Journal of Biology

BioMed Central

Minireview

The genetics of gender and life span

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Published: 29 April 2009

Journal of Biology 2009, **8**:38 (doi:10.1186/jbiol141)

The electronic version of this article is the complete one and can be found online at http://jbiol.com/content/8/4/38

Abstract

Several possible and potentially overlapping genetic mechanisms have been suggested to explain differences in life span between males and females. Two recent papers in *BMC Evolutionary Biology* on the effects of inbreeding provide additional insight into the genetic architecture underlying life span differences between genders in two different insects.

Differences in life span between males and females are commonly observed across many species. For example, where the heterogametic sex (XY sex chromosomes) is male, as in humans and *Drosophila*, females tend to live longer than males. Similarly, in *Caenorhabditis elegans*, where the hermaphrodite has two X chromosomes (XX) and the male has one (XO), the hermaphrodite tends to live longer. In contrast, in most bird species, where the heterogametic sex is female (ZW sex chromosomes), males tend to live longer than females.

Genetic and environmental interventions that affect life span tend to have a greater effect in one sex than the other [1,2]. For example, reduced insulin/insulin-like growth factor 1 (IGF-1) signaling and dietary restriction tend to increase life span more in females than males in *Drosophila* and mammals, whereas mild stress tends to increase life span more in males than in females, at least in *Drosophila* [3]. Quantitative genetic analyses have revealed a different genetic architecture of life span in males versus females. For example, quantitative trait loci (QTLs) that affect life span are often sex-specific or sex-biased in *Drosophila*, mice and humans, and studies over the past few years show strikingly different effects of inbreeding in male versus female insects [4,5]. Two recent studies in *BMC Evolutionary Biology* on the effects of inbreeding in a seed beetle (Bilde *et al*. [6]) and in *Drosophila* (Vermeulen *et al*. [7]), respectively, provide additional insight into the genetic factors involved. Taken together, all these data suggest that the genetic differences between males and females have a significant effect upon aging and life span.

Asymmetric inheritance of sex chromosomes and maternal effects

Several possible and potentially overlapping genetic mechanisms have been suggested to explain differences in life span between genders, including asymmetric inheritance of sex chromosomes, differences in physiology, maternal effects, and sex-specific selective pressures. For example, the asymmetric inheritance of the sex chromosomes, such that males inherit a single X chromosome in flies, *C. elegans* and humans, means that in males any X chromosome recessive mutant phenotype will be expressed (the 'unprotected X' model), whereas in females the presence of the second X chromosome means that there is likely to be a wild-type copy of the gene present, and the recessive phenotype will not be expressed. These deleterious

recessive mutations could lead to decreased life span, affecting males more than females. Consistent with this idea, inbreeding (which will tend to make recessive mutations homozygous) has been found to cause decreased life span in *Drosophila*, mice and several other species (called inbreeding depression of life span). However, several other studies, including that of Vermeulen *et al.* ([7] and see references therein) have failed to detect inbreeding depression of adult life span, or found effects that varied depending upon the particular strain, sex, or environmental conditions. For example, Vermeulen *et al.* mapped a recessive QTL on the second chromosome of *Drosophila* that causes a temperature sensitive reduction in life span in inbred males but not females.

Asymmetric inheritance of mitochondrial genomes and other cytoplasmic genomes is another possible contributor to sex-specific differences in life span. Given that the mitochondrial genome is inherited maternally in *Drosophila* and humans, natural selection cannot act to optimize mitochondrial function or nuclear-mitochondrial genetic interactions in the male genetic background. This might result in suboptimal mitochondrial function in males and reduced life span in males relative to females [1].

The maternal effect may also contribute to differences in life span between males and female. In many species, the mother makes a large contribution of gene products to the egg or embryo, and this has been shown to affect life span in a gender-specific way in certain species. Because the mother contributes these materials equally to eggs that will develop as either male or female, the genetic differences between male and female zygotes must underlie aspects of the sex-specific effects of maternal products on life span. One possibility is that because maternal-effect gene products are being produced by a female genome, they may be more optimized for female offspring, thereby contributing to the reduced life span often observed in males. Consistent with this idea, maternal effects on life span are greater in males than females for certain species such as the seed beetle [8].

Aging mechanisms and trade-offs

Finding mechanisms that explain the difference in life span between males and females is hindered by our lack of understanding of the basic mechanisms of aging and underlying causes of mortality. Life span appears to be limited by the accumulation of irreversible damage, probably including oxidative damage to macromolecules, mutations, and loss of epigenetic regulation, as well as more acute and dynamic modifiers of mortality rates, perhaps including the efficiency of detoxification and excretion. Mechanistic explanations often involve the concept of trade-offs, that is, the allocation of energy or other 'resources' to functions such as reproduction and behavior, at the expense of somatic maintenance pathways required for optimal longevity. In several recent studies, however, it was shown that life span can be increased by dietary restriction or altered insulin/IGF-1 signaling without a detectable decrease in reproduction or overall metabolism [2], and conversely, reproduction can be increased in old female flies with no detectable cost for life span [9].

Seed beetles (Figure 1) could be a particularly powerful model in which to look for trade-offs between somatic maintenance required for optimal life span and other traits such as fecundity. The adult is 'facultatively aphagous' and does not require food or drink, but can rely on nutrient stores accumulated during development. Bilde *et al.* [6] have examined the effects of inbreeding on male and female life span in the species *Callosobruchus maculatus*. They found that inbreeding reduced fitness of both males and females, as indicated by reduced total reproductive output. As expected, female life span was decreased by extreme inbreeding, but surprisingly, male life span was increased. Previous studies of seed beetles by Fox *et al.* [5] had found a large maternal effect on life span of males but not females [5]. However, the Bilde *et al.* study included an elegant control for maternal effects, in that animals with varying amounts of inbreeding had mothers of the same genotype, thus separating the effects of cytoplasmic factors such as mitochondria and maternally contributed gene products from the effects of inbreeding. Of course, this result does not rule out an important role for maternal products in modulating life span, but it does show that they are not the direct targets of the observed inbreeding effects. One possible explanation for the decrease in female life span is that inbreeding led to homozygosity of recessive alleles that are deleterious for female lifespan, providing support for the unprotected X hypothesis. However, this hypothesis cannot account for the increase in life span observed in males. Bilde *et al.* [6] suggest that the increase in male life span might be due to changes in energy-intensive behaviors, such as a reduction in courtship or aggression, thereby leading to longer life span.

Sex-specific genetic architectures

Sex-specific differences in genetic architecture could contribute to the observed differences in life span and the effects of inbreeding. For example, a recent study examined how evolution shapes variation in transcript abundance in male and female *Drosophila*, and sex-specific differences in the mode of transcriptome inheritance were identified [10]. In males, variation in gene expression was found to be due

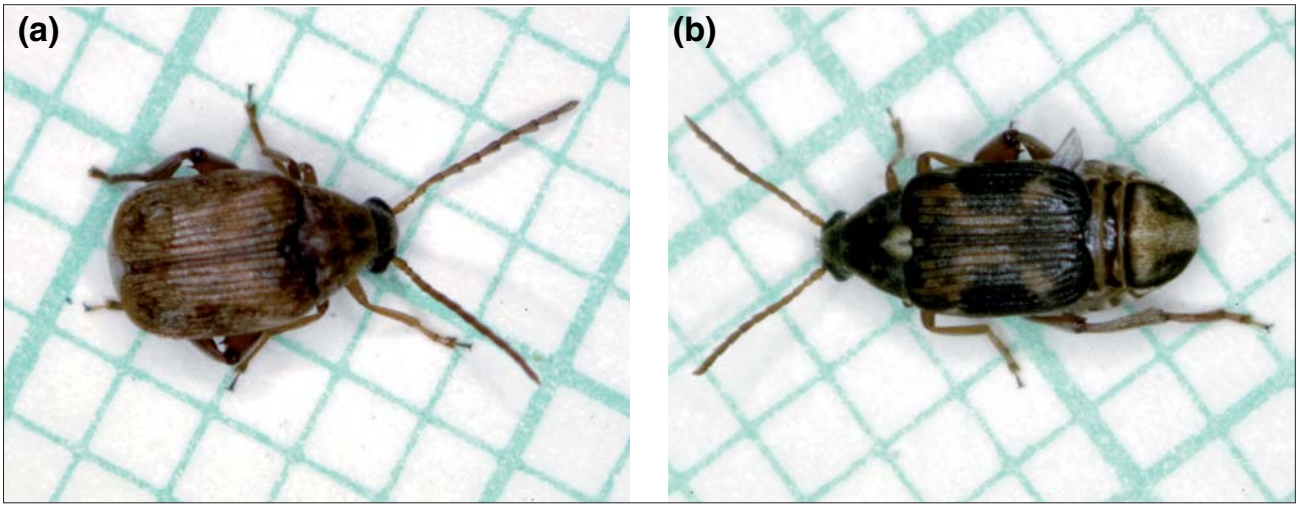

Figure 1
Dorsal view of male and female *Callosobruchus maculatus*. **(a)** Male and **(b)** female. The sex specific coloration of the posterior abdominal plate (pygidium) is shown. The squares are 1 mm. From beanbeetles.org. Photographs by Lawrence Blumer, reproduced with permission.

mostly to additive interactions of alleles, whereas in females, gene expression variation was found to be due mostly to non-additive (epistatic) interactions between alleles; a substantial X-chromosome effect was shown to underlie these differences. Similarly, in the seed beetle, loci affecting life span exhibited more non-additive interactions (dominance) in females than in males [8].

Given that additive variation responds to selection more quickly, because additive variation does not involve interactions of multiple loci, sex-specific differences in selection could underlie aspects of sexual dimorphism in life span observed in many species. Sex-specific selective pressures that result in higher male reproductive fitness may contribute to sexual dimorphism of life span. For example, costly male-biased metabolism or behaviors, such as aggression or specific courtship behaviors, might be positively selected for, but could result in decreased life-span in males relative to females.

Future studies may be directed toward further study of the underlying differences in genetic architecture between males and females, in particular, testing the idea that deleterious alleles affecting life span may be more exposed to selection in males than in females due to reduced non-additive effects in males, thereby reducing inbreeding load for male-specific deleterious alleles in the population [5]. It will be particularly interesting to ask if the increased life span observed in highly inbred male seed beetles by Bilde *et al.* [6] can be found to correlate with a reduction in specific costly aspects of metabolism, or behaviors such as locomotion and aggression.

Acknowledgements
We thank Sergey Nuzhdin for helpful discussions. This work was supported by grants from the Department of Health and Human Services to JT (1R01AG011833) and to MA (1R01GM073039).

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