Longevity, Genetics, Evolution

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Evolutionary Perspectives on Longevity and Genetics

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3 and to the National Research Council Committee on Population.

1997 Between Zeus and the Salmon
2001 Cells and Surveys
2008 Biosocial Surveys
Looking across at GWAS from the other side of the river:

- Definite phenotype.
- Single singles.
Looking across at GWAS from the other side of the river:

- Definite phenotype.
Looking across at GWAS from the other side of the river:

- Definite phenotype. Dead or Alive
Looking across at GWAS from the other side of the river:

- Definite phenotype. Dead or Alive
- Single singles.
Looking across at GWAS from the other side of the river:

- Definite phenotype. **Dead or Alive**
- Single singles. **One SNP at a Time**
1. Are there indeed large numbers of alleles with small *AGE-SPECIFIC* effects on survival and fertility?

2. Is there a wide variety among such effects in ages of major onset?
What math gives us

If YES and YES, then
then mathematics now gives us

- an account which couples Gompertzian (exponentially increasing) hazards at moderate old ages with plateaus at extreme ages.
- a prediction that alleles whose major effects are at late ages will have some effects also at early ages.
The human forkhead box O3A gene (FOXO3A) encodes an evolutionarily conserved key regulator of the insulin-IGF1 signaling pathway that is known to influence metabolism and lifespan in model organisms. A recent study described 3 SNPs in the FOXO3A gene that were statistically significantly associated with longevity in a discovery sample of long-lived men of Japanese ancestry [Wilcox et al. (2008) Proc Natl Acad Sci USA 105:13987–13992]. However, this finding required replication in an independent population. Here, we have investigated 16 known FOXO3A SNPs in an extensive collection of 1,762 German centenarians/nonagenarians and younger controls and provide evidence that polymorphisms in this gene were indeed associated with the ability to attain exceptional old age. The FOXO3A association was considerably stronger in centenarians than in nonagenarians, highlighting the importance of centenarians for genetic longevity research. Our study extended the initial finding observed in Japanese men to women and indicates that both genders were likely to be equally affected by variation in FOXO3A. Replication in a French centenarian sample generated a trend that supported the previous results. Our findings confirmed the initial discovery in the Japanese sample and indicate FOXO3A as a susceptibility gene for prolonged survival in humans.
“Minor allele frequency distribution of rs2802288 in Germans by age groups”. Table 6 of Flachsbart et al. (2009)

<table>
<thead>
<tr>
<th>Age</th>
<th>n</th>
<th>Frequency</th>
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<tr>
<td>60-75</td>
<td>731</td>
<td>0.385</td>
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<tr>
<td>95-99</td>
<td>631</td>
<td>0.402</td>
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<tr>
<td>100-104</td>
<td>362</td>
<td>0.441</td>
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<tr>
<td>105-110</td>
<td>21</td>
<td>0.524</td>
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<tr>
<td>Total</td>
<td>1745</td>
<td></td>
</tr>
</tbody>
</table>
Comparing Proportional and Additive Hazards

![Graph showing the comparison between proportional and additive hazards.]
Does a journey of a thousand miles begin with a single step?

- 1000 miles $\approx$ 1 million baby steps
- $=?$ 1 million SNPs
- The regularities in age-specific demographic schedules seen across populations and across species seem likely to be the outcome of some kind of “statistical mechanics” of genetic influences.
- For specific genetic influences on longevity, we seek and are starting to glimpse evolutionary stories behind them.
Cross the river?

- Should we ultimately expect evolutionary stories behind associations turned up by GWAS?
- How meaning-fraught or how accidental should we expect the interactions to be, when environments run up against existing genetic variation?
- Is it feasible for demographers to learn enough to make good use of GWAS?
- Or would it be wiser to stay on our side of the river, enjoying the view of the other shore?
J. B. S. Haldane in a Temple of Zeus

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