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Advanced paternal and grandpaternal age and schizophrenia: A three-generation perspective

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ABSTRACT

Background: Advanced paternal age has been linked with an increased risk of schizophrenia in the offspring. If age-related de novo mutations in the male germ line underlie this association, grandpaternal and paternal age would both be expected to influence the risk of schizophrenia. The aim of the current study was to explore the links between both paternal and grandpaternal age with respect to the risk of schizophrenia in a large, national register-based cohort.

Method: We linked the Swedish Multi-Generation and Hospital Discharge Registers and compared parents' ages at offspring birth for 20,582 schizophrenia-affected and 100,176 non-affected individuals. Grandparents' ages at the birth of the parent were compared between 2511 affected and 15,619 non-affected individuals. The risk of schizophrenia was examined with logistic regression when the predictor variable (parent or grandparent age) varied across age strata.

Results: After adjusting for maternal age, birth year and proband sex, we confirmed that offspring of older fathers had an increased risk of schizophrenia. Compared to those with paternal age 20–24 years, those with fathers >55 years had a two-fold increased risk of schizophrenia. With respect to grandparent age, older maternal (but not paternal) grandfather age was associated with an increased risk of schizophrenia. Compared to maternal grandfather age 20–24 years, those with maternal grandfathers >55 years had a significantly increased risk of schizophrenia (adjusted odds ratio and 95% confidence intervals; 2.79, 1.71–4.56). The pattern of results was essentially unchanged when we examined male and female probands separately.

Conclusion: This is the first study to report an association between grandpaternal age and risk of schizophrenia. The selective effect of advanced maternal grandfather age suggests that the biological mechanisms involving the X-chromosome may differentially contribute to the association between paternal age and offspring risk of schizophrenia.

1. Introduction

There is robust evidence indicating that offspring of older fathers have an increased risk of schizophrenia (Malaspina et al., 2001; Byrne et al., 2003; El-Saadi et al., 2004; Sipos et al., 2004). Apart from schizophrenia, advanced paternal age has also been associated with increased risk of autism spectrum disorder (Hultman et al., 2010; Reichenberg et al., 2010) and bipolar disorder (Frans et al., 2008). Offspring of older fathers also seem to have subtle deficits in neurocognitive development and behavior (Weiser et al., 2008; Saha et al., 2009a; Saha et al., 2009b). However, the mechanisms behind the association between advanced paternal age and increased risk of adverse neuropsychiatric outcomes in offspring remain unclear. It has been suggested that de novo mutations occurring in the male germ cell line are responsible for this association (Crow, 2000). In men, spermatogonia undergo cell division every 16 days, resulting in approximately 200 divisions by age 20 years and 660 divisions by age 40 years (Drake et al., 1998). Each time the cell divides, the replication of the genome introduces the possibility of copy error mutations, which might result in point mutations or larger copy number variants (e.g., deletions or amplifications). In humans, it has been confirmed that sperm from older men have more mutations

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(Crow, 2000; Bosch et al., 2003; Glaser et al., 2003). A mouse model of advanced paternal age has also recently confirmed that the offspring of older sires have significantly more de novo copy number variants (Flatscher-Bader et al., 2011).

It has been proposed that age-related mutations in the male germ line could accumulate over several generations, and influence the health of subsequent descendents after a "mutational threshold" has been breached and a phenotype could "breakthrough" (Crow, 2000; McGrath, 2006). Mendelian inheritance laws indicate that offspring who acquire a de novo autosomal mutation from their father's sperm should pass (on average) this mutation to half of their offspring (who should in turn pass the mutation to 50% of their offspring, etc.).

Based on linkage of population-based national Swedish registers, we explored the association between schizophrenia and a) parental age (i.e. maternal and paternal) and b) grandparental age (maternal grandmother, maternal grandfather, paternal grandmother, and paternal grandfather). Based on the hypothesis that paternal age-related mutations involve copy error mutations distributed across the entire genome, we predicted that paternal-age related mutations should follow classic Mendelian patterns of inheritance, and thus we predicted that advanced grandpaternal age on both sides of the family (i.e., maternal grandfather and paternal grandfather) would be associated with an increased risk of grandchild schizophrenia.

2. Method

2.1. Setting

We compared the ages of parents and grandparents at offspring birth among cases and controls by linking two national population-based Swedish registers. The primary key for the register linkage was the unique personal identification number assigned to each Swedish citizen at birth or upon arrival to the country (immigrants). The Hospital Discharge Register includes diagnostic data for practically all psychiatric hospitalizations in Sweden since 1973 recorded according to ICD-8 (World Health Organization, 1967), ICD-9 (World Health Organization, 1977) and ICD-10 (World Health Organization, 1992). The Hospital Discharge Register is tested regularly for misclassification and the quality is high (The National Board of Health and Welfare, 2003). The Swedish Multi-Generation Register enables the identification of an "index person", his/her biological parents and birth date (Statistics Sweden, 2005). A prerequisite for being included in the register is that the index person was born after January 1st 1932, and ever registered as living in Sweden after 1960. Ethical approval for this record linkage study was given by the Research Ethics Committee at Karolinska Institutet, Stockholm, Sweden.

2.2. Participants

We identified all subjects diagnosed with schizophrenia during inpatient care in Sweden between 1973 and 2004. Previous studies suggest that 90% of all individuals with schizophrenia in Sweden were admitted for inpatient care over a 10-year period (Hansson et al., 2001). In validation studies, Swedish register diagnoses of schizophrenia has displayed high concordance with diagnoses based on semi-structured interviews (Ekholm et al., 2005). To improve further the validity of the schizophrenia diagnoses we restricted our sample to individuals diagnosed with schizophrenia on at least two separate admissions (ICD-8 and ICD-9 code 295 and ICD-10 codes F20, F21, F23.1, F23.2, and F25). For each subject affected with schizophrenia, we randomly selected five unaffected control individuals matched on birth year and sex from the population register. Age data at birth for parents and grandparents were obtained from the Multi-Generation Register and linked to study subjects. Our study population consisted of 20,582 individuals affected with schizophrenia and 100,176 non-affected individuals with available data on both paternal and maternal age. After linking ages of the grandparents, our final study sample consisted of 2511 affected individuals and 15,619 unaffected individuals with complete data on both maternal and paternal grandparents.

2.3. Statistical methods

To quantify the paternal age effect, we performed logistic regression after categorizing parental/grandparental age into 5-year intervals, in keeping with several previous studies (Malaspina et al., 2001; Byrne et al., 2003; Sipos et al., 2004). These analyses were adjusted for age of partner/spouse, subject gender and birth year. Finally, these analyses were repeated for males and females separately.

All analyses were performed in SAS (version 9.1.3; SAS Institute Inc, Cary, North Carolina), using proc LOGISTIC for the logistic regression analyses. Statistical testing of hypotheses was based on the 2-sided 5% level of significance.

3. Results

In keeping with previous studies, we found that the offspring of older fathers were at increased risk of schizophrenia (Table 1). For example, compared to the reference group (paternal age 20 to 24 years), the highest risk was found in offspring of men aged 55 years or older (OR: 1.95; 95% CI: 1.58–2.40).

With respect to grandpaternal age, we found that only maternal grandfathers' age was associated with risk of schizophrenia (Table 2). Compared to the reference age category (20–24 years), those with maternal grandfathers aged greater than 55 years had a two- to three-fold increased risk of schizophrenia (adjusted OR = 2.79; 95% CI = 1.71–4.56). Across the range of paternal age, there was a significant trend with older age strata being associated with increased risk (chi-square test for trend = 21.28, $p<0.0001$). In contrast, there were no significant associations with paternal grandfathers' age. With respect to grandmothers' age, there was an isolated finding for paternal grandmother age (increased risk in those aged 40–44 compared to the reference category), but no indication of a significant trend across the age strata (chi-square test for trend = 0.24, $p = 0.62$).

We explored the influence of parental and grandparental age and risk of schizophrenia in males and females separately; however, the

Table 1
Associations between paternal and maternal age and offspring risk of schizophrenia based on 20,582 cases and 100,176 matched non-afflicted population controls in Sweden.

Age (years)	No. of cases	%	No. of controls	%	Adjusted odds ratio[a]	Lower 95% CI	Upper 95% CI
Father							
<20	297	1.44	1561	1.56	0.98	0.85	1.12
20–24	3005	14.60	16,027	16.00	Reference	–	–
25–29	5436	26.41	28,877	28.83	1.03	0.97	1.08
30–34	5075	24.66	25,156	25.11	1.09	1.03	1.16
35–39	3517	17.09	16,092	16.06	**1.16**	**1.08**	**1.24**
40–44	1960	9.52	8145	8.13	**1.25**	**1.16**	**1.36**
45–49	874	4.25	3032	3.03	**1.50**	**1.35**	**1.66**
50–54	281	1.37	918	0.92	**1.59**	**1.37**	**1.85**
≥55	137	0.67	368	0.37	**1.95**	**1.58**	**2.40**
Mother							
<20	1380	6.70	6952	6.94	1.06	0.99	1.14
20–24	5271	25.61	27,789	27.74	Reference	–	–
25–29	5896	28.65	30,520	30.47	0.98	0.94	1.03
30–34	4430	21.52	20,344	20.31	1.05	1.00	1.11
35–39	2647	12.86	10,917	10.90	**1.10**	**1.03**	**1.17**
40–44	879	4.27	3411	3.41	1.07	0.97	1.17
≥45	79	0.38	243	0.24	1.21	0.93	1.58

Note: Significant results ($p<.05$) are shown in boldface.
[a] Adjusted for age of spouse, birth year and sex of proband.

Table 2
Associations between grand-paternal and grand-maternal age at parent birth and risk of grandchild schizophrenia based on 2511 cases and 15,619 non-affected population controls in Sweden.

Age (years)	No. of cases	%	No. of controls	%	Adjusted odds ratio[a]	Lower 95% CI	Upper 95% CI
Maternal grandfather							
<20	31	1.23	188	1.20	1.06	0.71	1.59
20–24	327	13.02	2124	13.60	Reference	–	–
25–29	628	25.01	4277	27.38	0.96	0.83	1.12
30–34	618	24.61	4088	26.17	1.00	0.85	1.19
35–39	454	18.08	2786	17.84	1.09	0.90	1.32
40–44	265	10.55	1353	8.66	**1.33**	**1.07**	**1.66**
45–49	115	4.58	550	3.52	**1.47**	**1.12**	**1.94**
50–54	46	1.83	186	1.19	**1.76**	**1.21**	**2.58**
≥55	27	1.08	67	0.43	**2.79**	**1.71**	**4.56**
Maternal grandmother							
<20	155	6.17	970	6.21	1.06	0.86	1.29
20–24	628	25.01	4166	26.67	Reference	–	–
25–29	700	27.88	4499	28.80	1.01	0.89	1.15
30–34	551	21.94	3408	21.82	0.97	0.84	1.13
35–39	346	13.78	1859	11.90	1.00	0.83	1.20
40–44	118	4.70	670	4.29	0.83	0.64	1.08
≥45	13	0.52	47	0.30	1.12	0.58	2.15
Paternal grandfather							
<20	27	1.08	132	0.85	1.19	0.77	1.84
20–24	334	13.30	1964	12.57	Reference	–	–
25–29	655	26.09	4219	27.01	0.90	0.78	1.05
30–34	699	27.84	4169	26.69	0.96	0.82	1.14
35–39	412	16.41	2787	17.84	0.86	0.71	1.04
40–44	247	9.84	1521	9.74	0.91	0.73	1.14
45–49	84	3.35	566	3.62	0.80	0.59	1.08
50–54	35	1.39	189	1.21	0.99	0.65	1.49
≥55	18	0.72	72	0.46	1.40	0.80	2.44
Paternal grandmother							
<20	142	5.66	814	5.21	1.06	0.86	1.30
20–24	624	24.85	3987	25.53	Reference	–	–
25–29	760	30.27	4596	29.43	1.07	0.95	1.22
30–34	552	21.98	3507	22.45	1.04	0.90	1.21
35–39	295	11.75	2020	12.93	0.99	0.82	1.19
40–44	132	5.26	655	4.19	**1.36**	**1.06**	**1.76**
≥45	6	0.24	40	0.26	0.94	0.39	2.30

Note: Significant results ($p<.05$) are shown in boldface.
[a] Adjusted for age of spouse, birth year and sex of proband.

general pattern of results was unchanged (see Supplementary Material Appendix 1, Tables A1–A4). As an additional post-hoc analysis, we also repeated the main analyses after removing probands who had a parent with a history of psychotic or bipolar disorder defined as ICD-8 and ICD-9 codes 290–299 (except 296.2 and 296B) and ICD-10 codes F20–31 in the Hospital Discharge Register. The overall pattern of findings remained unchanged (results available from the authors on request).

4. Discussion

We show, for the first time, that maternal grandfathers' age is associated with increased risk of schizophrenia. Compared to the reference category (20 to 24 years), those with a maternal grandpaternal age of 40 years or more, have an increased risk of schizophrenia. Unexpectedly, we find that paternal grandfathers' age is not associated with risk of schizophrenia. Consistent with previous studies (Malaspina et al., 2001; Byrne et al., 2003; Sipos et al., 2004), we also confirm a statistically significant association between advanced paternal age and an increased offspring risk of schizophrenia.

The selective effect for maternal but not paternal grandpaternal age may provide clues to biological mechanisms underpinning the link between advanced paternal age and risk of schizophrenia. One key difference between maternal versus paternal grandfathers is the segregation of the X chromosome. The paternal grandfather's X chromosome is not inherited by his son, nor any of this son's children (i.e., grandsons and granddaughters). In contrast, the maternal grandfather's X chromosome is inherited by his daughter and to half of her sons, and half of her daughters. In many instances, X-linked transmission is associated with disease phenotypes emerging in males only (for X-linked recessive disorders) or in a more prominent fashion in males compared to females (for X-linked dominant disorders). The incidence of schizophrenia has been reported to be higher in men compared to women (Aleman et al., 2003; McGrath et al., 2008) and there are many sex differences in the features of schizophrenia in women versus men (Leung and Chue, 2000). However, when we examined the variables of interest in men and women separately, we did not detect any appreciable difference according to the sex of the proband. A study based on Danish mental health registries identified, in fathers older than 50 years, a higher risk of schizophrenia in female compared to male offspring (Byrne et al., 2003). The authors also speculated that paternal age might specifically influence X-chromosome linked genes. A study based on the Jerusalem birth cohort also reported a substantially increased risk of schizophrenia in the sisters of women with schizophrenia who have older fathers — this pattern of affected female sibpairs suggests that paternal age may differentially impact on the X chromosome (Perrin et al., 2010). Goldstein and colleagues recently reported sex-specific patterns of inheritance within a cohort at high risk of psychosis (Goldstein et al., 2011). Overall, these findings suggest that within the complex genetic architecture underpinning schizophrenia, X-linked factors may be differentially represented. Crow has previously drawn attention to the genetic and/or epigenetic factors related to the pseudoautosomal region of the X and Y chromosomes in order to build a hypothesis that links cerebral laterality, language and schizophrenia (Crow, 1993; Crow, 1999; DeLisi et al., 2000).

However, the findings with respect to advanced paternal age and sex-specific inheritance are less clear. A recent systematic review did not detect any sex difference in risk of schizophrenia in the offspring of older fathers (as would be expected in sex-specific transmission) (Miller et al., 2010). Our findings related to the specificity of association with maternal versus paternal grandfather adds weight to the hypothesis that the X chromosome may be differentially affected by age-related mutagenesis in the male germ line. However, on first principles, age-related de novo mutations should impact on autosomes as well as the sex chromosomes. Thus, the lack of association between paternal grandfathers' age and risk of schizophrenia in grandchildren is hard to explain.

Apart from mutations that change the DNA sequence, epigenetic mechanisms may also be involved in the links between paternal age and offspring risk of schizophrenia (Perrin et al., 2007). For example, epigenetic changes are known to occur in sperm at an elevated rate with increased age (Oakes et al., 2003; Oakes et al., 2007). The pattern of inheritance of epigenetic changes in human germ cells is incompletely understood (Rakyan et al., 2002; Daxinger and Whitelaw, 2010; Hochberg et al., 2010). In general, normal epigenetic marks are "wiped" between fertilization and implantation, however the dynamics of this varies for maternal versus paternal chromosomes, and "imprinted" regions of the genome are generally protected from this genome-wide reprogramming (Morgan et al., 2005; Weaver et al., 2009). These mechanisms may also influence the relationship between grandpaternal age and risk of schizophrenia. Psychosocial factors should also be explored. A recent Danish study found that paternal age at the birth of the first child (rather than paternal age per se) accounted for the paternal age-associated risk of schizophrenia (Petersen et al., 2011). This finding suggests that factors other than de novo mutations may contribute to the observed association (e.g. personality and age of first parenthood, assortative mating, etc.).

Recently, it has been demonstrated that the expression of genes on maternal versus paternal chromosomes operate in different regions of the brain during development and in adulthood. For example, genes on maternal chromosomes are transcribed preferentially in the

developing brain, while genes from paternal chromosomes are transcribed later; preferentially in the adult brain (Gregg et al., 2010a). To further complicate the complex links between genotype and phenotype, there are also differences in maternal versus paternal genome transcription in male versus female offspring (Gregg et al., 2010b). Additionally, there is evidence that candidate single nucleotide polymorphisms (SNPs) within known imprinted regions of the genome can be either protective or harmful for disease outcomes depending on the parent of origin of the variant (Kong et al., 2009) This type of biological complexity cannot be unraveled easily with epidemiology (McGrath and Richards, 2009), but recently developed animal models related to advanced paternal age may provide clues to underlying mechanisms (Smith et al., 2009; Foldi et al., 2010; McGrath et al., 2011).

The main strengths of the present study were the large sample size, the nation-wide coverage of psychiatric inpatient care in Sweden, the standardized routines for ICD diagnostic reporting in Sweden (which optimizes the reliability of case ascertainment) (Ekholm et al., 2005) and access to the Multi-Generation Register. However, the study has several limitations. The registers are currently limited regarding follow-up time for the three-generation study, resulting in a much smaller sample with both parental and grandparental age data compared to the sample with parental age data only. Further, our three-generation sample would over-represent early-onset patients and those with younger parents. With respect to age of onset, there is some evidence to suggest that advanced paternal age is associated with an earlier age of onset of schizophrenia (Rosenfield et al., 2010; Lee et al., 2011), so this feature could lead to over-estimated effects in our sample. With respect to a possible over-representation of younger second-generation parents, some studies examining paternal age and risk of schizophrenia have identified a J-shaped curve, with a slight excess risk in the offspring of younger fathers and a larger effect for older fathers (Miller et al., 2010). It is not clear how this feature would impact on our findings — it is plausible that different biological and/or psychosocial mechanisms underlie the J shaped curve. Regardless of this speculation, it will be important to follow if the pattern of associations persists as the Swedish register includes more three-generation pedigrees in the years ahead. It would also be of interest to explore if other neurodevelopmental disorders associated with higher paternal age also show differential maternal versus paternal grandfather effects.

In conclusion, following replication of earlier findings of a positive association between advanced paternal age and schizophrenia, we report that advanced age of maternal but not paternal grandfathers is associated with an increased risk of schizophrenia in the grandchild.

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Contributors

CH, JM, EF and SS were involved in the design of the study. SS supervised the statistical analysis. All authors contributed to data interpretation and manuscript preparation. All authors have approved the final manuscript.

Conflicts of interest

The authors have no conflicts to report.

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