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Paternal Age and Genetic Load

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Abstract The incidence of base substitutions in humans increases with the age of the father, which shows up as an increased incidence of mutational disorders in the children of older fathers. There is a less obvious implication: an extended period of high average paternal age in a population will lead to increased genetic load. We mention some societies that have had high average paternal age for many generations. This may explain some surprising regional differences in recent measurements of deleterious mutations. High average paternal age also influences life history evolution, strengthening selection against mortality in late life while weakening selection against child mortality.

It is now clear that most mutations occur in males, and that the number of mutations transmitted increases approximately linearly with the father's age. The recent DECODE study (Kong et al. 2012) determined the mutation rate by direct sequencing of family trios. They found that mothers contribute an average of 15 new mutations, regardless of age, while men contribute $(25 + 2(g - 20))$ new mutations, where g is the paternal age. If both parents are 30, each child inherits 60 new nucleotide changes on average, 15 from the mother and 45 from the father. If the father is 45, each child inherits 90 nucleotide changes—a 50% increase.

The age-related increase in mutations of paternal origin is believed to be caused by the large number of cell divisions in spermatogenesis, leading to copying errors (Penrose 1955). Before puberty, gonocytes divide some 30 times to produce spermatogonial stem cells. After puberty, those stem cells continue dividing indefinitely. The spermatocytes in a 30-year-old man have undergone 380 divisions, while those in a 50-year-old man have undergone 840. This is in strong contrast with egg formation, which involves only 24 cell divisions, all completed before a women's birth (Glaser and Jabs 2004).

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Mutation Mechanisms

A number of different mechanisms cause mutations. Some are strongly dependent on paternal age, and some are not. Base substitutions, which account for the great majority of all mutations, increase dramatically with paternal age, but chromosomal abnormalities such as Down syndrome are associated with high maternal age. Most large deletions are generated by nonallelic homologous recombination (also known as illegitimate recombination), which occurs during meiosis and does not show a paternal age effect (Crow 2000; Glaser and Jabs 2004; Veltman and Brunner 2012).

Generally, the rate of base substitutions increases nearly linearly with paternal age—which also means linearly with the number of cell divisions, which is what one would expect. For a few hotspots, such as those causing achondroplasia and Apert syndrome, the age-related increase is exponential. Those syndromes are almost always caused by very specific mutations that are overwhelmingly of paternal origin. There is now good reason to believe that the particular mutations seen in these syndromes confer a somatic selective advantage in spermatogonia. Over time, mutated spermatogonia increase in number and produce an increasing fraction of sperm carrying the mutations causing these syndromes (Goriely et al. 2003, 2005).

In this article, we consider classes of mutations whose rate increases linearly with paternal age, which make up the vast majority of paternal-age syndromes and the majority of all mutations. We use the model described above, based on the recent DECODE study (Kong et al. 2012), in which mothers contribute 15 new mutations (on average), regardless of age, while fathers contribute $(25 + 2(g - 20))$ new mutations, where g is the paternal age. The measured data in the DECODE study are nearly linear: a linear fit explains 94% of the variance. However, a model in which mothers contribute a fixed number of mutations while paternal mutations increase by 4.28% a year gives a slightly better fit, explaining 97.1% of the variance. That slight improvement is driven by only 2 out of 78 data points, the two oldest fathers in the data set. We decided to use the linear model for three reasons. First, it is conservative: if anything, it may slightly underestimate the increase in mutations from fathers older than 40. Second, it is tractable: with a linear model, our analysis does not require detailed information about the distribution of paternal age, only the average paternal age, which is available for many populations. Third, it is more straightforward: a slightly nonlinear model would not improve our model's accuracy much but would make our analysis much more difficult to follow.

Family-Level Effects

Driven by the increased mutation rate, many disorders are more common in the children of older fathers. Many, such as Marfan syndrome and Waardenburg syndrome (both autosomal dominant), as well as hemophilia A (X-linked), are well-understood Mendelian genetic disorders. A number of congenital anomalies, such as cleft palate and heart defects, also increase with paternal age (Green et al. 2010). Such complex defects appear to be (at least in part) collections of monogenic

syndromes with similar phenotypes. As such, they can be much more common than a disorder caused by mutations in a single gene. In general, adaptive functions that involve the expression of more genes present larger mutational targets and are more subject to the paternal-age effect.

Population Effects

It is known that the children of older fathers suffer from increased risks for many disorders, but most such children do not suffer serious problems. It might seem that an increased number of mutations from older fathers is a real but limited public health threat. Advanced paternal age can, however, cause deeper problems in a population that has had a high average paternal age for many generations. This is because mildly deleterious mutations increase over time and should lead to an increased genetic load (specifically, mutational load) in the population.

Disorders known to be associated with advanced paternal age are caused by dominant mutations with fairly large effects, since only dominants manifest in the first generation, whereas problems attract the attention of medical researchers only if they exceed a certain threshold of practical importance. If a person has schizophrenia or a cleft palate, a medical problem is deemed to exist. But suppose there was a mutation that decreased stature by a millimeter—it would never be noticed. Recessive or mostly recessive mutations resulting from advanced paternal age would also go unnoticed. There is every reason to think that advanced paternal age increases the rate of all base substitutions, regardless of severity or penetrance.

Therefore, advanced paternal age must also increase the rate of mildly deleterious mutations. High average paternal age over many generations would markedly increase the number of such mutations, since they are removed slowly by selection.

Theory of Genetic Load

At equilibrium, deleterious mutations are removed by selection at the same rate at which they are created. For example, if a class of mutations reduces fitness by 1%, the equilibrium frequency must be 100 times the mutation rate. For a class of dominant mutations that reduces fitness by s, the equilibrium frequency is μ/s, where μ is the mutation rate for that class, as shown by J. B. S. Haldane (1937). If a deleterious mutation is recessive, the equilibrium frequency is $(\mu/s)^{1/2}$.

In the case of dominant mutations, the population mean fitness is $1 - 2sp$, where p is the frequency of the dominant, μ/s, or simply $1 - 2\mu$. In the recessive case, the population mean fitness is $1 - sp^2$ and the frequency p is $(\mu/s)^{1/2}$, so the mean fitness is just $1 - \mu$ at that locus. The net decrease in fitness is independent of s. As Brian Charlesworth and Deborah Charlesworth (2010) put it, "Although weakly selected mutations cause fewer selective deaths among their carriers than strongly selected mutations, they rise to higher equilibrium frequencies. Provided that these frequencies are still sufficiently low that the relevant approximations are

valid, the two effects exactly cancel out." At equilibrium, the mutation rate, not the effect size, determines the net decrease in fitness. This means that the mutation rate for mild mutations (compared with those that severely reduce fitness) is important. If they occur more often than severe mutations, they will, at equilibrium, have a greater effect on fitness.

Mutations of medium to small effect can occur in a number of ways. They include mutations that slightly affect the function of key proteins, mutations that seriously interfere with the function of relatively unimportant proteins, and mutations that affect regulatory sequences. Functional regulatory sequences seem to account for quite a bit more of the genome than those sequences that code for proteins (Ponting and Hardison 2011), but mutations in regulatory sequences account for only a small fraction of recognized Mendelian diseases (Choi et al. 2009), which suggests that regulatory mutations are born to be mild.

Looking only at missense mutations (which change amino acids in a protein), the mutation rate for mild mutations (those that reduce fitness between 1% and 10%) is at least twice as high as the rate of severe mutations (those which reduce fitness by more than 10%) (Eyre-Walker and Keightley 2007). If one adds regulatory mutations, it seems likely that the mutation rate for mild mutations is considerably greater than the rate of severe mutations, and therefore mild mutations must have a greater impact on fitness, in the long run.

Consequences of an Increase in the Mutation Rate

We are, however, more interested in the medium run, since it seems likely that high average paternal age originated after the development of agriculture. Imagine a population near mutational equilibrium. What would happen if its members adopted a new social pattern that increased the average paternal age from 30 to 45, resulting in a 50% increase in the mutation rate? Figure 1 shows how different components of the mutational load would change over time. These calculations are based upon a toy model of the distribution of mutational effects, realistic to the extent that it has a higher mutation rate for small-effect mutations than for large-effect mutations. We assume that the distribution of mutations, as a function of their selective disadvantage, is given by a gamma function with a shape parameter of 0.23 and a mean of 425 (Eyre-Walker et al. 2006)

The top curve in figure 1 shows the load at the original equilibrium. After just one generation (not shown), lethal mutations reach their new equilibrium level, 50% higher than before, but the load associated with small-effect mutations has barely begun to change. After 10 generations (Figure 1, second curve), the load stemming from mutations that decrease fitness by 10% is about two-thirds of the way to the new equilibrium. After 100 generations (third curve), the load stemming from mutations that decrease fitness by 1% is about two-thirds of the way to the new equilibrium. Individuals from a population that has had a high average paternal for a long time will have increased amounts of both large-effect and small-effect mutations.

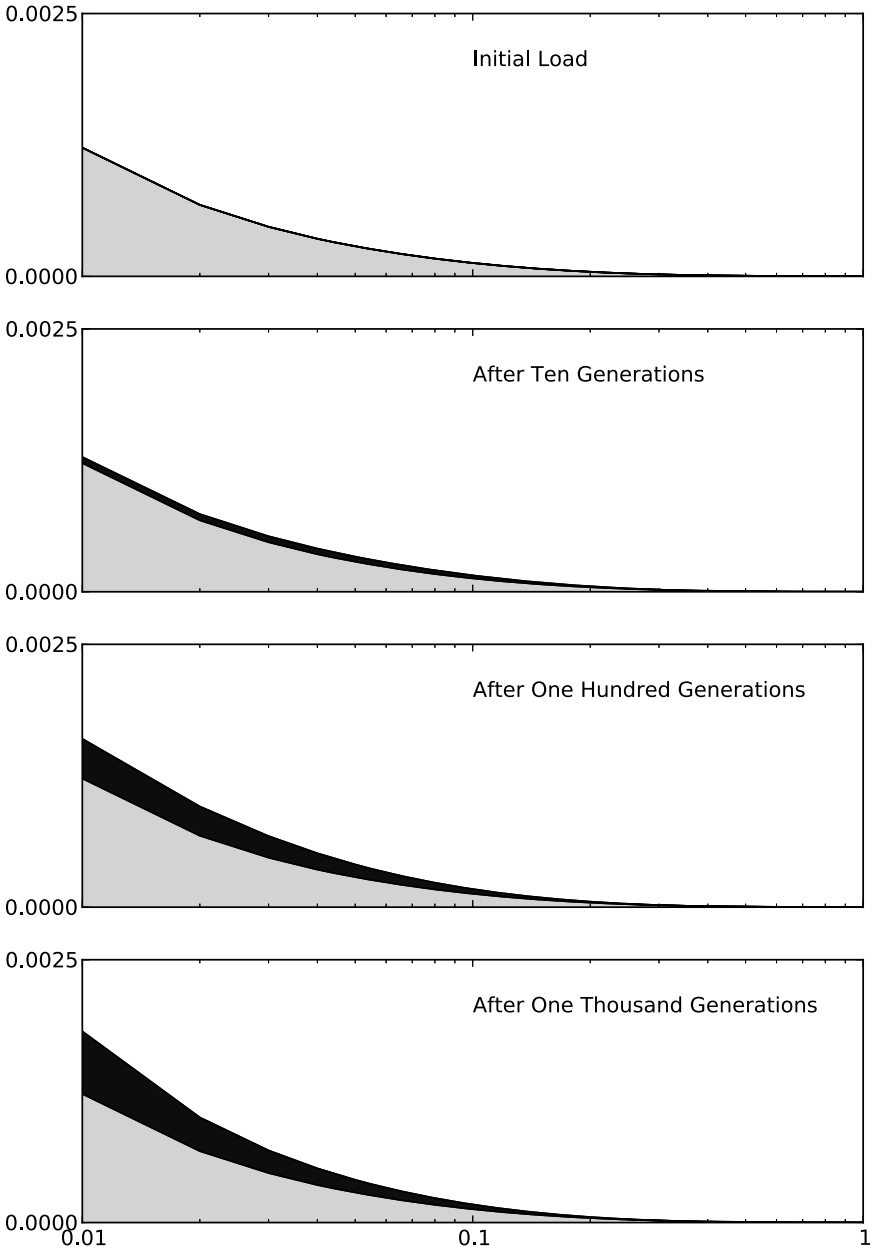

Figure 1. Genetic load over time after an increase in paternal age. The *x*-axis is the selection coefficient against the mutations.

Eventually, the amount of neutral diversity would also increase significantly if the population had a higher mutation rate, but that would take a *very* long time—on the order of N_e generations, where N_e is the effective population size. At minimum, it would take hundreds of thousands of years, and the increase would have no impact on health or fitness.

If the mutation rate decreased, the frequency of large-effect deleterious mutations would decline immediately, while the frequency of small-effect deleterious mutations would take many generations to approach the new, lower equilibrium level.

The distribution of this genetic load would be approximately Poissonian (Charlesworth and Charlesworth 2010). It would vary among individuals, but there might not be much overlap in load across populations. For example, imagine populations A and B, with members of A having an average of 80 small-effect deleterious mutations and members of B having 100 (similar to the numbers in MacArthur et al. 2012 that discussed below). Since the standard deviation of a Poisson distribution is the square root of the mean—10 for population B—the mean number of mutations in population A is 2 SD lower than that of B. Only 2.2% of population B will have a genetic load as small as or smaller than that of the average member of A.

Individuals with a single large-effect deleterious mutation often have a characteristic phenotype, since large-effect mutations are usually pleiotropic, but someone with considerably more small-effect deleterious mutations than average probably would not—the small-effect mutations would push in different directions in phenotype space and would tend to cancel out, not with respect to function and fitness but with respect to minor pleiotropic effects of the small-effect mutations. Such individuals would show reduced performance, particularly in organs like the brain that are large mutational targets, but would not look unusual.

Average Paternal Age in Various Populations

Existing populations certainly differ in their average paternal age. Hunter-gatherers typically have an average paternal age around 31.5 years (Fenner 2005). For the Polar Eskimos of northern Greenland, average paternal age was 32 years (Matsumura and Forster 2008). African hunter-gatherers, at least those we have data for, seem to have somewhat higher paternal ages. The !Kung have an average paternal age of 35.8 (Howell 2000), and for the Hadza it is 35.5 (N. B. Jones, personal communication). The Australian Aborigines are an exception among hunter-gatherers, with a typical average paternal age of 42 (Denham 2012). This is a result of their unusual pattern of gerontocratic polygyny: there, men averaged about 14 years older than their wives.

High average paternal age is also seen in polygynous agricultural societies, mainly in sub-Saharan Africa. The average paternal age was 46 in Gambia (Mace 2000), 46.6 in Cameroon (Paget and Timæus 1994), and 42 among the Herero (Pennington and Harpending 1993). Polygyny both delays and extends male fertility, so the average paternal age increases (Heyer et al. 2012).

Average paternal age has varied over time in Western countries. It seems to have been relatively low in the 20th century but has increased in recent years. In Iceland, average paternal age averaged between 34 and 38 in the 17th and 18th centuries, was 28 in 1980, and was 33 in 2011 (Helgason et al. 2003). Average paternal age was 30.6 in France in 1980 (Paget and Timæus 1994).

Measurements of Deleterious Mutations

Genetic load in humans was once a hot topic in biology, partly because of its theoretical importance but also because of concern about the effects of radioactive fallout from above-ground nuclear tests. Partly because of inability to make any direct measurements of genetic load and partly because of mysterious changes in scientific fashion, interest in genetic load began to decrease around 1970. However, that is about to change, because techniques for measuring genetic load are becoming available.

There have been two recent reports on the incidence of deleterious variants in the human genome (MacArthur et al. 2012; Tennessen et al. 2012). MacArthur et al. 2012 used high-accuracy whole-genome sequencing to identify loss-of-function variants, those that severely disrupt protein-coding genes. They looked at the HapMap populations—mixed northern Europeans (CEU), Africans (YRI, Yoruba from Nigeria), and a Chinese/Japanese sample (CHB/JPT)—and found that the number of high-confidence loss-of-function variants is 25% higher in the Nigerian sample than in the three Eurasian-origin populations. MacArthur and colleagues suggested that this was a consequence of greater genetic variation in Africans, presumably because of a larger effective population size in prehistory. That is unlikely to be the case. Although the diversity of neutral genes is determined by the population history and mutation rate, the frequency of deleterious mutations is largely determined by the mutation-selection balance. Note that the number of loss-of-function variants was almost exactly the same in the CEU and CHB/JPT samples, even though neutral genetic variation is noticeably smaller in East Asians than in Europeans (Li et al. 2008). Interestingly, the excess in deleterious variants found in the YRI sample was in stop, splice, and indel mutations. The YRI population had no excess of large deletions—they had slightly fewer than the CEU sample and almost exactly the same number as the CHB/JPT sample. As mentioned before, large deletions show no paternal age effect, but base substitutions (the cause of stop and splice mutations) certainly do. Thus, the pattern seen in the YRI population could be the consequence of high average paternal age over a fairly long period. This is especially plausible considering that the Yorubans are known to be highly polygynous (Boserup 2010).

Tennessen et al. (2012) looked at single-nucleotide variants (SNVs) in the exome in European and African American samples and found a higher level of probably deleterious variants in the mostly African population. The number of rare nonsynonymous variants (usually at least slightly deleterious) was 20.6% higher than in the European sample; the number predicted to be more deleterious was

~21.6% higher, and the number predicted to be even more deleterious was ~27% higher. Considering that African Americans have about 80% African ancestry, a pure African sample would presumably exhibit higher numbers—perhaps 32% higher than Europeans in the most deleterious category. (Note that Simons et al. (2013) argue for the existence of bias in PolyPhen-2, one of the codes used in predicting the severity of nonsynonymous variants by Tennessen et al. (2012), so these results should be viewed with caution.)

Tennessen et al. (2012) looked only at SNVs, which are largely of paternal origin and show a strong paternal-age effect. MacArthur et al. (2012), in contrast, looked at a larger class of mutations, including kinds that are not much influenced by paternal age. We believe that the results of these two reports are reasonably consistent. The Tennessen report does tell us two more things. First, although the ancestors of African Americans mainly originated in West Africa, those ancestors came from a number of places, not just the area of northern Nigeria where the Yoruba live. So this pattern of higher than average levels of genetic load must have been generally true of West Africa, not just of the Yoruba. Second, since the pattern existed in the African ancestors of African Americans, who mostly arrived two to three centuries ago, the pattern is at least two or three centuries old. Moreover, since it seems that the excess is greater in classes of mutations that are more deleterious, it seems likely that this pattern has not been around forever. As we pointed out above, an increase in deleterious mutations of large effect shows up rapidly, but mutations with mild effects increase gradually. Polygyny in West Africa succeeds in the context of a female-farming system, where wives increase wealth (Boserup et al. 2007). Polygyny of this kind probably did not exist before the development of agriculture and is not practiced by contemporary African hunter-gatherers.

Australian aborigines managed a form of gerontocratic polygyny as hunter-gatherers. Since their system did not depend on agriculture, it could be older than the Neolithic. On the other hand, Australians experienced major cultural change about 5,000 years ago, exemplified by the advent of the dingo and new lithic technologies, change that may have been introduced by settlers from India (Pugach et al. 2013). So perhaps high paternal age is not pre-Neolithic in Australia. Genetic investigations might be able to resolve this question. One possible approach would be to look at the branch length—the total mutational distance from an outgroup such as chimpanzees. In a population with high paternal age, the per-year mutation rate increases, although not as much as the per-generation rate, which is the relevant number for genetic load. If the average paternal and maternal ages are equal, the per-year mutation rate is just 2.0. If the average maternal age was 28 (a typical number) while the average paternal age was 42 (typical for Australian foragers), the per-year mutation rate would be 2.4, 20% higher than in a population in which the parents were the same age. The resulting change in branch length might be measurable if high paternal age goes far back in Australian prehistory.

Higher genetic load in some populations, due to high average paternal age over an extended period, may explain some puzzling medical mysteries, such as the higher rates of infant mortality and stillbirths among African Americans

(MacDorman and Mathews 2011), or some of the serious health problems found in Australian Aborigines (Vos et al. 2009).

It is possible that differences in local selective pressures could compensate for the increased mutation rates in societies with high average paternal age. If, for example, men with low genetic load had higher fertility in polygynous societies, more so than in more monogamous societies, that could conceivably compensate for the higher mutation rate. This can certainly be the case for functions that made a greater contribution to fitness in some situations than in others. For example, color blindness is much more common among long-agricultural European and East Asian populations than it is in among hunter-gatherers.

However, judging from the reports of MacArthur et al. (2012) and Tennessen et al. (2012), such compensation has not prevented an overall higher incidence of deleterious mutations. High paternal age also causes some qualitative changes in selection pressures, which we discuss in the next section.

Effects on Life History Evolution

W. D. Hamilton (1966) derived expressions for the force of selection on birth and death rates in stable populations. His results provide insight into how a shift to reproduction by older males should change the hazard of mortality over the life span. Hamilton's theory is woefully inadequate to describe human life history in general since it does not incorporate menopause or indirect fitness, such as the effects of providing parental care to offspring. Nevertheless, it is an important starting point for understanding life history.

An accessible treatment of Hamilton's theory is in Alan Rogers's unpublished textbook available from his website (Rogers 2010). He shows that the partial derivative of fitness with respect to a change in the probability of survival at age z is

$$\frac{\partial r}{\partial P_z} = \frac{\sum_{x=z+1}^{\infty} e^{-rx} l_x m_x}{P_z T}, \tag{1}$$

where P_z is the probability of survival from age z to $z + 1$, l_x is the probability of survival from birth to age x, m_x is the birth rate of x-year-olds, and T is the mean generation time. This number at any age describes how fitness is changed by a change in mortality at any age, that is, the "force of selection on mortality."

For illustration, this can be simplified by assuming a stationary population so that the rate of increase r is zero and the exponential term disappears. For computation, we use an empirical l_x that describes mortality of Herero males before 1965 from Pennington and Harpending (1993) and two fertility functions, with average ages of reproduction of 30 and 50 years, respectively. In each case, the window of reproduction is 20 years, distributed over the interval in proportion to the sine of age. For 30-year-old fathers, for example, the fertility rate rises from zero at age 20 to a maximum at 30 and declines to zero at 40. For 50-year-old fathers the

curve is the same shape, but is nonzero from age 40 to age 60, with the maximum at age 50. In each case, total fertility is normalized so that the corresponding stable population is stationary.

In the case of older fathers, selection against mortality is extended 20 years later into the life span—this is no surprise since in the Hamilton model there is no selection against mortality once the reproductive span is over. This might have something to do with the observed black/white mortality crossover, in which death rates for Europeans are lower than those for people of African descent until about age 75 (Wing et al. 1985). At the oldest ages, supercentenarians, African Americans are more numerous than would be expected based on their share of the elderly population (Kestenbaum and Ferguson 2010).

A second difference between the two regimes is not so obvious: in the case of older fathers, selection against prereproductive mortality is greatly reduced. A heuristic explanation is this: if the probability that a child reaches reproductive age is, for instance, 1/4, then the death of that child has a fitness cost proportional to 1/4. If the age of paternity is shifted up so that the probability of reaching reproductive age is 1/8, for example, then the cost of the loss of a child is reduced from 1/4 to 1/8; that is, the force of selection is less.

This decline in selection for early survival has been much discussed in the human life history literature, but it may be quite important. If, for example, parental age were to decline in a society, then selection against childhood mortality would increase, in our example by a lot, and this could have important consequences for epidemiology after several generations. Another prediction is that, other things being equal, infant and childhood mortality is predicted to be higher in groups with high average parental age in either sex. In our not implausible example here, the force of selection against childhood mortality is with average parental age of 30 is about 1.75 times as great as that in a group with mean parental age of 50 (Figure 2).

Of course, all these considerations are embedded in selection at the level of individuals. How mean paternal age varies across populations must depend in complex ways on the abilities of males to sequester females, on choice of mates by females and their families, and so on. We have neither theory nor, at this time, insight into these considerations.

Conclusion

The per-generation mutation rate increases rapidly with increasing paternal age, so one would expect populations that have maintained high average paternal ages for long periods to have more genetic load. Some highly polygynous cultures have high average paternal ages, 10–15 years greater than in monogamous cultures, and those polygynous cultures measured thus far show the expected higher load. In addition, those polygynous cultures experience a different pattern of life history evolution, with stronger selection against late-life mortality and weaker selection against child mortality. Thus, average paternal age is an unexpectedly important influence on human health and life history evolution.

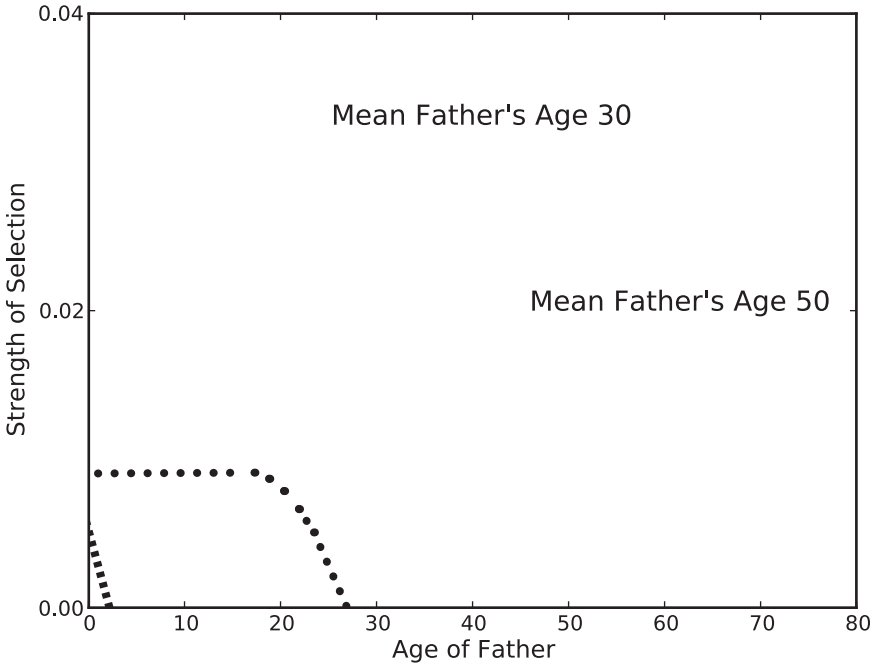

Figure 2. Strength of selection for two different paternal ages.

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