Published in final edited form as:
*Am J Med Genet*. 2002 April 8; 114(3): 299–303.

# Paternal Age and Sporadic Schizophrenia:

## Evidence for De Novo Mutations

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## Abstract

Schizophrenia is an etiologically heterogeneous syndrome. It has a strong genetic component and exists in clinically indistinguishable familial and nonfamilial (sporadic) forms. A significant role for de novo genetic mutations in genetic schizophrenia vulnerability is suggested by a strong monotonic increase in schizophrenia risk with advancing paternal age. However, an alternative explanation for the paternal age effect in schizophrenia is that childbearing is delayed in fathers who themselves have genetic schizophrenia vulnerability. In this study, we compared paternal birth ages between patient groups with familial (n = 35) and sporadic (n = 68) patients with DSM-IV schizophrenia from an inpatient schizophrenia research unit. If later age of fathering children is related to having some genetic schizophrenia vulnerability, then paternal birth age should be later in familial schizophrenia cases than in sporadic cases, and any association of father's age and schizophrenia risk in offspring would be a spurious finding, unrelated to etiology. However, if de novo mutations cause sporadic schizophrenia, then patients without a family history of schizophrenia would have older fathers than familial patients. We found that patients without a family history of schizophrenia had significantly older fathers (4.7 years) than familial patients; so later childbirth was not attributable to parental psychiatric illness. These findings support the hypothesis that de novo mutations contribute to the risk for sporadic schizophrenia.

### Keywords

schizophrenia; paternal age; sporadic; familial; mutation; IQ

## INTRODUCTION

Schizophrenia is a severe neuropsychiatric illness with onset in late adolescence or early adulthood. Typified by distorted perceptions of reality (hallucinations and delusions), social deficits, disorganized language and behavior, and mild cognitive dysfunction, it is a devastating and relatively common disorder, affecting about 1% of worldwide population. The prevailing theory is that schizophrenia results from anomalous neurodevelopment, either from a teratogenic fetal exposure or from defective genes. Scores of family, twin, and adoption studies have confirmed a major hereditary component for schizophrenia risk, yet no particular gene has been identified for the disorder. The present consensus is that schizophrenia is an



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etiologically heterogeneous syndrome, with multiple genes, various exposures, and gene-environment interactions producing a common phenotype. For many genetic diseases, the birth of an affected individual into an otherwise unaffected family (sporadic case) signals a possible de novo mutation. In contrast, sporadic cases of schizophrenia are usually presumed to originate from environmental factors that either act independently or through synergistic effects with underlying genes.

Nonetheless, it would be reasonable to consider that de novo mutations might account for some of the risk for schizophrenia, as they do in a number of other neurodevelopmental disorders that occur in both sporadic and familial forms. While it was previously well known that a number of mendelian diseases were related to de novo mutations, recent findings implicate de novo mutations as a mechanism for some complex genetic disorders as well, including prostate cancer [Zhang et al., 1999], nervous system cancer [Hemminiki et al., 1999], and several birth defects [McIntosh et al., 1995]. Thus, this mechanism is reasonable to examine with respect to schizophrenia risk. Since new human mutations arise primarily in the male germline in proportion with father's age [Crow, 1999], we had previously investigated the association of schizophrenia risk and paternal age in an 89,722-member population birth cohort. in this cohort, advancing paternal age was associated with a strong monotonic increase in schizophrenia risk, accounting for fully a quarter of the schizophrenia cases, which is consistent with a role for de novo genetic mutations in a schizophrenia vulnerability gene [Malaspina et al., 2000].

Several earlier studies had also found older mean paternal birth ages for schizophrenia patients [Gregory, 1966; Schooler and Parkel, 1966; Bojanovsky and Gerylovova, 1967; Farina and Holzberg, 1967; Johanson, 1968; Hare and Moran, 1979; Kinnell, 1983], but new mutations were not generally considered to mediate this association. Rather, a number of authors speculated that men with genetic schizophrenia vulnerability might simply have children at a later age. This may be a fair alternative explanation for the paternal age effect in schizophrenia, since even mild schizophrenia cases are typified by impaired social behavior that could plausibly impact on the age structure of marriage and fatherhood. Psychiatric information on the fathers of schizophrenia cases in our birth cohort study was not available to address this critique adequately in the earlier study.

The comparison of paternal birth ages between groups of patients with familial and sporadic forms of a disorder can also be used to test hypotheses about the origin of disease genes, with later paternal ages in sporadic than in familial cases taken to suggest that de novo mutations in disease genes have occurred in spermatogonia. This study design is widely used in genetic epidemiology (Table I). It may be particularly advantageous for research in psychiatric conditions, in which parental mental disorders might affect childbearing patterns. Consequently, if later age of fathering children is related to having some genetic schizophrenia vulnerability, then paternal birth age should be later in familial schizophrenia cases than in sporadic cases, and any association of father's age and schizophrenia risk in offspring would be a spurious finding, unrelated to etiology. However, if de novo mutations cause sporadic schizophrenia, then patients without a family history of schizophrenia would have older fathers than familial patients. We examined these possibilities in a large series of schizophrenia research patients for whom we had information about family psychiatric disorders.

## MATERIALS AND METHODS

We studied a series of patients with DSM-IV schizophrenia who were consecutively admitted to our inpatient schizophrenia research unit and who had participated in clinical and family history assessments. The subjects all provided written informed consent for these institutional review board–approved protocols. They were physically healthy and had normal physical examinations and laboratory tests, including normal thyroid function. Psychiatric diagnosis

was based on a research interview using the Diagnostic Interview for Genetic Studies [Nurnberger et al., 1994], which was administered by master's degree–level clinicians, as well as clinical data, past records, and symptom ratings. The final psychiatric diagnosis represented a consensus among clinical and research staff. Since the focus of this study was parental age and family history in those with a DSM-IV schizophrenia diagnosis, the patients who received other final diagnoses (including schizoaffective disorder, psychotic affective disorders, or other nonaffective psychoses) were not included in this analysis. Other patient data included age, gender, education, age of onset of psychotic symptoms, socioeconomic status based on the patient's education and vocational achievement, and intelligence testing.

Family assessments were conducted blind to patient information using clinical interview information and/or information from a family informant that was obtained with the Family Interview for Genetic Studies (NIMH-Molecular Genetics Initiative). All axis I and II diagnoses for which there was sufficient information were made for all first- and second-degree relatives. Probands who had a relative with a chronic nonaffective psychosis were considered to have a familial illness ($FH^+$) and those without any illness recurrence in a relative were assigned to the family history negative ($FH^-$) or sporadic group. The familial cases were further subdivided into those who had illness in a first-degree relative (FH1) and those who had unaffected first-degree relatives but had illness in a second-degree relative (FH2). The $FH^+$ group was comprised of the FH1 plus the FH2 patients. All data available were included in these analyses, with different sample sizes reflecting missing data.

## RESULTS

The sample size included 103 patients with DSM-IV schizophrenia, 34 females and 69 males. Family history categorization was negative, or sporadic ($FH^-$), for 68 patients and was positive, or familial ($FH^+$), for 35 cases. Of the familial cases, 18 had an ill first-degree relative (FH1), and 17 patients had well first-degree relatives but had an illness recurrence in a second-degree relative (FH2), including grandparents, aunts, or uncles.

Initially, we performed a three-FH group analysis of variance (ANOVA) for maternal and paternal age for the FH1, FH2, and $FH^-$ patient groups. Both parents' ages showed a family history group effect: (maternal age: $F = 3.15$, df = 2, $P = 0.047$; paternal age: $F = 3.87$, df = 2, $P = 0.024$), with parental birth ages being increasingly older as the degree of genetic relatedness to an affected relative became more distant (Tables II and III). Maternal and paternal age also significantly differed for the inclusive familial group (FH1 + FH2) compared to the ($FH^-$) sporadic groups, and for the group with illness recurrence in first-degree relatives (FH1) compared to the sporadic ($FH^-$) group. The parental ages of the FH2 group were intermediate to the FH1 and sporadic parents, but in this small sample the age differences did not reach significance. We thus combined the FH1 and FH2 groups into a single familial group for the additional analyses.

Since maternal and paternal ages were highly correlated ($r = 0.74$, df = 82, $P<0.001$), we used multi-variate analyses to examine their independent associations to the family history groups. Paternal age showed a significant relationship with family history when entered on the first step (Wald = 4.877, df = 1, $P = 0.027$), with maternal age failing to enter the equation. In contrast, there was no effect of maternal age when it was entered on the first step (Wald = 0.285, df = 1, $P = 0.593$), but paternal age on the next step still tended to be associated with family history (Wald = 3.43, df = 1, $P = 0.067$). We concluded that paternal age explained the family history groups; the association of FH and maternal age was a consequence of the strong correlation between the parental ages.

We next compared the familial $FH^+$ (combined FH1 and FH2) to the sporadic $FH^-$ groups on demographic and symptom measures (Table IV). The familial and sporadic groups did not differ in age, proportion of male and female subjects, or age of onset. Socioeconomic status and years of education were greater for the sporadic patients, as might be expected, since none of the parents of these cases had schizophrenia themselves. The groups also differed in full-scale IQ, with familial cases having a lower mean full-scale IQ than sporadic cases, which was attributable to group differences in verbal IQ scores. These IQ differences could be a result of the better education and socioeconomic status (SES) of the sporadic patients or reflect greater dysfunction in the familial patients.

## DISCUSSION

We found older fathers for sporadic than for familial groups of schizophrenia patients, demonstrating that advanced paternal age in schizophrenia is unlikely to result from delayed childbearing by fathers who carry genetic schizophrenia vulnerability. The mean paternal age difference between these familial and sporadic schizophrenia patients (29.3 vs. 33.9 years, respectively) is similar to the paternal age differences reported in other diverse genetic diseases that arise from de novo mutations. For illustrative purposes, the crude mean paternal age in the familial forms of the various genetic disorders was 30.1 years in Table I, in contrast with 34.7 years for the sporadic cases, leading to a paternal age difference of 4.6 years. This result is remarkably similar to the 4.7-year mean paternal age difference we found between the familial and sporadic subgroups of schizophrenia cases in the present study.

A de novo mutation causing schizophrenia would likely occur in a dominant or partially dominant allele, since inheritance of a single mutation confers the increased risk. Schizophrenia patients have low fertility [Fananas and Bertranpetit, 1995; McGrath et al., 1999], which would appear to select against a role for a dominant gene. However, a dominant gene that is replenished through new mutations can be sustained in the population, notwithstanding its impact on reproductive fitness. If sporadic schizophrenia can originate from de novo mutations, then genes involved in neurodevelopment are reasonable candidate genes. De novo mutations in genes that participate in neurodevelopment have been shown to affect cerebral morphology, cytoarchitecture, neuroanatomy, and functional neurocircuitry. For example, two broad groups of diseases causing neural abnormalities, the craniosynostosis syndromes and the cortical dysplasia disorders, can result from de novo point mutations arising in proportion to paternal age [Schell et al., 1995; Hehr and Muenke, 1999; Singer et al., 1999; Vajo et al., 2000].

The present consensus favors both allelic and etiological heterogeneity for schizophrenia risk and many studies have compared familial to sporadic patients in an attempt to identify homogeneous subgroups of patients. However, if a de novo mutation that was responsible for sporadic schizophrenia vulnerability were subsequently inherited, then some familial patients would have the same allelic basis for their disease as sporadic patients. The group of familial patients might then be more diverse. The group of sporadic cases is likely to be heterogeneous also. In complex disorders that show oligogenetic inheritance, cases without a family history are not unexpected even in the absence of de novo mutations.

Indeed, more global and diffuse deficits are commonly reported for sporadic schizophrenia patients, in comparison with more severe, but variable, specific abnormalities in familial cases. Familial patients are reported to be more impaired than sporadic patients on complex motor tests (visual motor coding; motor control, reaction time, neurointegration) and show greater deficits in abstraction, attention, and problem solving [Orzack and Kornetsky, 1971; Asarnow et al., 1978; Walker and Shaye, 1982; Sautter et al., 1994; Griffiths et al., 1998]. Using cluster analysis of neuropsychological test scores, Sautter et al. [1995] found three distinct clusters for familial patients but only one for sporadic patients. The familial cluster associated with the

lowest familial recurrence risk (7%) reflected general neuropsychological impairment. This was similar to the sporadic patient pattern, as might be expected if they had inherited a particular subtype from a de novo mutation in an earlier generation. Lateralized neural abnormalities are also reported in familial but not in sporadic schizophrenia patients. These include asymmetric eye movement gain [Schwartz et al., 1995], abnormal functional asymmetries on dichotic tasks [Malaspina et al., 1998], and ventricular and temporal horn asymmetry [Roy et al., 1994]. Familial patients may also have greater thought disorder [Kendler and Hays, 1982] and show less treatment response for the so-called negative symptoms (deficits in motivation, social drive, and emotional processing) [Malaspina et al., 2000] than sporadic patients. In contrast, more generalized abnormalities are reported in sporadic patients, such as reduced neural volumes, widened ventricles [Reveley et al., 1984; Schwarzkopf et al., 1991], EEG abnormalities [Hays, 1977; Kendler and Hays, 1982], global impairments in eye movement quality [Malaspina et al., 1998], and primary neurological abnormalities [Griffiths et al., 1998].

The results of this patient series analysis complement the findings from our prior population birth cohort study in suggesting that new mutations may play an essential role in schizophrenia vulnerability. New mutations can explain how schizophrenia persists in the population despite the low fecundity of affected individuals. This approach may help us to define phenotypes for particular subtypes of schizophrenia and may entail novel methods for gene discovery in schizophrenia.

## Acknowledgments

We thank Xavier Amador, David Printz, Roberto Gil, Ezra Susser, and Alan Brown. Supported by a mid-career patient-oriented research award k24 (to D.M.) G. Harold and Leila Y. Mathers Charitable Foundation (to J.G.), and a Jerusalem Perinatal Chohort Study (NIMH type 1 ro1 MH59114-01A1).

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**TABLE I**

Paternal Age in Sporadic and Familial Forms of Genetic Disorders

| Disease (reference) | Samples | Familial or control (years) | Sporadic (years) | Age difference |
|---|---|---|---|---|
| Idioopathic torsion dystonia [Fletcher et al., 1990] | 58 familial cases, 49 sporadic cases | 30.13 (familial), 29.3 (population) | 32.8 | 2.7 years, $P$=0.05 |
| Achondroplasia [Orioli et al., 1995] | 78 sporadic cases, 160 controls | 31.66 (5.74, Italy), 27.53 (5.98, S. American) | 36.30 (6.74, Italy), 37.19 (10.53, S. American) | 4.6 years, $P$<0.01<br>9.7 years, $P$<0.01 |
| Retinitis pigmentosa [Kaplan et al., 1990] | 93 families | 29.1 | 38.8 | 9.7 years, $P$<0.001 |
| CHARGE syndrome [Tellier et al., 1996] | 41 cases | 30.8 (5.0) | 33.7 (8.0) | 2.9 years |
| Osteogenesis Imperfecta [Young et al., 1987] | 60 cases | 29.6 (6.1) population | 34.2 (7.7) | 4.6 years, $P$<0.01 |
| Duchene muscular dystrophy[a] [Bucher et al., 1980] | 55 families | 29.5 (1.3) paternal grandfather | 33.7 (1.6) maternal grandfather | 4.2 years, $P$=0.025 |
| Thanatophoric dysplasia [Orioli et al., 1995] | 64 sporadic cases, 133 controls | 31.03 (5.20, Italy), 28.82 (6.24, S. American) | 33.60 (7.08, Italy), 36.41 (9.38, S. American) | 2.57 years, $P$<0.05<br>7.59 years, $P$<0.01 |
| Alzheimer disease [Bertram et al., 1998] | 103 familial cases, 50 controls | 31.3 (6.9) familial, 32.6 (6.8) controls | 35.7 (8.1) | 4.4 years, $P$=0.004 |
| Crouzon syndrome, Pfeiffer syndrome [Glaser et al., 2000] | 42 cases | 30.45 (1.28) | 34.50 (7.65) | 4.05 years, $P$=0.01 |
| Retinoblastoma [Derkinderen et al., 1990] | 104 cases | 32.5 | 33.7 | 1.2 years, $P$<0.05 |
| Von recklinghausen neurofibromatosis [Riccardi et al., 1984] | 187 cases | 29.65 | 32.8 | 3.15 years, $P$<0.001 |
| Fibrodysplasia ossificans progressive [Rogers and Chase, 1979] | 38 cases | 29.8 (6.9) population | 32.9 (7.6) | 3.1 years |

[a] An X chromosome–linked disorder, arises de novo in maternal grandfather's germline.

**TABLE II**

Mean Parental Ages for Familial History Groups

| | FH1: familial (years) | FH2: familial (years) | $FH^+$: all familial (years) | $FH^-$: sporadic (years) |
|---|---|---|---|---|
| Maternal age | n = 16, 24.3 ± 5.1 | n = 16, 27.4 ± 7.3 | n = 32, 25.8 ± 6.4 | n = 64, 28.6 ± 6.1 |
| Paternal age | n = 15, 28.3 ± 5.5 | n = 16, 29.9 ± 7.3 | n = 31, 29.2 ± 6.4 | n = 64, 33.9 ± 8.5 |

**TABLE III**

Posthoc Comparisons

| Groups | Statistics | Mean age difference, years |
|---|---|---|
| $FH^+$ vs. $FH^-$ | Maternal age: t=2.04, df=94, *P*=0.045 | 2.75 ± 1.35 |
| | Paternal age: t=2.74, df=91, *P*=0.007 | 4.73 ± 1.73 |
| FH1 vs. $FH^-$ | Maternal age: t=−2.61, df=78, *P*=0.014 | 4.34 ± 1.73 |
| | Paternal age: t=−2.41, df=75, *P*=0.016 | 5.55 ± 2.27 |
| FH2 vs. $FH^-$ | Maternal age: t=0.65, df=78, *P*=0.52 | 1.16 ± 2.21 |
| | Paternal age: t=1.71, df=76, *P*=0.073 | 3.95 ± 2.21 |
| FH1 vs. FH2 | Maternal age: t=1.43, df=30, *P*=0.16 | 3.19 ± 2.23 |
| | Paternal age: t=0.69, df=29, *P*=0.50 | 1.60 ± 2.33 |

**TABLE IV**

Demographics and Intelligence in Familial and Sporadic Schizophrenia Cases

| | Familial patients (n = 35) | Sporadic patients (n = 68) | |
|---|---|---|---|
| Age (years) | 31.5 ± 10.5 | 32.2 ± 10.0 | t=0.37, df=101, *P*=0.715 |
| Sex (male;female) | 24:11 | 45:23 | Chi-square=0.06, df=1, *P*=0.81 |
| Socioeconomic status | 26.8 ± 12.0 | 37.5 ± 11.1 | t=3.22, df=47, *P*=0.002 |
| Education, years | 11.8 ± 3.0 | 13.7 ± 4.8 | t=2.08, df=93, *P*=0.041 |
| Age of onset, years | 21.1 ± 7.2 | 19.5 ± 5.1 | t=1.28, df=97, *P*=0.204 |
| Full-scale IQ | 81.7 ± 11.5 | 89.8 ± 13.5 | t=2.31, df=51, *P*=0.025 |
| Verbal IQ | 84.0 ± 12.0 | 94.2 ± 15.0 | t=2.65, df=51, *P*=0.011 |
| Performance IQ | 79.9 ± 11.8 | 85.5 ± 12.5 | t=1.67, df=51, *P*=0.10 |