Specificity of the fivefold increase in AD in mothers of adults with Down syndrome

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Article abstract—*Background:* In a previous study, the authors found that the risk of AD among mothers who were 35 years or younger when their children with Down syndrome (DS) were born was five times that of mothers of children with other forms of mental retardation. The current study investigated the specificity of the familial aggregation of DS and AD by examining whether mothers who gave birth to children with DS before age 35 are also at increased risk of other age-related neurologic or medical disorders. *Methods:* The authors used survival methods to compare cumulative incidence and relative risk of AD, other dementias, and common age-related disorders in parents of 200 adults with DS and parents of 252 adults with other forms of mental retardation. *Results:* Mothers who were ≤35 years of age when their children with DS were born were four to five times as likely to develop AD as control mothers (rate ratio = 4.8, 95% CI 2.1, 11.2), whereas risk of AD among mothers who were >35 years when their children with DS were born was not significantly increased (rate ratio = 1.8, 95% CI 0.6, 5.1). Risk of AD among fathers of probands with DS was similar to that of control fathers, and did not vary by age at proband birth. Risk of other dementias and of other age-related medical condition was similar among mothers and fathers of probands with DS and control parents, regardless of age at proband birth. *Conclusion:* These findings suggest that the increased risk of AD among mothers who gave birth to children with DS before age 35 appears to represent a specific vulnerability to AD, as opposed to other age-related degenerative disorders.

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An increased frequency of Down syndrome (DS) births in the families of individuals with AD and an increased frequency of AD in relatives of DS probands suggest a shared genetic susceptibility to DS and AD.[1-6] In a previous study we investigated whether factors associated with increased risk for having a child with DS might account for this association. In 95% of DS trisomies, the nondisjunction event is of maternal origin.[7,8] Thus, the frequency of AD should be increased in mothers, but not fathers, of individuals with DS. After age 35, the risk of bearing a child with DS increases with increasing maternal age.[9,10] It has been proposed that the association between advanced maternal age and autosomal trisomy reflects the diminution of the oocyte pool with age.[11-13] In contrast, a genetic susceptibility to early nondisjunction of chromosome 21 may play a role in risk for a child with DS among young mothers. We hypothesized that this genetic susceptibility might also account for the familial aggregation of DS and AD.[14] In this case, we would expect to observe an increased risk of AD among mothers who were young, but not among mothers who were older, when their child with DS was born.

The current study investigated the specificity of the familial aggregation of DS and AD by examining whether mothers who gave birth to children with DS before age 35 are also at increased risk of other age-related neurologic or medical disorders. No previous study has examined these relationships. We compared the frequency of AD, other dementias, and common age-related disorders in an expanded sample of parents of 200 adults with DS and parents of 252 adults with other forms of mental retardation. We found that the risk of AD among mothers who were 35 or younger when their children with DS were born was five times that of mothers of children with other forms of mental retardation. In contrast, risk of AD among mothers who were older (>35 years) at the proband's birth was similar to that of control mothers. Among fathers of DS cases and fathers of controls, there was no difference in the frequency of AD, and risk of AD did not vary by paternal age at proband birth. Risk of other demen-

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tias and of other age-related medical condition was similar among mothers and fathers of probands with DS and control parents, regardless of age at proband birth.

Materials and methods. *Subjects.* Adults with mental retardation residing in the nine-county downstate region of New York were identified through the Developmental Disabilities Profile, a computerized database maintained by the New York State Office of Mental Retardation and Developmental Disabilities, and by an independent survey of all state and voluntary service providers of persons with DS in New York state.[15] The first group (probands) consisted of a random sample of adults with DS, aged 30 to 70 years, and the comparison group consisted of probands with other forms of mental retardation who were frequency matched to the DS probands for sex, age, and severity of mental retardation. We chose these individuals and their parents as the comparison group to allow for nonspecific factors associated with significant lifelong impairment in a family member and to control for possible biases introduced by ascertainment procedures, rates of participation, and recall bias.

Families of the probands were contacted with the help of the responsible service provider agencies. To avoid selective participation of families with a history of dementia, the study was described as a survey of age-related diseases in individuals with developmental disabilities and their families. Probands without first-degree relatives and who had no contact with second-degree relatives were ineligible (30%; no difference between groups). Participation rates among eligible families were 72.3% for DS families and 73.5% for comparison families.

Proband interviews. A semi-structured interview with a caregiver (direct care staff, case supervisor) was used to collect information about case and control probands and to confirm information provided on the Developmental Disabilities Profile. Blood samples were collected from 143 probands with DS for karyotyping and determination of apolipoprotein E genotypes. All probands with DS were confirmed to have trisomy 21 by cytogenetic analysis. Ten subjects (7.0%) showed mosaicism for DS, ranging from 3% to 20% disomic cells, one proband (0.7%) had a translocation involving chromosome 21 and chromosome 1, and two probands (1.4%) had a translocation involving chromosome 21 and chromosome 14. Families of the three DS probands with translocations were excluded from the analysis.

Family medical history. We attempted to interview more than one informant in each family in order to increase the sensitivity and specificity of the family history data. The mean number of informants was 2.9 (range 1 to 5) for DS families and 2.6 (range 1 to 7) for control families. A semi-structured family history questionnaire for AD and other common age-related neurologic and medical disorders was used. Interviewers were naive with respect to our hypotheses and were also unaware of the case/control status of the family. Interviews were conducted in the informant's home unless the relative lived out of the tri-state metropolitan area, in which case they were conducted by telephone (24%).

The family history questionnaire asked for an enumeration of all first- and second-degree relatives, their vital status, date of birth, ethnicity, birth order, level of education, and current age or age at death and cause of death. Family medical history was ascertained by questions on the presence or absence and age at onset of dementia, and a number of common age-related medical conditions.

Classification of AD and other dementia in parents. We ascertained the occurrence of dementia in several ways. In addition to a direct question on the history of dementia, senility, hardening of the arteries, AD, or other mental changes, five screening questions were used to obtain information on the occurrence of memory loss, difficulty in activities of daily living, and confusion or disorientation. For individuals who were reported positive on any direct or screening question, we used the Dementia Questionnaire (DQ) to provide detailed information on dementia symptoms and age at onset of symptoms. The DQ is a structured informant interview originally developed to diagnose dementia among relatives of probands with AD in family history studies.[16] The DQ includes questions on the occurrence and age at onset of memory loss, language and expression difficulties, loss of activity of daily living skills, other medical problems, progression of memory loss (sudden/slow onset; abrupt/gradual progression or no change), and family awareness of the problems. We modified the DQ to obtain more detailed information on history and age at onset of stroke. If there was a history of stroke, the interviewer asked questions on the number of strokes, stroke symptoms (change in speech with slurring, loss of sensation on one side of the body, weakness on one side of the body), persistence of symptoms, type of stroke, and whether the memory problems occurred before or after the stroke. If the memory problems occurred after the stroke, the interviewer asked whether onset of memory problems occurred within 3 months, between 3 and 6 months, or more than 6 months after the stroke. Comparison of dementia status ascertained with the DQ with the criterion standard of clinical diagnosis established by examination and laboratory studies has been found to have a sensitivity and specificity for dementia status of 100% and 90%, respectively.[17] We applied operational criteria to the responses to the DQ to arrive at a diagnosis of primary degenerative dementia; these included a history of progressive memory loss, confusion, and disorientation, and difficulty with activities of daily living such as dressing and eating. Parents were considered affected if they were reported to have progressive memory loss and one or more other symptoms in these categories. All parents meeting criteria for dementia, a random sample of parents not reported positive on any direct or screening question, and parents reported to have had medical conditions that might result in dementia were referred to the study neurologist (R.M.), who was blind to the case/control status of the family, for differential diagnosis of AD and other dementia disorders. Dementia cases were classified as probable AD, possible AD, mixed AD, vascular dementia (VaD), Parkinson's dementia, other dementia, none, or unable to diagnose. All analyses used the neurologist's diagnosis as the outcome measure for dementia. Only cases with probable AD were considered affected with AD. For analyses, cases with mixed dementia, Parkinson's dementia, and other dementia were classified as other-cause dementia.

Ascertainment of other age-related medical conditions. The semi-structured family medical history questionnaire was used to obtain information on parent's medical history and exposure

to risk factors for age-related medical conditions. The medical history questionnaire included questions on the occurrence of neurodegenerative disorders (e.g., PD), cardiovascular and cerebrovascular disease, malignancy, respiratory disease, diabetes, head injury resulting in loss of consciousness, autoimmune diseases, thyroid disorders, hypertension, smoking history, alcoholism, and psychiatric conditions. Additional questions probed for any other conditions not directly addressed in the questionnaire. For each condition named, we ascertained age at onset, duration, and treatment history. Diagnoses of medical conditions were based on a consensus review of all information collected on each parent (direct interview, multiple informant interviews, reported treatment and medication for that condition). For each parent, the consensus review was carried out blindly with respect to the information collected on the other parent or the proband.

Statistical analysis. We employed *t*-tests and χ^2 tests to compare demographic characteristics of parents. Two models for estimating risk of AD were tested. Model I: parents who had a stroke or other dementia that preceded the onset of AD were considered at risk of AD until onset of stroke or other dementia, as were parents with a history of other medical conditions that might result in dementia (n = 55). Thus, other-cause dementia cases and cases with dementia-related medical conditions were considered as independent censoring events because their occurrence prevents detection of AD. Model II: these same parents were considered uninformative and were excluded from the analysis. Similar competitive risk models were used for estimating cumulative incidence and relative risk of VaD, other-cause dementias, and other age-related medical conditions. We estimated cumulative incidence of AD and other conditions using a "reconstructed cohort" design in which each parent was considered to be at risk of the outcome from birth until current age or age at death (if unaffected) or age at onset of the condition.[18] We used life table methods to assess the relative risk of AD, other dementias, and other age-related medical conditions among case and control parents within strata defined by parent's age at DS birth (≤35 years versus >35 years), because this is the age at which risk of bearing a child with DS is clearly increased. Cumulative incidence of AD and other conditions was estimated to age 85, because our hypothesis specifies an earlier age at onset distribution among mothers who were relatively young when their child with DS was born. Multivariate Cox proportional hazards models were then used to calculate rate ratios (RR) for AD, other dementias, and other medical conditions in mothers and fathers of probands with DS versus mothers and fathers of probands with other forms of mental retardation, adjusting for age, ethnicity, and education.[19] The final analysis compared mothers who were ≤35 years of age at the birth of their child with DS and mothers who were >35 years of age when their child with DS was born against all control mothers. This analysis was repeated for fathers. All analyses were conducted using SPSS for Windows, 8.0.[20]

Results. Parents of probands with DS did not differ from control parents in current age, ethnicity, or level of education, but as we expected, both mothers and fathers of probands with DS were significantly older at proband birth than the corresponding control parents (table 1). Informants were self, first-degree relatives, or spouses for 92.3% of the parents of DS probands and for 90.8% of the parents of control probands.

Table 1 *Characteristics of parents*

Parents	Down syndrome	Other mental retardation
Sample size†	395	495
Age, y, mean (SD)		
Mothers	74.0 (11.2)	72.8 (11.9)
Fathers	70.5 (11.5)	70.4 (12.1)
Age at proband birth, y, mean (SD)		
Mothers	33.6 (7.2)	29.3 (6.0)*
Fathers	36.5 (8.1)	33.6 (7.1)*
Education less than high school, n (%)†		
Mothers	88 (44.2)	111 (44.4)
Fathers	83 (44.9)	101 (41.2)
Ethnicity: Mothers, n (%)†		
White	180 (90.9)	229 (91.6)
African American	14 (7.1)	14 (5.6)
Other	4 (2.0)	7 (2.8)
Ethnicity: Fathers, n (%)†		
White	179 (91.3)	229 (91.9)
African American	14 (7.1)	12 (4.8)
Other	3 (1.5)	8 (3.2)

* $p < 0.05$.
† Excludes parents with unknown values.

We present the detailed results from the first, more conservative, model because the same pattern of results was obtained using the two analysis models where parents with other cause dementia were either considered unaffected or were excluded. Mothers who were 35 years or younger when their children with DS were born were four to five times as likely to develop AD as control mothers (table 2, figure). In contrast, the risk of AD among mothers who were older than 35 years when their children with DS were born was similar to that of control mothers. To rule out the possibility that there was a maternal age effect among the controls, we repeated these analyses with both DS and control groups stratified by age at proband birth and found the same increased risk in younger DS mothers (RR for DS mothers within mothers ≤35years at proband birth = 4.8, 95% CI 1.9, 12.2: RR for DS mothers within mothers >35 years at proband birth = 2.0, 95% CI 0.4, 10.5). To provide confirmation of our original finding, we repeated the analyses using only the second half of the study sample. Risk of AD in mothers who were ≤35 years at proband birth remained elevated when we excluded all parents from our original analysis (see table 2). Risk of AD among fathers of probands with DS was similar to that of control fathers, and did not vary by age at proband birth (see table 2, figure).

Risk of VaD and other-cause dementia was similar among mothers of probands with DS and control mothers, regardless of age at proband birth; the same pattern of results was found in fathers (table 3).

Table 2 *Cumulative incidence of AD in parents of adults with Down syndrome (DS) and parents of adults with other forms of mental retardation (MR)*

Parents	No.	Affected, n (%)	Cumulative incidence to age 85	Ratio (95% CI)
Mothers*				
Total group				
Probands with DS				
≤35 y at birth†	112	16 (14.3)	0.33	4.8 (2.1–11.2)‡
>35 y at birth§	87	6 (6.9)	0.14	1.8 (0.6–5.1)
Other MR	250	9 (3.6)	0.09	1.0 (reference)
New sample only				
Probands with DS				
≤35 y at birth†	58	5 (8.6)	0.24	4.0 (1.2–13.7)‡
>35 y at birth§	48	4 (8.3)	0.13	1.9 (0.5–7.6)
Other MR	171	5 (2.9)	0.09	1.0 (reference)
Fathers†				
Total group				
Probands with DS				
≤35 y at birth†	97	3 (3.1)	0.13	1.0 (0.3–3.2)
>35 y at birth§	99	5 (5.1)	0.14	1.2 (0.4–3.4)
Other MR	245	12 (4.9)	0.18	1.0 (reference)
New sample only				
Probands with DS				
≤35 y at birth†	52	1 (1.9)	0.03	0.7 (0.1–6.4)
>35 y at birth§	53	2 (3.8)	0.15	1.2 (0.3–5.8)
Other MR	167	8 (4.8)	0.20	1.0 (reference)

* Rate ratio for AD, adjusted for age, ethnicity, and level of education.
† Parents who were ≤35 years of age at proband birth.
‡ $p < 0.05$.
§ Parents who were >35 years of age at proband birth.

Table 3 *Cumulative incidence of dementia in parents of adults with Down syndrome (DS) and parents of adults with other forms of mental retardation (MR)*

Parents	No.	Affected, n (%)	Cumulative incidence to age 85	Ratio (95% CI)
Mothers*				
Vascular dementia				
Probands with DS				
≤35 y at birth†	112	1 (0.9)	0.01	0.4 (0.04–3.0)
>35 y at birth‡	87	4 (4.6)	0.09	1.7 (0.5–5.9)
Other MR	250	6 (2.4)	0.05	1.0 (reference)
Other dementia				
Probands with DS				
≤35 y at birth†	112	6 (5.4)	0.18	1.5 (0.5–4.3)
>35 y at birth‡	87	3 (3.4)	0.15	0.8 (0.2–3.1)
Other MR	250	10 (4.0)	0.17	1.0 (reference)
Fathers†				
Vascular dementia				
Probands with DS				
≤35 y at birth†	97	1 (1.0)	0.01	0.4 (0.05–3.7)
>35 y at birth‡	99	3 (3.0)	0.07	0.9 (0.2–4.8)
Other MR	245	6 (2.4)	0.11	1.0 (reference)
Other dementia				
Probands with DS				
≤35 y at birth†	97	3 (3.1)	0.05	0.9 (0.2–3.3)
>35 y at birth‡	99	3 (3.0)	0.09	0.7 (0.1–3.1)
Other MR	245	9 (3.7)	0.13	1.0 (reference)

* Rate ratio for dementia, adjusted for age, ethnicity, and level of education.
† Parents who were ≤35 years of age at proband birth.
‡ Parents who were >35 years of age at proband birth.

Risk of all heart disease and other age-related disorders, including stroke, congestive heart failure, cardiac arrhythmia, diabetes, hypothyroidism, or PD, did not differ among mothers or fathers of adults with DS and control parents (for additional data, please access the on-line version of this article at www.neurology.org). However, mothers who were ≤35 years of age when their child with DS was born were twice as likely to develop coronary artery disease (RR = 2.0, 95% CI 1.2, 3.3), whereas risk of coronary artery disease did not differ among mothers who were >35 years of age at proband birth and control mothers (RR = 0.6, 95% CI 0.3, 1.5).

Discussion. This study confirms and extends our previous report of the familial aggregation of DS and

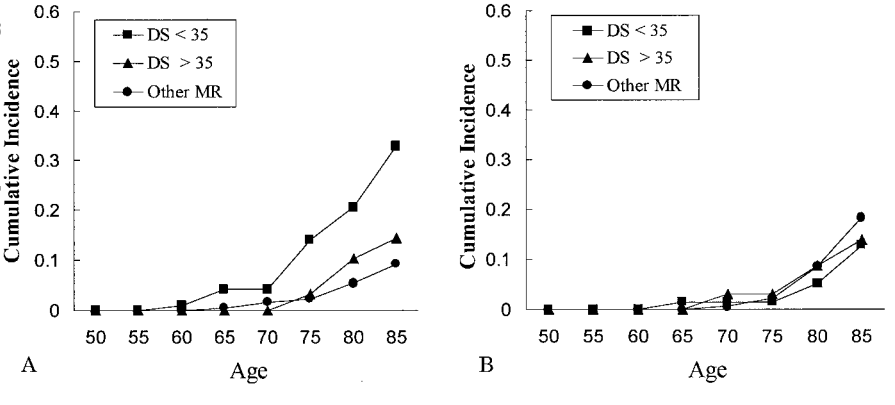

Figure. Cumulative incidence to age 85 of AD in parents of adults with Down syndrome (DS) and parents of adults with other forms of mental retardation (MR). A, mothers; B, fathers.

AD. Our finding that risk of AD was increased in mothers, but not fathers, who were ≤35 years of age at birth of their child with DS is consistent with evidence that 95% of DS trisomies are associated with a nondisjunction event in maternal meiosis,[7,8] and we were able to replicate our findings using an independent sample.

It is likely that our diagnosis of AD includes some misclassification, as it was based on family history methods with information collected retrospectively from parents, children, and other relatives. For this reason we chose to classify as affected with AD only cases with a diagnosis of probable AD, although this method will have reduced sensitivity for AD. Most primary degenerative dementia without any other symptoms or comorbid conditions is likely to be classified as AD in clinical settings. Nonetheless, it is possible that parents with AD with "silent strokes" were included as AD. Conversely, some cases of dementia with overt stroke who were classified as having VaD might represent "mixed AD," with coincident AD and VaD. We would expect this misclassification to be nondifferential with respect to AD and VaD, and to reduce the strength of the association between maternal age at DS birth and risk of AD.

A shared genetic susceptibility to DS and AD could reflect a general vulnerability to age-related degenerative disorders, raising risk both for having a child with DS and for developing AD and other age-related medical conditions. However, the frequency of other dementias or of other common age-related disorders, including cardiovascular disease, cancer, hypothyroidism, diabetes, or PD, was not increased, except for coronary artery disease. These results suggest that the association of DS and AD appears to be relatively specific to AD, as opposed to other age-related degenerative disorders.

We found an increased risk of coronary artery disease among mothers, but not fathers, who were ≤35 years of age at DS birth. Several studies have reported an association between cardiovascular disease and AD, possibly mediated by the effects of the *APOE* ϵ4 allele.[21-23] One study found an association between meiotic stage of nondisjunction and the *APOE* ϵ4 allele among mothers who gave birth to a DS child when <32 years of age,[24] and suggested that the shared susceptibility to DS and AD might be mediated by an increased frequency of the ϵ4 allele. In that study, the frequency of the ϵ4 allele was greater in young mothers with meiosis II nondisjunction than in young mothers with a meiosis I nondisjunction (30% versus 19%), but did not differ between young mothers with meiosis I events and control mothers (19% versus 17%). However, this finding could not be replicated in another study.[25] Although we did not genotype parents in our study, the *APOE* ϵ4 allele frequency among the 143 probands who we genotyped did not differ among offspring of mothers who were younger or older at DS proband birth (13.4% versus 12.9%), as would be expected if there were an excess of the ϵ4 allele in young mothers. Although we cannot rule out some role, it is unlikely that the *APOE* ϵ4 allele is a significant risk factor in our sample for chromosome 21 nondisjunction.

In sum, our findings suggest that the increased frequency of AD in mothers who gave birth to children with DS before age 35 reflects a specific vulnerability to AD, as opposed to other degenerative disorders. Considerable evidence that chromosome specific mechanisms may underlie meiotic nondisjunction is accumulating.[26] For example, the associations between recombination frequency and the timing of nondisjunction appear to differ for trisomies of chromosomes 21, 15, and 18.[27-29] We have reported that risk of AD was not raised among parents of women with trisomic losses of other autosomal chromosomes, which also suggests the possibility that familial aggregation with AD is specific to chromosome 21.[30] An alternative hypothesis, that mosaicism in the germ cells and brain accounts for familial aggregation of AD and trisomy 21, seems unlikely.[31] Although the prevalence of mosaicism in lymphocytes may underrepresent the prevalence of mosaicism in germ cells and brain, mosaicism in lymphocytes of mothers of trisomy 21 pregnancies has been reported to be in the range of 1.9 to 2.4%, too low to account for the four- to fivefold excess risk of AD that we observed in young mothers.[32]

A limitation of our study is that we evaluated primarily risk for common major age-related disorders, but could not examine a wider range because of small sample size and low power to detect an increase in the frequency of relatively rare disorders. It is possible that mothers who gave birth to children with DS before age 35 are at increased risk for other, less common disorders, but the broad pattern of our results suggests a specific association of DS and AD. Based on these results, it is likely that the probability of having a DS birth early in life and developing AD later is genetically influenced. It is attractive to consider the possibility that one or more genes on chromosome 21—for example, polymorphisms in the gene for amyloid precursor protein—could be involved. However, family-based studies will be required to identify the gene or genes involved in this dual process.

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