Gm allotypes as a marker of susceptibility to AD (table 2). Most of the information comes from the descendants of V-40, in which the effects of inbreeding are not a problem. Although a peak lod score of 1.37 is not high enough to establish a linkage relationship, the results are of particular interest in view of the association between immunoglobulins and the amyloid in the senile plaque of AD [13].

Two-Locus Susceptibility Gene Hypothesis

Vertical transmission of AD in this family indicates a major effect from a single dominant gene. However, the extensive inbreeding and the possibility that inbreeding or the closeness of relationship may correlate not only with the occurrence but also with the duration of illness suggests that at least two and possibly several genes may contribute to susceptibility.

A probability for the correspondence between inbreeding and the nonrandom transmission of *HLA* haplotypes to affected and unaffected offspring or for the coincidence concerning the *HLA* haplotypes inferred for the apparently unrelated affected parents of the probands is difficult to determine. However, based on this evidence and the pattern of distribution of *HLA* haplotypes among affected and unaffected siblings in published families [2], we conclude that a locus in or near the HLA region of chromosome 6 does contribute to susceptibility to AD. Since genes tightly linked to *HLA* cannot account for the vertical pattern of transmission of AD in this and other families [3, 11], a second locus, not linked to the *HLA* loci, may also be an important determinant of susceptibility. The hypothesis that such a second susceptibility locus may be linked to the *Gm* loci is not inconsistent with data in this pedigree. The hypothesis is tenable given the increasing evidence that immune response genes linked to Gm are second locus determinants of susceptibility in some other HLA-related diseases [14, 15] and in view of the fact that AD may be a disorder of immune function [13, 16].

There is insufficient information on the distribution of Gm types in pedigree A to distinguish between dominant inheritance of a *Gm*-linked immune response gene or an interaction between specific *HLA*-linked immune response genes and genes in linkage disequilibrium with the alleles determining Gm allotypes, as proposed by Whittingham et al. [14] for chronic active hepatitis. Depending on the nature of the interaction between the susceptibility genes at the two loci and on whether there is a different effect from one or two susceptibility alleles at each locus, it may be possible to account for both familial and sporadic AD under a single genetic model. On the other hand, the evidence favoring a difference in the in vitro cell-fusing activity of brain suspensions from familial as compared with sporadic AD patients [17] suggests an etiologic, if not genetic, difference between the two forms of disease.

NOTE ADDED IN PROOF: Since completion of this study, two individuals, VII-14 and VII-20, have developed AD at ages 55 and 53, respectively. Individual VII-20 and her older, affected brother, VII-18, inherited the same *HLA* haplotype (A26 C- B12 F 2) and the same *Gm* allotype (fb) from their unaffected father. The other *HLA* haplotype of VII-20 (A24 C2 B12 S 1) is present in her newly affected maternal first cousin, VII-14. This new information increases the evidence for a relationship between AD and both *HLA* and *Gm* in this family.

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