Grandma plays favourites: X-chromosome relatedness and sex-specific childhood mortality†

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Biologists use genetic relatedness between family members to explain the evolution of many behavioural and developmental traits in humans, including altruism, kin investment and longevity. Women’s post-menopausal longevity in particular is linked to genetic relatedness between family members. According to the ‘grandmother hypothesis’, post-menopausal women can increase their genetic contribution to future generations by increasing the survivorship of their grandchildren. While some demographic studies have found evidence for this, others have found little support for it. Here, we re-model the predictions of the grandmother hypothesis by examining the genetic relatedness between grandmothers and grandchildren. We use this new model to re-evaluate the grandmother effect in seven previously studied human populations. Boys and girls differ in the per cent of genes they share with maternal versus paternal grandmothers because of differences in X-chromosome inheritance. Here, we demonstrate a relationship between X-chromosome inheritance and grandchild mortality in the presence of a grandmother. With this sex-specific and X-chromosome approach to interpreting mortality rates, we provide a new perspective on the prevailing theory for the evolution of human female longevity. This approach yields more consistent support for the grandmother hypothesis, and has implications for the study of human evolution.

Keywords: longevity; grandmother; altruism; human evolution; X-chromosome; kin investment

1. THE GRANDMOTHER HYPOTHESIS

With menopause occurring around age 50, women survive several decades longer than their gametes (Dorland et al. 1998; Hawkes 2003). Why should women have such conservative life histories that they save up enough energy for 25 years of reproductive retirement? Human females represent a particular conundrum in evolutionary studies: after menopause they are unable to reproduce and have no obvious way to increase their genetic contribution to future generations. As this is the basis for natural selection, many researchers have sought to explain how post-menopausal longevity is adaptive in women.

Among evolutionary biologists, the ‘grandmother hypothesis’ is the most widely recognized explanation for human female post-reproductive longevity. It suggests that vigorous, skilled, elderly women are able to contribute to their grandchildren’s survivorship through nutritional provisioning (Hawkes et al. 1998; Hawkes 2003). According to Hamilton’s relatedness coefficients (Hamilton 1966), grandmothers share a quarter of their DNA with grandchildren, and so a woman can increase her genetic contribution to subsequent generations by keeping her grandchildren alive and healthy. Supporters of this model often refer to the Hadza, a modern foraging society in Tanzania, where grandmothers are more effective than children at extracting tubers from the dry ground. While a mother is breastfeeding an infant, and thus unable to forage enough to provide for weaned children, the grandmother provides food for the older siblings (Hawkes 2003; Hawkes & Jones 2005). The grandmother hypothesis posits that during the Plio–Pleistocene (1.7–1.9 Myr), the African savannah climate became more arid, and tubers became a more important component of the hominid diet (Vrba 1985; Foley & Lee 1991). Extracting tubers from the ground takes strength and skill, so recently weaned children required an adult provider. The mother usually filled this role, but when the mother was occupied with a newborn, the grandmother would step in. The grandmother’s invaluable role in caretaking led to higher fertility in her daughter, and thus provided a strong inclusive fitness advantage to those grandmothers who survived longer. In recent years, the grandmother hypothesis has also been interpreted to include all tactics a grandmother could use to increase the fitness of her grandchildren, as opposed to Hawkes’ original hypothesis that focused on dietary provisioning (Cant & Johnstone 2008). Among our species, alloparents play an important role in assisting mothers with childcare,

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and so the participation of a grandmother in child-rearing could make a serious impact on a child's likelihood of survivorship (Hrdy 2009). For criticism of the grandmother hypothesis, see Pececi (2001) and Zeller (2004).

Tests of the grandmother hypothesis have been carried out on modern and historical populations. Most of the data correlate grandchild survivorship with grandmother survival and/or proximity, and it is often reported that only maternal grandmothers (MGMs) are found to have a positive effect on grandchild survivorship (Sear et al. 2002; Voland & Beise 2002). Studies that have not distinguished between MGMs and paternal grandmothers (PGMs) have found no correlation between grandmother’s presence and grandchild survivorship (Hill & Hurtado 1991; Lahdenperä et al. 2004). To date, only two previous studies known to the authors have distinguished between boys and girls when investigating the effect of both grandmothers. A study of a Japanese population found that the presence of a PGM had a negative effect on boys and a positive effect on girls, while the presence of an MGM had a positive effect on children of both sexes, especially on boys (Jamison et al. 2002). They point to cultural features of the society as a possible mechanism for these findings. A study of an Ethiopian population reported the sex-specific information, but it was not analysed in the paper (Gibson & Mace 2005). More tests of the grandmother hypothesis are summarized in Sear & Mace (2007).

2. A NEW PERSPECTIVE ON THE GRANDMOTHER HYPOTHESIS

The grandmother hypothesis is based on the fact that women are genetically related to their grandchildren, and we should not overlook the nature of that genetic relatedness. Grandsons and granddaughters differ in the proportion of their X-chromosomes shared with MGMs and PGMs (figure 1). According to our proposed X-linked grandmother hypothesis, if grandmothers invest in grandchildren because of their genetic relatedness with them, then their adaptive incentive to invest may vary in a way that mirrors this variation in genetic relatedness. As a consequence, grandmothers’ differential investment in grandchildren could cause differential survivorship of those grandchildren.

(a) Differential X-relatedness between grandmothers and grandchildren

(i) Paternal grandmother—girl: 50 per cent
The PGM has two X-chromosomes, and passes one of them to her son. Therefore, any individual gene on her X-chromosome has a 50 per cent likelihood of being inherited by her son. This is the one and only X-chromosome a man has. He passes this chromosome on to his daughter, and so the X-relatedness between a PGM and granddaughter is, just as between a woman and her son, 50 per cent (figure 1).

(ii) Paternal grandmother—boy: 0 per cent
Because the only heterosomal relatedness boys have with their fathers is the Y-chromosome, they have no X-relatedness with the PGM.

(iii) Maternal grandmother—boy and maternal grandmother—girl: 25 per cent
The MGM has two X-chromosomes, and so any given X-linked gene of hers has a 50 per cent chance of being transmitted to her daughter. Her daughter has one X from the MGM and one X from the maternal grandfather (‘MGF’). She will pass down one of those two X chromosomes to each child, regardless of whether the child is a male or a female. Thus, the transmission likelihood for any particular X-linked gene is 0.5 inheritance from MGM to mother, and 0.5 from mother to child. Therefore, the likelihood of a grandchild inheriting any particular gene from the MGM is 25 per cent (0.5 × 0.5 = 0.25). It is worth noting that females exhibit X-inactivation, so the likelihood that any particular X-linked gene in granddaughters will be expressed is only 50 per cent compared with 100 per cent in grandsons, but for the purpose of this analysis, we have focused on probability of genetic transmission, not the probability of gene expression.

Although the X-chromosome contains only about 4.4 per cent of our DNA, with its estimated 1529 genes, it contains perhaps approximately 8 per cent of all human genes (Pennisi 2003; NIH 2007; Parang et al. 2008; NCBI 2009a). The dramatic differences in X-relatedness between grandmothers and grandchildren confound the Hamiltonian concept that grandchildren are 25 per cent genetically related to each grandparent. If approximately 92 per cent of our genes are autosomes, then a grandmother shares one-quarter of that, or approximately 23 per cent of her total genes with a grandchild, plus X-relatedness.1 If a grandmother shares no X-chromosome with a grandchild, then their overall genetic relatedness is approximately 23 per cent, and if they share an entire X-chromosome, then it would be approximately 31 per cent. Therefore, MGMs and granddaughters are likely to share 25 per cent of their genomes, while PGM and granddaughter may share a total of approximately 31 per cent of their genes, with a likelihood of 27 per cent inheritance, while a PGM and grandson may share only approximately 23 per cent.

Studies on the grandmother hypothesis often suggest that grandmother provisioning is only adaptive along the maternal line owing to paternity uncertainty (Hawkes et al. 1998; Ragsdale 2004). Uncertainty, which ranges from 0.4 to 10 per cent in extant societies (Simmons et al. 2004; Bellis et al. 2005) would diminish the genetic relatedness factor between PGMs and their grandchildren. Therefore, it is generally believed that grandmother provisioning is more adaptive along the maternal line. We suggest here that boys are even further removed in their genetic relatedness with PGMs, but girls are so closely genetically related to their PGMs that it may counteract, or even overshadow, the adaptive influence of paternal discrepancy.

(b) Predicted trends for grandmother investment in grandchildren
We predict that this variation in genetic relatedness should cause the following pattern in the amount of investment. Grandmothers provide grandchildren (table 1): PGM—girl should be the combination exhibiting the highest amount of grandmaternal investment, as they share 50 per cent X-relatedness. The least grandmaternal investment should be with PGM—boy, as they share no X-relatedness. Between those two groups should rank
3. RESULTS: GRANDMOTHERS’ EFFECTS ON GRANDCHILD SURVIVORSHIP

We analysed sex-specific grandchild survival in the presence of grandmothers in seven populations in Japan, Germany, England, Ethiopia, The Gambia, Malawi and Canada (electronic supplementary material, table S1). These are all traditional populations in which grandparents are an integral part of the family unit, and we defined a grandmother as ‘present’ if she resided in the home with a child, or in the same village as the child, depending on the residential customs of each population, and ‘absent’ if she lived in a different village or died (electronic supplementary material). The results demonstrate that the effect of a grandmother’s presence on grandchild mortality corresponds to the degree of X-relatedness to the grandchild (figure 2; electronic supplementary material, tables S2–S15). The higher the X-relatedness between a grandmother and grandchild, the more beneficial effect the grandmother has on that child’s survivorship. As far as we are aware, this is the first analysis to describe the relationship between X-relatedness and grandchild mortality rates.

These data follow the predicted trends based on X-relatedness (table 2). In all seven populations, boys survive better in the presence of MGMs than PGMs. In all but one population, PGMs have a more beneficial effect on girls than they do on boys. It is evident that PGM–boy is the least beneficial combination, ranking last in five of the seven populations. All of the populations exhibit a detrimental effect of PGMs on boys (figure 2; electronic supplementary material, tables S2–S15). They share no heterosomal relatedness at all, making their overall relatedness approximately 23 per cent. Less consistently upheld was our hypothesis that girls would survive better in the presence of their PGM than their MGM, yet this was still true in the majority of cases.

We performed a statistical meta-analysis to evaluate the dataset as a whole (electronic supplementary material).
In seven out of seven populations, grandsons survived significantly better in the presence of their MGM than their PGM (Wilcoxon signed ranks test $p = 0.0081$). In six of the seven populations, the presence of a PGM improved the likelihood of the granddaughters’ survival more than the grandsons’ (Wilcoxon signed ranks test $p = 0.0587$). Additionally, in seven out of seven populations, PGMs had a negative effect on grandsons, and in six of the seven populations, PGMs had a positive effect on granddaughters. Using a Fisher’s exact test to measure the strength of the PGM’s sex-specific effect, the result was highly significant ($p = 0.0046$).

Figure 2. Grandmother’s effect on grandchild survivorship. Grey bars, girls; black bars, boys. These graphs represent a grandchild’s odds ratio of survivorship based on the presence of a grandmother. Values above 1.0 indicate that the presence of the grandmother has a positive effect on the grandchild’s survivorship, and therefore a beneficial effect. Values of 1.0 indicate no effect. Values below 1.0 indicate that the grandmother has a negative impact on the grandchild’s survivorship, and therefore a detrimental effect. There were not many instances of statistical significance, but the consistent patterns between the different populations are noteworthy. The overall opposite effect of the PGM on boys versus girls was significant ($p = 0.0046$). $^*$p < 0.05, +p < 0.10. (a) Germany (Krummhoern) 1720–1874, (b) England (Cambridgeshire) 1770–1790, (c) Ethiopia (Arsi) 1998–2003, (d) Canada (Quebec) 1680–1750, (e) Japan (Nagano) 1671–1871, (f) Gambia (West Kiang) 1950–1975, and (g) Malawi (southern region) 1994–1997.
For now, we can only hypothesize a mechanism to explain the sex-specific grandmother effects. Perhaps there is a behavioural adaptation in women that they should favour certain grandchildren based on sex. Or, perhaps there is some signal the grandchild sends or presents to the grandmother that indicates genetic relatedness, such as physical resemblance, a certain smell or a pheromone. Smells and pheromones have been shown to influence physiological processes and behaviour in humans, such as mate choice and maternal/neo-natal recognition (Bergquist et al. 1979; Porter et al. 1986; Horth 2007; Thom et al. 2007), and physical resemblance has been shown to affect investment patterns among kin (Platek et al. 2002). This could result in differential investment from the grandmother that could cause the differential survivorship (e.g. provisioning, protecting, teaching). Haig (2000) pointed to X-relatedness to explain favouritism within kin. He theorized that X-relatedness could be a factor encouraging female philopatry in mammals, as the genetic relatedness between mothers and daughters is greater than the genetic relatedness between fathers and sons, owing to X-inheritance as well as paternity uncertainty.

However, there is evidence against a behavioural mechanism. Two studies (Chrastil et al. 2006; Pollet et al. 2009) that used questionnaires to measure the relationship between preferential care and heterosomal relatedness among grandparents found no support for a correlation. The preferences cited by grandchildren and grandparents did not consistently correspond to genetic relatedness (Chrastil et al. 2006; Pollet et al. 2009), which could be evidence for the possibility that the correlation in survivorship demonstrated here is due to a mechanism other than conscious behaviour.

The X-chromosome contains a high percentage of genes affecting reproductive success. Many genes associated with fertility and intelligence are X-linked (Vines 1997; Zechner et al. 2001; Ananthawamy 2002). A study by Zechner et al. (2001) illuminated the X-chromosome’s importance in other realms. By looking at a random assortment of heritable defect phenotypes, Zechner et al. (2001) found that these phenotypes were an average of 2.35 times more likely to be X-linked than to derive from any single autosome (range: 2.14–2.76). This finding implies that the X-chromosome could account for a high proportion of our general phenotypic variation, or at least that it accounts for a high proportion of abnormal conditions. As a result, variation in X-chromosome relatedness could cause wide variation in fitness.

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We are not the first to suggest that there is distinct intergenerational genomic inheritance in humans. The genetic connection between grandparents and grandchildren is complex, and previous students have shown that grandparental behaviour, physiology, life experience and genetics have an influence on trends in grandchild mortality rates and other aspects of grandchild growth and development. For example, Susser & Stein (1994) and Lumey & Stein (1997) report that women who had restricted nutrition during pregnancy not only gave birth to underweight children, but also the grandchildren were underweight at birth. Harper (Harper 2005) argues that imprinting in the germ line responsible for X-chromosome inactivation exemplifies epigenetic
intergenerational transfer, as it involves pathways carrying patterns of gene expression from one generation to the next.

Cropley et al. (2006) showed that environmentally induced epigenetic modifications in mice (i.e. a diet rich with methyl donor foods, which alters the methylation of the agouti-controlling gene) can persist through the epigenetic reprogramming of the germ line. In this case, two mothers with identical genotypes and phenotypes could produce phenotypically dissimilar offspring and grandoffspring as a consequence of environmental changes during pregnancy.

The genetic relationship between girls and PGMs is particularly unique, as the X-chromosome they share is not subject to extensive crossing-over (figure 1). At fertilization, much of the maternal and paternal imprinting from the gamete genome is erased, but there are some parts of the embryonic genome that escape erasure and thus maintain maternal or paternal imprinting. Among these are the paternally methylated imprinted genes (Morgan et al. 2005). Therefore, epigenetic markers on the X-chromosome may be conservative along the paternal line, as the X-chromosome itself is uniquelyunaltered in its inheritance from a PGM to a granddaughter. It is possible, therefore, that there is some imprinting passed down the paternal line to a girl, potentially contributing to PGMs’ beneficial effect on granddaughters.

5. CONCLUSION

Genetic relatedness between kin is often used to explain behavioural phenomena associated with altruism and caretaking, as well as biological traits and developmental trends. The grandmother hypothesis is the prevailing theory to explain why human female longevity extends beyond menopause. It suggests that elderly women are able to contribute to their grandchildren’s survivorship through nutritional provisioning, which would increase a woman’s inclusive fitness because she shares one-quarter of her genes with a grandchild. In seven previously studied populations, separating grandchild survivorship rates by sex reveals that X-chromosome relatedness correlates with grandchild survival in the presence of MGMs and PGMs. In all seven populations, boys survive better in the presence of their MGM than PGM. In all bar one population, the PGM has a more beneficial effect on girls than on boys. Our X-linked grandmother hypothesis demonstrates how the effects of grandmothers could be sex-specific because of the unusual inheritance pattern of the X-chromosome. This provides a more universally applicable model to explain differential survival of grandchildren in the presence of their grandmothers.

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ENDNOTES

1The Y-chromosome contains only 89 genes, accounting for only approximately 0.4 per cent of all human genes (NCBI 2009), and so it has been left out of this analysis.

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