Paternal Age Predicts Offspring Chances of Marriage and Reproduction

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Objectives: Mutation-selection balance theory proposes that a balance of forces between constantly arising mildly harmful mutations and selection causes variation in genetic configuration and phenotypic condition. As mutations are predominantly deleterious, the entry of variation due to mutations is kept at low frequencies by selection. It has recently been demonstrated that nearly all de novo mutation are caused by paternal age.

Methods: We examined on basis of the Wisconsin Longitudinal Study (n = 6,182) whether a subject’s probability of having ever married as well as having ever reproduced is associated with that subject’s father’s age at subject’s birth.

Results: We find that advanced paternal but not maternal age at subject’s birth predicts a lower chance of ever being married and a higher chance of childlessness, even controlling for various confounders.

Conclusions: As marriage is a prerequisite of reproduction in this sample, we discuss that mate choice may provide a mechanism to prevent too high mutation load in the progeny. Am. J. Hum. Biol. 27:339–343, 2015.

According to mutation-selection balance theory, a balance of forces between constantly arising mildly harmful mutations and selection causes variation in genetic configuration and phenotypic condition (Keller, 2007; Miller, 2000). As mutations are predominantly deleterious and thus expected to reduce fitness (Keightley, 2012), the entry of variation due to mutations is kept at low frequencies by selection. On the other hand, mutations may also be fixed due to positive selection of phenotypically advantageous traits (Schneider et al., 2011).

Mutations originating in human sperm outnumber mutations originating in human eggs (Crow, 2000). The reason is that women are born with their full supply of eggs, whereas men go on with sperm production throughout reproductive life (Crow, 2000). This difference results in a higher number of cell divisions in male compared to female gametogenesis, the difference increasing with advancing age at which sperm are produced. Indeed, Kong et al. (2012) demonstrated that a much higher number of mutations are transmitted by the father than the mother to their children. They showed that it is the age of the father which explains nearly all of new mutations in a child, the number of new mutations doubling with each 16.5 years of father’s age. In line with these findings, growing evidence shows that advanced paternal age at conception is linked with an increased risk of a wide range of neuropsychiatric disorders (D’Onofrio et al., 2014), including schizophrenia (Brown et al., 2002; Malaspina, 2001; Sipos et al., 2004), autism spectrum disorder (Hultman et al., 2011; Reichenberg et al., 2006), bipolar disorder (Frans et al., 2008), and epilepsy, as well as Mendelian disorders (Vestergaard et al., 2005) and aspects of physical health (Bray et al., 2006). Increasing paternal age also appears to be associated with poorer performance on intelligence tests (Cannon, 2009; Saha et al., 2009) and a higher risk of obesity (Eriksen et al., 2013).

Here we investigate whether the age of a subject’s father at conception is also associated with the subject’s chances of having ever married and having ever reproduced (or its opposite remaining childless). On the assumption that mate preference could be a potential mechanism to prevent high mutation load in the offspring, we hypothesize that individuals at risk for high mutation load might possibly be less preferred as marriage and hence reproductive partners. In addition, high mutation load may directly affect fertility. We thus predict that advanced father’s age at subjects’ conception should be associated with the subjects’ lower probability of having ever married and a higher chance of childlessness. We used the Wisconsin Longitudinal Study (WLS) to test this prediction, controlling for potential confounders such as sex, subject’s as well as parent’s socio-economic status as indicated by education and income, number of siblings, and mother’s age at subject’s birth.

MATERIALS AND METHODS

The WLS is a long-term study of a random sample of 10,317 men and women who graduated from Wisconsin high schools in 1957, born in the years from 1937 to 1940. We used data on marital status in year 2004 (encoded as 1 = married at some point, n = 5,944, 0 = never married, n = 238) as an indicator for mating success as well as childlessness (1 = at least one child, n = 5,484; 0 = childless, n = 442). In addition, we included sex (encoded as 1 = male, 2 = female) and father’s (mean = 31.55 yr, SD = 6.8) as well as mother’s (mean = 27.77 yr, SD = 5.90) age at subject’s birth in the analysis. As socio-economic background is known to influence mating prospects and reproduction, we further included both subject’s own as well as parental socio-economic status (SES) in the analysis. Subject’s SES was measured by highest education after high school (encoded as 1 = less than one year of college, 2 = 1–3 year college, 3 = bachelor completed, 4 = master or more completed) and yearly income (wages before taxes in 1,000 $) in the year 1993. Parental SES

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was measured by father's highest education (encoded as
1 = no high school, 2 = attended high school, 3 = graduated from high school, 4 = attended trade/business school, 5 = attended college, 6 = graduated from college, 7 = has masters or PhD) as well as parental income (recorded in 1957 in 1,000 $). In addition, as available resources in a family are diluted by the number of siblings, which in turn may influence an individual's mating and reproduction prospects, we also included total number of siblings in the analysis.

We further performed a sibling comparison approach, which rules out to some extent genetic and environmental factors shared by the siblings (D’Onofrio et al., 2014) to attribute potential effects more clearly to father’s age at subject’s birth. Wisconsin Longitudinal provides information on a randomly selected sibling (except when the subject was a twin, in which case the twin was selected). We included only full siblings (n = 4,727) and used data on that sibling’s sex, marital status in 1993 (encoded as 1 = married at some point, 0 = never married), childlessness (encoded as 0 = childless, 1 = at least one child), highest education (encoded as years of education), and age difference to the subject surveyed in 1975 (calculated on a yearly basis) in the analysis.

We used SPSS 19 and R version 3.0.2 for statistical analysis. We calculated on the basis of a binomial error structure following general linear models (GLM), regressing the subject’s father’s and mother’s age at subject’s birth, respectively, the subject’s sex, birth year (encoded as 37–40), highest education (as continuous variable) and income, as well as father’s highest education (as continuous variable), parental income in 1957, and total number of siblings (i) on the subject having ever married, and (ii) on the subject having ever reproduced. We first included all one-way interactions between sex and the other explaining variables in the model, as well as the one-way interactions between the subject’s and parental SES-indicators (i.e., subject’s education × father’s education; subject’s income × parental income) because parental SES probably influences subject’s SES. We then reduced the model stepwise according to Akaike information criterion. In addition, to account for environmental and genetic factors shared by the siblings and control for the unmeasured cluster level covariates, we calculated a stratified Cox regression (i.e., conditional regression) “sibling comparison” (subject and selected sibling are stratified) model (Allison, 2009; D’Onofrio et al., 2014) using the function “clogit” from R library “survival” (http://cran.r-project.org/web/packages/survival/survival.pdf): we regressed the age difference between the selected sibling and the subject (the age difference is positive if the selected sibling is older than the subject and negative if subject is older than selected sibling), the selected siblings’ and subjects’ sex, as well as selected siblings’ and subjects’ highest education on (i) having ever married, and (ii) having ever reproduced. We further calculated a χ² test on (i) the proportion of never married siblings and (ii) the proportion of never reproducing siblings according to the categorized age difference (i.e., whether the selected sibling is older, same age, or younger than the subject). Sample sizes vary because some data are missing.

**RESULTS**

**Marriage prospects**

The percentage of never married subjects increases both with advancing father’s as well as mother’s age at subject’s birth (Fig. 1). However, in a multivariate model including subject’s sex, year of birth, highest educational attainment, and income as well as father’s and mother’s age at subject’s birth, parental income, father’s highest education, and number of siblings, the effect of father’s age at subject’s birth on the subject having ever married remains significantly negative, indicating that the probability of having ever married decreases with advancing paternal age, whereas the effect of mother’s age at birth is no longer significant (Table 1). In addition, subject’s education exerts a significantly negative, subject’s sex and income a significantly positive effect, meaning that higher own education decreases, whereas a higher own income and being female increases the subjects’ chances of having ever married. The effects of subject’s year of birth as well as father’s highest education are marginally significantly positive, that of parental income marginally significantly negative, and the effect of total number of siblings is not significant. Further, the interaction between subject’s sex and own income is significantly negative, which means that the significant positive effect of income is only seen in males but not females. The interaction between subjects’ own and parental income is marginally significantly positive and that between subjects’ income and father’s education marginally significantly negative, suggesting that the effect of own income on marriage prospects increases by trend with increasing parental income but decreasing father’s education (Table 1).

We also find that the probability of having ever married is higher in selected siblings older than subjects (i.e., their father was younger at selected sibling’s than at subject’s birth) than in selected siblings younger than subjects (i.e., their father was older at selected sibling’s than at subject’s birth): 3.7% of the older siblings but 5.8% of the younger siblings remain never married (χ² = 12.747, P = 0.002, n = 4,985). Also in the conditional logistic regression “sibling comparison model,” regressing sex, highest education, and the age difference between

![Fig. 1. Percentage never married subjects for each 10-year category of father’s (dark gray bars) and mother’s (light gray bars) age at subject’s birth.](image-url)
selected sibling and subject on having ever married, the age difference exerts a significant positive effect, implying that the selected sibling's chances of having ever married increase the older the selected sibling (i.e., the younger the father at the selected sibling's birth) is in relation to the subject (Table 2).

**Childlessness**

The percentage of childless subjects also usually increases with increasing father's as well as mother's age at subject's birth (Fig. 2). But again, in a multivariate model including subject's sex, year of birth, highest educational attainment, and income as well as father's and mother's age at subject's birth, parental income, father's highest education, and number of siblings, the effect of father's age at subject's birth on the subject having ever reproduced remains significantly negative, indicating that the prospects of childlessness increases with advancing paternal age, whereas the effect of mother's age at birth is not significant (Table 3). Subject's education also exerts a significantly negative, subject's sex and income a significantly positive effect, which means that the chances of childlessness are higher in male than in female subjects and increase with increasing education but decrease with increasing income. Additionally, the effect of subject's year of birth is marginally significantly positive, those of parental income, father's highest education, and total number of siblings are not significant. Again, we find a significant interaction between subject's sex and income, suggesting that own income reduces the risk of childlessness only in male subjects (Table 3).

In addition, we also find that childlessness was more frequent in selected siblings younger than the subjects (i.e., their father was older when the selected sibling was born) than in selected siblings older than subjects (i.e., their father was younger when the selected sibling was born): 14.4% of the younger siblings but 8.0% of the older siblings remain childless ($\chi^2=50.713, P<0.0001, n=4,991$). Likewise in the conditional logistic regression "sibling comparison model," regressing sex, the highest education and the age difference between selected sibling and subject on having ever reproduced, the age difference exerts a significant positive effect, implying that the selected sibling's chances of having ever reproduced increase the older the selected sibling (i.e., the younger the father at the selected sibling's birth) is in relation to the subject (Table 4).

**DISCUSSION**

We find that advanced paternal but not maternal age at subject's birth predicts a lower chance of having ever married and a higher chance of childlessness. This finding is in line with preliminary results from historical Quebec and Krummhörn, also showing negative effects of paternal age on offspring marriage and number of children.
Table 3. GLM on the basis of a binomial error structure of subjects' sex, year of birth, highest educational attainment, income, number of siblings, as well as father’s and mother’s age at subjects’ birth, father’s highest educational attainment, and parental income, regressing on the subject having ever reproduced (encoded as 0 = childless, 1 = at least 1 child)

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. error</th>
<th>z value</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Intercept)</td>
<td>-4.3042</td>
<td>4.5092</td>
<td>-0.9550</td>
<td>0.0135</td>
<td>0.3398</td>
</tr>
<tr>
<td>Sex (reference: male)</td>
<td>1.2657</td>
<td>0.1842</td>
<td>6.8730</td>
<td>3.5456</td>
<td>0.0000</td>
</tr>
<tr>
<td>Year of birth (1937–1940)</td>
<td>0.2094</td>
<td>0.1167</td>
<td>1.7170</td>
<td>1.2218</td>
<td>0.0859</td>
</tr>
<tr>
<td>Father’s age at subjects’ birth</td>
<td>-0.0286</td>
<td>0.0142</td>
<td>-2.0240</td>
<td>0.8718</td>
<td>0.0224</td>
</tr>
<tr>
<td>Mother’s age at subjects’ birth</td>
<td>-0.0082</td>
<td>0.0142</td>
<td>-0.5740</td>
<td>0.9919</td>
<td>0.0567</td>
</tr>
<tr>
<td>Parental income in 1957</td>
<td>0.0115</td>
<td>0.0097</td>
<td>1.1790</td>
<td>1.0116</td>
<td>0.2384</td>
</tr>
<tr>
<td>Subjects’ income</td>
<td>0.0164</td>
<td>0.0030</td>
<td>5.4050</td>
<td>1.0165</td>
<td>0.0000</td>
</tr>
<tr>
<td>Father’s highest education</td>
<td>0.0075</td>
<td>0.0511</td>
<td>0.2170</td>
<td>1.0075</td>
<td>0.8279</td>
</tr>
<tr>
<td>Subjects’ highest education</td>
<td>-0.3508</td>
<td>0.0511</td>
<td>-6.8710</td>
<td>0.7041</td>
<td>0.0000</td>
</tr>
<tr>
<td>Total number of siblings</td>
<td>0.0226</td>
<td>0.0014</td>
<td>2.2840</td>
<td>1.0000</td>
<td>0.1982</td>
</tr>
<tr>
<td>Sex female: Subjects’ income</td>
<td>-0.0147</td>
<td>0.0047</td>
<td>-9.4590</td>
<td>0.9563</td>
<td>0.0000</td>
</tr>
<tr>
<td>N = 4,768; AIC = 2,455</td>
<td></td>
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</table>

Table 4. Conditional logistic regression “sibling comparison” model, regressing sex, highest education, and the age difference between selected sibling and subject on having ever reproduced (encoded as 0 = childless, 1 = at least 1 child)

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>Std. error</th>
<th>z value</th>
<th>OR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex female (ref. male)</td>
<td>0.0146</td>
<td>0.1104</td>
<td>0.1320</td>
<td>1.0147</td>
<td>0.8948</td>
</tr>
<tr>
<td>Highest education</td>
<td>-0.0976</td>
<td>0.0283</td>
<td>-3.4450</td>
<td>0.0970</td>
<td>0.0006</td>
</tr>
<tr>
<td>Age difference between selected sibling and subject</td>
<td>0.0627</td>
<td>0.0105</td>
<td>5.9980</td>
<td>1.0647</td>
<td>0.0001</td>
</tr>
<tr>
<td>N = 6,501; R² = 0.05</td>
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(Arslan et al., 2014), though in the reproducing subjects (i.e., excluding childless subjects) of our study, no significant effect of paternal age on the number of children emerged (data not shown).

The effect of father’s age remains significant even after controlling for confounding variables such as socioeconomic status indicators and size of the originating family. The paternal age effect is even apparent by comparing marriage prospects and the chances of childlessness between siblings older and siblings younger than the subject, which to some extent controls for genetic and environmental factors shared by the siblings (D’Onofrio et al., 2014).

The magnitude of this effect, with odds ratios of 0.9389 and 0.9718 for having ever married and having ever reproduced, respectively, for each year increase in paternal age (meaning that the prospects of having ever married as well as having ever reproduced decrease with increasing father’s age) is within the range of paternal age effects on other traits, such as schizophrenia, autism spectrum disorders, and various psychiatric disorders. For example, for schizophrenia, relative risks of 1.47 and 1.71 have been shown for each 10-year increase in paternal age (Brown et al., 2002; Sipos et al., 2004). For autism spectrum disorders, a wide range of adjusted relative risk have been reported, ranging from 1.28 with each 10-year increase in paternal age (Croen et al., 2007) to 5.75 in offspring of men aged 40 years and older compared to men aged 15–29 years (Reichenberg et al., 2006). And very recently, D’Onofrio et al. (2014) reported hazard ratios ranging between 2.44 and 2.47 for various psychiatric disorders in offspring of fathers aged 45 years and older compared to offspring of fathers aged 20–24 years.

A possible interpretation of our results is that birth order effects may play a role. According to Sulloway (2007), birth order is associated with differential parental investment as well as intra-familial niche construction, which may affect later behavior. Children of older fathers may thus make different lifestyle decisions influencing their own desire as well as their prospects to marry and reproduce.

As paternal age explains most of the new mutations in a child (Kong et al., 2012), however, the found paternal age effect on marriage probability may also suggest that new mutations may hamper an individual’s chances at the marriage market. Although mutations owing to father’s age are spread among a total of 1,896 genes over all human chromosomes (ranging from 1 to 10 mutations in one single gene: http://www.nature.com/nature/journal/v488/n7412/full/nature11396.html; Kong et al., 2012), it is reasonable to assume that a complex trait like popularity at the marriage market, which is the result of an interaction of a high number of genes, regulatory elements, morphological and physiological functioning, but also social as well as behavioral factors, is influenced if mutations occur randomly anywhere in the genome.

The paternal age effect on the chances of childlessness may likewise result from new mutations, this time hampering fertility. This view, however, is not supported by the fact that we did not find any association between paternal age and the number of children in reproducing subjects. Moreover, as 95.5% of the never married subjects but only 3.9% of the ever married subjects remained childless in this sample, we suggest, that the paternal age effect on childlessness may be more likely the result of the link between paternal age and marriage prospects, although both possibilities are not mutually exclusive.

As mating success in terms of marriage is a prerequisite of having ever reproduced in this sample, we argue that mating may provide a mechanism to prevent too high mutation load in progeny. If individuals at risk for high mutation load are less preferred as mating and, thus, reproductive partners, then one would expect that subtle cues exist that signal potential high mutation load.

Indeed, very recently Huber and Fieder (2014) found that advanced paternal age predicts lower facial attractiveness. In addition, D’Onofrio et al. (2014) only just reported that the risk of various psychological conditions is also strongly associated with father’s age at conception.

In line with mutation selection theory, the increasing probability of mating and reproduction failure with advancing paternal age could thus be interpreted as some sort of a balancing process reducing the potential ...
accumulation of deleterious mutations in the gene pool. But then, even though the majority of mutations are deleterious, on rare occasions mutations can also be advantageous. What is more, these rare advantageous mutations, which are under positive selection, are of crucial importance for evolution, even though due to their rarity, any reproductive advantage caused by those rare mutations could probably only be measured over generations. Assuming that father’s age is the major cause of new mutations (Kong et al., 2012), father’s age might thus be considered as an important factor in evolutionary dynamics both by eliminating high mutation load and spread of rare advantageous mutations. Future research should address the role of father’s age in evolution and whether the changing mating patterns may have long lasting evolutionary consequences.

ACKNOWLEDGMENTS

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LITERATURE CITED


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