Advancing Paternal Age and the Risk of Schizophrenia

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Background: A major source of new mutations in humans is the male germ line, with mutation rates monotonically increasing as father's age at conception advances, possibly because of accumulating replication errors in spermatogonial cell lines.

Method: We investigated whether the risk of schizophrenia was associated with advancing paternal age in a population-based birth cohort of 87,907 individuals born in Jerusalem from 1964 to 1976 by linking their records to the Israel Psychiatric Registry.

Results: Of 1337 offspring admitted to psychiatric units before 1998, 658 were diagnosed as having schizophrenia and related nonaffective psychoses. After controlling for maternal age and other confounding factors (sex, ethnicity, education [to reflect socioeconomic status], and duration of marriage) in proportional hazards regression, we found that paternal age was a strong and significant predictor of the schizophrenia diagnoses, but not of other psychiatric disorders. Compared with offspring of fathers younger than 25 years, the relative risk of schizophrenia increased monotonically in each 5-year age group, reaching 2.02 (95% confidence interval, 1.17-3.51) and 2.96 (95% confidence interval, 1.60-5.47) in offspring of men aged 45 to 49 and 50 years or more, respectively. Categories of mother's age showed no significant effects, after adjusting for paternal age.

Conclusions: These findings support the hypothesis that schizophrenia may be associated, in part, with de novo mutations arising in paternal germ cells. If confirmed, they would entail a need for novel approaches to the identification of genes involved in schizophrenia.

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In humans, as in other mammals, it is the males who introduce the overwhelming majority of new mutations into the gene pool. Men's constantly dividing spermatogonia accumulate mutations as they age. Before puberty, spermatogonia undergo some 36 divisions; thereafter, there may be 23 divisions per year. At ages 20 and 40 years, respectively, a man's germ cell precursors will have undergone about 200 and 660 such divisions. In contrast, the numbers of such divisions in female germ cells is usually 24, all but the last occurring during fetal life. New mutations related to advancing paternal age have been implicated as a cause of several autosomal dominant diseases, when these occur as sporadic (nonfamilial) cases, such as achondroplasia, Apert syndrome, and progeria. Furthermore, recent studies show that common complex diseases may also be related to advancing paternal age, including prostate cancer, nervous system cancer, and certain birth defects.

More than half a century ago, Book raised the possibility that new mutations might be constantly replenishing the population with genetic abnormalities contributing to schizophrenia. This idea lost favor, however, because the necessary mutation rates were thought to be unrealistically high to account for schizophrenia.

Recent data, however, show a high human mutation rate. Because schizophrenia is a complex disease for which there is overwhelming evidence of some sort of a genetic component, a role for new mutations merits renewed attention. The mode of inheritance of schizophrenia has eluded discovery, and the disease presents a number of puzzles. Although an array of genetic models have been proposed for the disease, none can explain all of the patterns of occurrence within families. It is also unclear how the disease is maintained in the population, given the reduced reproductive fitness of affected individuals. Assuming that several (perhaps many) genetic loci would be involved in vulnerability to schizophrenia.
SUBJECTS, MATERIALS, AND METHODS

DATA SOURCES

This study uses data assembled from 2 independent sources: a population-based research database based on a birth cohort and a national registry of psychiatric disease. As a first step in a large project aiming to study the incidence of schizophrenia, we linked information from the psychiatric registry to the birth cohort. Our immediate objective was to determine the numbers of schizophrenia individuals potentially available for study and to establish the utility of studying the disease in various subgroups.

The Jerusalem Perinatal Study is a research file of all births from 1964 to 1976 to residents of a defined geographic area in Jerusalem and nearby. It recorded parental ages and demographic information from birth certificates augmented with data from obstetric and pediatric departments, municipal well-baby clinics, follow-up of vital status, and interviews with some mothers. Its methods have been summarized elsewhere and some 75 reports from the study have focused on short- and long-term outcomes. In the past decade, studies using the Jerusalem Perinatal Study, linked to other databases in Israel, showed that the offspring’s identification numbers, sex, birth dates, and basic demographic information, including parental age, were more than 99.9% accurate.

The State of Israel maintains a national registry of psychiatric illness, one of several disease registries used there for planning health services, understanding disease etiology, and evaluating measures for prevention. Established in the Ministry of Health in 1930, the Psychiatric Case Registry receives information about all psychiatric diagnoses, including reports from patients admitted to specialized psychiatric hospitals, psychiatric wards within general hospitals, and psychiatric day-care facilities. The Registry’s design and methods have been described in detail elsewhere and it has been used for clinical and epidemiologic research in schizophrenia.

In a pilot study to estimate losses to follow-up through emigration or death, personnel at the Ministry of Health linked a random sample of 200 of the Jerusalem Perinatal cohort to the Population Registry. In August 1998, less than 5% had left Israel, most of them recently (presumably for vacations). Because such a high percentage of the random sample was alive, and in Israel, we concluded that it would be appropriate to use the available data to examine paternal age and other demographic variables as risk factors for schizophrenia-related diagnoses in the cohort.

The Ministry of Health matched the Perinatal Study data to the Psychiatric Registry, using 7-digit identification numbers. These numbers, names, and other information that might identify individuals were then removed to create a new, anonymous file limited to psychiatric diagnoses and dates of psychiatric admission. This match was preliminary to a detailed investigation of the cohort that is presently under way. For this purpose, Ministry personnel used a broad definition of schizophrenia (International Classification of Diseases, 10th Revision [ICD-10] F20-F29) that included hospital discharge diagnoses of schizophrenia, schizotypal disorder, delusional disorders, nonaffective psychoses, and schizoaffective disorders, hereafter considered the schizophrenia-related diagnoses. All other psychiatric diagnoses were placed in the “other” category. These included a full range of other psychiatric conditions leading to treatment, such as affective, anxiety, substance abuse, personality, and eating disorders. The Registry had routinely upgraded diagnoses recorded in earlier International Classification of Diseases criteria into the newer codes.

SUBJECTS

There were 89,722 offspring in the cohort who survived the first year of life. From these, we excluded 1816 who were missing 1 or more of the following: 416 (0.5%) with paternal age unknown, 105 (0.1%) with maternal age unknown, and 1330 (1.5%) with an unknown or no year of marriage. To be conservative, we also excluded 79 (<0.1%) with the father’s year of birth given as more than 10 years after the mother’s, as this group of outliers may have included some transcription errors. The incidence of schizophrenia (20 cases [3.0%]) among those who were excluded did not differ significantly from that in the remaining cohort.

STATISTICAL ANALYSIS

As offspring born in different years were followed up to different ages, we used Cox proportional hazards models to estimate effects of the parents’ ages, employing the PROC PHREG methods provided by SAS (SAS Institute Inc, Cary, NC). Time intervals were rounded to the nearest year and individuals were censored on the last day of follow-up: December 31, 1997. Results are given as adjusted rate ratios (RRs) with 95% confidence intervals (CIs). We treated categories of each parent’s age as a series of dummy variables (1, present; 0, absent), with the reference category set at age 20 to 24 years for maternal age, and younger than 24 years for paternal age. For some analyses, such as for control of confounding factors, we treated maternal and paternal age as continuous variables. In doing this, we re-coded each parent’s age as the number of years of deviation from the group median (30 and 27 years, respectively, for fathers and mothers) when using it as a continuous variable. We also explored whether there was confounding factors by other variables, with sex, ethnic groups and education (to reflect socioeconomic status) as dummy variables and duration of marriage as a continuous variable.
accepted case-control methods and matched the cases for social class. These studies have been criticized for methodological limitations, and the findings have not had a strong impact on the field.

We recognized the importance of this question in light of the hypothesis that new mutations may contribute to schizophrenia vulnerability. Because of the scarcity of schizophrenia in the population and the decades-long duration from birth to disease onset, we realized that considerable sample size, study duration, and sociodemographic data would be necessary to adequately examine this question. We were able to examine the association of paternal age and schizophrenia using data from a large, population-based birth cohort in Israel that was free from most of the methodologic limitations of the previous studies.

RESULTS

INCIDENCE

Linkage to the Psychiatric Registry identified 1337 individuals who were common to both databases, and who were diagnosed through December 31, 1997, 658 of them as having schizophrenia and related nonaffective psychoses. By this date, the youngest survivors in the Perinatal Study cohort (N=89722) had all reached age 21 years, and some of the oldest were already 34 years. Age-specific incidence rates and cumulative life-table incidence for the schizophrenia-related disorders are shown in Figure 1. The incidence rose rapidly at puberty, reaching a maximum in the late teens and early 20s. Cases continued to be diagnosed at older ages, although with a declining incidence. Using Kaplan-Meier methods, the cumulative incidences at ages 25, 30, and 34 years were estimated to be 6.1 per 1000, 8.4 per 1000, and 9.6 per 1000, respectively. There was no trend effect of year of birth.

PARENTAL AGE EFFECTS

We first investigated the crude cumulative incidence of schizophrenia and related nonaffective psychoses at age 21 years, since this length of follow-up was available on the whole cohort (N=87907); there were 335 cases diagnosed by this age. The risk was related to paternal age at the offspring's birth. The lowest risk of the schizophrenia disorders (2.5/1000) was observed in the offspring with the youngest paternal age (ie, those <25 years). The incidence increased progressively in subsequent 5-year paternal age groups through 3.5 per 1000, 3.7 per 1000, 4.4 per 1000, 4.6 per 1000, and 5.0 per 1000, reaching 11.4 per 1000 in the offspring of fathers 50 years or older ($\chi^2=15.1, P=.01$). Next, we made use of the all the cases diagnosed through December 31, 1997 (n=658). We employed proportional hazards models to estimate the relative risk of schizophrenia conditions in the offspring evaluated for varying time intervals. Table 1 shows an analysis of effects of paternal age, both unadjusted and adjusted for the age of the mother; similarly, it shows effects of maternal age, both unadjusted and adjusted for age of father. Note that the raw numbers of cases and offspring cannot be used to calculate an incidence rate, because different individuals were followed up for varying time intervals. Although the unadjusted RR suggests that the ages of both parents significantly influenced outcome, adjustment of one for the other confirmed that their effects were fundamentally different, and only paternal age was a strong linear predictor of schizophrenia. After adjusting for maternal age, there was a monotonic increase in the relative risk of schizophrenia as paternal age progressed, leading to a 3-fold excess of the disease in offspring for whom paternal age was 50 years or more, relative to those of paternal age less than 25 years. Beyond age 30 years, offspring in all categories of paternal age showed significant excesses of schizophrenia, relative to the reference category of younger than 25 years. In contrast, when maternal age was adjusted for paternal age, no category showed a significant difference from the reference category. We confirmed these results in cross-tabulations of paternal vs maternal age.

EFFECTS OF SEX AND DURATION OF MARRIAGE

Because the effect of paternal age increased monotonically, we treated it as a linear (continuous) variable. With this approach, we estimated that each decade of increase in paternal age multiplied the risk of schizophrenia in his offspring by 1.56 (95% CI, 1.36-1.78) before adjusting for maternal age, or by 1.45 (95% CI, 1.23-1.70) after adjustment. Further adjustment for sex and duration of marriage (see below) caused only a small change in this estimate, to 1.41 (95% CI, 1.21-1.65).

The incidence of schizophrenia was higher in males than in females. Compared with females, the RR for males reaching 5.7 per 1000 in the offspring of mothers 40 years or older ($\chi^2=15.1, P=.01$).
orders for each decade of paternal age. However, when adjusted for the other parent’s age, each decade of paternal age multiplied the incidence of the other psychiatric conditions by 1.13 (95% CI, 0.96-1.34), compared with 1.10 (95% CI, 0.89-1.35) for each decade of maternal age. Thus, the other psychiatric conditions, while weakly related to the age of either parent, failed to show the strong paternal age effect manifest in schizophrenia.

We recognized that a percentage of the individuals with other diagnoses, especially in the younger members of the cohort, might eventually be diagnosed as having schizophrenia.

We also explored the relationship of paternal age to the age of schizophrenia onset, controlling for sex, and found no significant relationship. For cases diagnosed before the offspring were aged 20 years (n=263), the RR for the effect of father’s age was 1.41 (95% CI, 1.21-1.66); for groups diagnosed when younger than 25 years (n=509), younger than 30 years (n=619), and younger than 34 years (n=638), the RRs were 1.34 (95% CI, 1.19-1.51), 1.33 (95% CI, 1.20-1.48), and 1.33 (95% CI, 1.20-1.48), respectively.

PUBLIC HEALTH IMPACT

We estimated the fraction of schizophrenia attributable to paternal age in this cohort using the data in Table 1. We found that a quarter (26.6%) of the cases could be attributed to paternal age. For offspring of fathers 50 years or older, 2 of 3 cases of schizophrenia could be attributed to the effects of paternal age. We also estimated the cumulative risk of schizophrenia to age 34 years assuming an overall incidence of 0.96% (Figure 2). The percentage of offspring predicted to have schizophrenia increased with advancing paternal age from 1 in 141 for

SPECIFICITY OF THE PARENTAL AGE EFFECT FOR SCHIZOPHRENIA

These data also demonstrated the specificity of the effect of father’s age on schizophrenia-related disorders, in comparison with its effect on the 679 subjects with other psychiatric conditions. In models that did not adjust for the other parent’s age, both the age of the father (RR, 1.20; 95% CI, 1.08-1.33) and that of the mother (RR, 1.24; 95% CI, 1.09-1.41) seemed to alter the probability of hospital admission for the group with other psychiatric di-

Table 1. Effects of Paternal and Maternal Age Groups on Incidence of Schizophrenia-Related Diagnoses

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Cohort, No.</th>
<th>Cases, No.</th>
<th>Not Adjusted for Age of Other Parent, RR† (95% CI)</th>
<th>Adjusted for Age of Other Parent, RR‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paternal age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>227</td>
<td>3</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>20-24‡</td>
<td>11 497</td>
<td>58</td>
<td>1.13 (0.84-1.51)</td>
<td>1.14 (0.84-1.53)</td>
</tr>
<tr>
<td>25-29</td>
<td>28 145</td>
<td>167</td>
<td>1.40 (1.04-1.99)</td>
<td>1.42 (1.03-1.96)</td>
</tr>
<tr>
<td>30-34</td>
<td>22 212</td>
<td>169</td>
<td>1.59 (1.17-2.16)</td>
<td>1.64 (1.13-2.38)</td>
</tr>
<tr>
<td>35-39</td>
<td>14 547</td>
<td>126</td>
<td>1.67 (1.18-2.36)</td>
<td>1.73 (1.11-2.70)</td>
</tr>
<tr>
<td>40-44</td>
<td>7 424</td>
<td>67</td>
<td>1.94 (1.24-3.03)</td>
<td>2.02 (1.17-3.51)</td>
</tr>
<tr>
<td>45-49</td>
<td>2 626</td>
<td>28</td>
<td>2.82 [1.70-4.68]]</td>
<td>2.96 [1.60-5.47]]</td>
</tr>
<tr>
<td>50-54</td>
<td>794</td>
<td>14</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>≥55</td>
<td>435</td>
<td>6</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Maternal age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
<td>3 031</td>
<td>18</td>
<td>0.96 (0.59-1.56)</td>
<td>1.01 (0.62-1.64)</td>
</tr>
<tr>
<td>20-24‡</td>
<td>26 790</td>
<td>161</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>25-29</td>
<td>28 529</td>
<td>190</td>
<td>1.12 (0.90-1.38)</td>
<td>1.01 (0.81-1.26)</td>
</tr>
<tr>
<td>30-34</td>
<td>17 686</td>
<td>148</td>
<td>1.36 (1.09-1.70)</td>
<td>1.10 (0.84-1.44)</td>
</tr>
<tr>
<td>35-39</td>
<td>9 225</td>
<td>93</td>
<td>1.65 (1.27-2.12)</td>
<td>1.18 (0.84-1.67)</td>
</tr>
<tr>
<td>40-44</td>
<td>2 376</td>
<td>25</td>
<td>1.70 [1.14-2.54]]</td>
<td>1.08 [0.65-1.80]]</td>
</tr>
<tr>
<td>≥45</td>
<td>270</td>
<td>3</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
†The RRs were calculated from proportional hazards regressions.
‡Reference group.
§Includes younger age group.
||Includes older age groups.

was 1.37 (95% CI, 1.17-1.60) (P<.001). Significant effects of paternal age on the incidence of schizophrenia were found within both sexes. Treating it as a continuous variable, we estimated that each decade of paternal age changed the RR by 1.40 (95% CI, 1.21-1.59) in male and 1.26 (95% CI, 1.07-1.48) in female offspring. As the CIs in these 2 estimates overlap, the difference between the sexes may be caused by chance. Next, we considered the length of marriage. Because longer-married couples tend to be older, we first investigated categories of length of marriage and paternal age. Holding length of marriage constant, we found that advancing paternal age was still consistently associated with an increasing incidence of schizophrenia. But, holding paternal age constant, the incidence of schizophrenia tended to decrease with increasing duration of the marriage. We concluded that these variables were independent risk factors, and entered both into a proportional hazards model (Table 2). Treating duration of marriage as a continuous variable, and adjusting for paternal age, sex, and ethnic group, we estimated that each 5 years of marriage decreased the incidence of schizophrenia by 0.86 (95% CI, 0.79-0.95).
offspring of fathers younger than 25 years, to 1 in 99 for those with fathers aged 30 to 35 years, and 1 in 47, for those with fathers 50 years or older.

The mean ages of the parents were significantly older for those with schizophrenia. The mean (SD) paternal age for offspring with schizophrenia was 33.12 (7.55) years, compared with 32.52 (7.45) years for those with other psychiatric disorders and 31.49 (6.82) years for all other offspring (F89,304=25.81, P<.001). The mean (SD) maternal ages were 28.40 (6.01) years for offspring with schizophrenia, 28.60 (6.04) for the other psychiatric disorders group, and 27.65 (5.65) years for all other offspring (F89,615=15.04, P<.001). The mean (SD) parental ages of the 2 psychiatric groups did not differ in post hoc analyses. While significant, the actual magnitude of the mean parental age differences among the groups was not very large.

COMMENT

Our data show a strong and consistent effect of advancing paternal age on the incidence of schizophrenia and related psychoses, clearly separate from, and not explained by, the age of the mother. Although schizophrenia is a heterogeneous disorder, hypothesized to result from both genetic and environmental origins, these results suggest that de novo genetic mutations may substantially contribute to the risk for schizophrenia. Indeed, more than a quarter of schizophrenia cases in this cohort were attributable to the paternal age effect.

COMPARISON WITH OTHER STUDIES

The advanced paternal age for schizophrenia demonstrated in this study is in accord with a sizable earlier literature with similar findings. However, our sample and study design offers significant methodological advantages. Our large sample size allowed us to examine the impact of paternal age on schizophrenia, which has a low incidence, and to generate relative risk estimates for fathers of different ages. This study used prospectively acquired data on paternal age and potential confounding factors and provided a continuous follow-up of schizophrenia cases. In addition, we were able to show that the effects of paternal age were not observed for the group of patients with other psychiatric diagnoses.

As it stands, the study has a number of drawbacks that might limit the validity of some of the results. One is that we have not yet ascertained losses to follow-up through emigration or death. To explain our results, however, such losses would have to be massive, and would have to be grossly biased by paternal (but not maternal) age. This seems unlikely, as our pilot study of deaths and emigration showed them to be rare, justifying our deci-

Table 2. Effects of Parental Ages and Duration of Marriage on Incidence of Schizophrenia, Compared With Other Psychiatric Illness

<table>
<thead>
<tr>
<th>Variable</th>
<th>Schizophrenia Cases, No.</th>
<th>RR (95% CI)</th>
<th>Other Psychiatric Illness Cases, No.</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age, y†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30†</td>
<td>369</td>
<td>1</td>
<td>381</td>
<td>1</td>
</tr>
<tr>
<td>30-34</td>
<td>148</td>
<td>1.24 (0.98-1.58)</td>
<td>149</td>
<td>1.16 (0.91-1.46)</td>
</tr>
<tr>
<td>≥35</td>
<td>119</td>
<td>1.59 (1.16-2.20)</td>
<td>119</td>
<td>1.42 (1.03-1.97)</td>
</tr>
<tr>
<td>Paternal age, y†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30†</td>
<td>228</td>
<td>1</td>
<td>263</td>
<td>1</td>
</tr>
<tr>
<td>30-34</td>
<td>169</td>
<td>1.20 (0.90-1.61)</td>
<td>184</td>
<td>1.00 (0.77-1.31)</td>
</tr>
<tr>
<td>35-39</td>
<td>126</td>
<td>1.56 (1.14-2.13)</td>
<td>120</td>
<td>1.24 (0.93-1.65)</td>
</tr>
<tr>
<td>40-44</td>
<td>67</td>
<td>1.79 (1.25-2.57)</td>
<td>68</td>
<td>1.21 (0.86-1.70)</td>
</tr>
<tr>
<td>45-49</td>
<td>28</td>
<td>1.89 (1.24-2.88)</td>
<td>31</td>
<td>1.32 (0.88-1.99)</td>
</tr>
<tr>
<td>≥50</td>
<td>20</td>
<td>2.60 (1.63-4.15)</td>
<td>13</td>
<td>1.60 (1.00-2.56)</td>
</tr>
<tr>
<td>Duration of marriage, y§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>221</td>
<td>1.62 (1.20-2.20)</td>
<td>126</td>
<td>1.31 (0.97-1.78)</td>
</tr>
<tr>
<td>2-4</td>
<td>178</td>
<td>1.48 (1.12-1.95)</td>
<td>186</td>
<td>1.24 (0.94-1.63)</td>
</tr>
<tr>
<td>5-9</td>
<td>157</td>
<td>1.18 (0.92-1.52)</td>
<td>180</td>
<td>1.16 (0.91-1.49)</td>
</tr>
<tr>
<td>≥10‡</td>
<td>182</td>
<td>1</td>
<td>187</td>
<td>1</td>
</tr>
</tbody>
</table>

*RR indicates relative risk; CI, confidence interval.
†Adjusted for years married (continuous), sex, and ethnic group.
‡Reference group.
§Adjusted for father’s age (continuous), mother’s age (30-34 and ≥35 years), sex, and ethnic group.
sion to ignore losses in the present analyses. Other drawbacks are that the Ministry did not provide us with data on diagnostic subsets and the Registry's diagnoses have yet to be validated. While it is likely that some cases will have been misclassified, such misclassification would more likely obscure an effect of paternal age (if present) rather than show a spurious association were none present. However, it is possible that certain other specific psychiatric disorders within our “other psychiatric disorders” category might also show a paternal age effect. Other limitations of the present report, which will be remedied with the completion of our study several years hence, are the lack of information on family psychiatric history, survival of parents, and knowledge of which offspring were in sibling groups. It has been proposed that parental loss may be associated with later schizophrenia, and elderly parents are likely to be at increased risk of mortality or physical disease. But it seems unlikely that parental loss could explain the differing patterns for maternal and paternal age effects that we observed. In addition, one might expect parental mortality to influence other causes of psychiatric illness, and not be specific to schizophrenia, were mortality the explanation for the effects of paternal age.

DE NOVO MUTATIONS AND SCHIZOPHRENIA RISK

With these caveats, our demonstration of a strong, independent effect of paternal age is consistent with the hypothesis that new point mutations may contribute, in part, to the etiology of schizophrenia. Estimates of mutation rates are considerably higher than had been previously thought, and mammals may acquire up to 100 per individual per generation. Most are thought to be neutral and there are uncertainties regarding the percentage that are deleterious (or advantageous) and their rates of elimination from the population (or increase) by natural selection. One recent estimate suggests that humans acquire 4.2 deleterious mutations per generation in the population with 1.6 to 3 persisting in the gene pool.

If de novo point mutations do explain our paternal age effect, then we would expect to observe the age of father to have a stronger influence in sporadic cases than in familial ones. On the other hand, if a genetic mechanism based on expansion of trinucleotide repeat elements in DNA is involved, such as those that disrupt the genes for spinocerebellar ataxias and Huntington disease, then we would expect paternal age to operate within families, especially those affected by other cases or by other, milder conditions. With genetic anticipation there is a greater risk of illness or increasing severity of the disease in subsequent generations, which can sometimes be explained by progressive trinucleotide repeat expansion mutations in each generation. For spinocerebellar ataxia, Huntington, and other diseases, this happens more often when the gene is inherited from the father. For schizophrenia too, familial risk has suggested anticipation in some studies and this, too, seems stronger for paternal than for maternal transmission of the disease.

DURATION OF MARRIAGE

Increasing duration of the marriage significantly reduced the incidence of schizophrenia in the offspring, showing an independent and opposite effect of advancing paternal age on schizophrenia risk. This effect did not materially alter the association of paternal age and schizophrenia risk. One possible explanation of this effect would be that parents with schizophrenia (who can transmit that vulnerability) have shorter marriages, possibly because psychiatric illness reduces their capacity to sustain a marriage. However, physiological models for this association may also be feasible. For example, pregnancy-related hypertension (preeclampsia), previously considered to be a disease of first pregnancies, might instead be a disease of new couples that is related to the duration of the sexual relationship between the parents.

IMPLICATIONS OF THE DATA

These findings accord well with the American College of Medical Genetics Statement on Guidance for Genetic Counseling in Advanced Paternal Age that the risk of genetic defects (specifically, sporadic dominant single-gene mutations) may be 4 to 5 times greater for fathers 45 years and older than for their 20- to 25-year-old counterparts. The risk for genetic defects does not increase suddenly at age 40 years, but rather, increases linearly with age. These predictions are in line with the results we have demonstrated for schizophrenia. There is increasing evidence that the father's age, no less than the mother's, contributes variability to the risk of a suboptimal reproductive outcome; some authors have pondered whether the upper limit for the age of sperm donors should be revised downward. Nonetheless, there have been limited experimental data on advancing paternal age and mutations in humans, and much of the published literature is theoretical in nature. There has been some work attempting to categorize parental age-related mutations. The type of mutations most clearly associated with paternal aging are those involving point substitutions at a single base pair. Other types of genetic changes (eg, small deletions and inversions) seem to be more frequently inherited from mothers and may be less clearly associated with increased maternal age. In addition to gene mutations, however, there are de novo rearrangements of chromosomes (translocations and large inversions), or gain or loss of whole chromosomes, of which some are associated with aging of mothers and others with that of fathers.

While we confirm the presence of a strong independent effect of paternal age, we cannot rule out some effect of maternal age. However, the former supports our hypothesis that several puzzling phenomena in the epidemiology of schizophrenia could be explained by de novo mutations. If confirmed, this explanation could have a number of implications. One is that taking this possibility into account might change strategies in the search for genes contributing to the disease. It might facilitate a better discrimination between sporadic and familial cases, leading to enrichment of the latter. Effects of grandpar-
ents’ ages would become relevant. Clustering of schizophrenia with unrelated diseases that also have a relationship with paternal age might be observed within sibships, or in the offspring of siblings.

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