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GENETIC CORRELATION BETWEEN RESISTANCE TO OXIDATIVE STRESS AND REPRODUCTIVE LIFE SPAN IN A BIRD SPECIES

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Evolutionary theories propose that aging is the result of a trade-off between self-maintenance and reproduction, and oxidative stress may play a crucial role in such a trade-off. Phenotypic manipulations have revealed that a high investment in reproduction leads to a decline in the organism's resistance to oxidative stress, which could in turn accelerate aging. Here, by using quantitative genetic analyses as a tool to disentangle genetic effects from phenotypic variances, the relationship between resistance to oxidative stress at sexual maturity and two key reproductive life-history traits (i.e., number of breeding events during life and age at last reproduction) was analyzed in cross-fostered zebra finches. The age of last reproduction had high narrow-sense heritability, whereas the number of breeding events and oxidative stress resistance showed medium and low heritabilities, respectively. We detected positive genetic correlations between early resistance to oxidative stress and both life-history traits, suggesting that the efficiency of the antioxidant machinery at maturity may be related to individual reproductive investment throughout lifetime, possibly by influencing the pattern of cellular senescence. Genes encoding for resistance to oxidative stress would have pleiotropic effects on reproductive capacity and aging. Further work is required to confirm this assert.

KEY WORDS: **Disposable-soma, free radicals, life-history, pleiotropy, quantitative genetics, reactive oxygen species.**

In aerobic organisms, the imbalance between the production of pro-oxidative molecules (i.e., Reactive Oxygen Species; ROS) and the efficiency of the antioxidant and repair machineries leads to oxidative stress (Finkel and Holbrook 2000). More than half a century ago, oxidative stress was proposed as a mechanistic explanation to the aging process (Harman 1957). Evolutionary biologists, however, have only recently begun to consider the role of this physiological mechanism in life-history evolution, including aging (reviews in Dowling and Simmons 2009; Monaghan et al. 2009). Life-history traits such as reproductive success and life span are constrained by physiological trade-offs that prevent a simultaneous increase in both traits (Stearns 1992; Harshman and Zera 2007). Because oxidative stress has not only been related to senescence (Harman 1957; Kirkwood 2005), but also to sexual reproduction (Nedelcu et al. 2004), expression of secondary sexual traits (von Schantz et al. 1999; Velando et al. 2008), and breeding effort (Salmon et al. 2001; Alonso-Alvarez et al. 2004), it might constitute a potential mechanism underlying main life-history trade-offs.

Senescence and life span may be influenced by different fitness effects of genes expressed early and late in life (Williams 1957): genes that improve early life performance may have negative effects in later life. At the phenotypic level, physiological aging and reduced late life performance may result from the

accumulation of damage due to insufficient investment in somatic maintenance (Kirkwood 1977). Life span may be regulated by genes associated with somatic maintenance, including protection against oxidative damage (Partridge and Barton 1993; Beckman and Ames 1998; Kirkwood and Austad 2000). Thus, evolution in oxidative-stress-related genes involved, for example, in the allocation of antioxidants between competing functions, such as reproduction and somatic maintenance, could give rise to pleiotropic effects on aging and reproductive traits (e.g., Cohen et al. 2008).

The role of oxidative stress in life-history evolution has been tested mainly through phenotypic manipulations by experimentally increasing or reducing oxidative stress (reviewed in Dowling and Simmons 2009; Monaghan et al. 2009). An important assumption in these evolutionary studies is that phenotypic data are reliable predictors of underlying genetics (Lloyd 1977; Maynard-Smith 1978). However, the generality of this assumption remains controversial (Hadfield et al. 2007). In this context, quantitative genetics is probably the best tool for establishing genetic contributions to phenotypic variations. The analysis of genetic correlations between oxidative-stress-related traits and life-history traits (with nonzero heritability) would allow us to understand the correlated response of these traits to selection and the presence of potential trade-offs among them. Genetic correlation, that is, inheritance of traits as associated units, can arise from pleiotropy or linkage disequilibrium (Roff 1997). Pleiotropy, in particular, is of great interest to evolutionary biologists because pleiotropic effects may greatly alter the rate and direction of evolution. Evidence for pleiotropy in life-history traits and underlying physiological mechanisms is scarce, although genetic correlations within life-history traits have been reported in recent studies using quantitative genetic analyses (e.g., Charmantier et al. 2006).

During the last decade, the best evidence of a genetic link between oxidative stress and life-history traits has been provided by studies on classical model species. In fruitflies *Drosophila melanogaster*, overexpression of genes encoding the production of certain antioxidant enzymes (i.e., catalase, glucose-6-phosphate dehydrogenase [G6PD], methionine sulfoxide reductase A [msrA], and superoxide dismutase [SOD]) was linked to increased longevity (reviewed in Paaby and Schmidt 2009). In the worm *Caenorhabditis elegans*, mutations or inactivation of genes required for mitochondrial function prolonged life span (Ishii et al. 1998; Dillin et al. 2002; Lee et al. 2003), consistent with the central role of mitochondria in ROS production (Hulbert et al. 2007). In mice, individuals whose insulin-like growth factor type-1 receptor (IGF-1R) gene was inactivated exhibited both extended longevity as well as a higher short-term survival when they were experimentally exposed to free radicals (Holzenberger et al. 2003). The link between oxidative stress and life span suggests that oxidative stress plays an important role in determining individual fitness. Nonetheless, the potential pleiotropic effects of oxidative-stress-related genes on reproductive life-history traits have not been explored.

Here, we analyzed a dataset obtained from a previous study carried out in a captive population of zebra finches *Taeniopygia guttata* (see Alonso-Alvarez et al. 2006 for details) to explore quantitative genetics underlying the link between oxidative stress and life history, for the first time to our knowledge. The objective of Alonso-Alvarez et al. (2006) was to establish, beyond any genetic mechanism, how environmental conditions experienced during the early life determine life-history trajectories and resistance to oxidative stress. Alonso-Alvarez et al. (2006) showed that early condition can have long-term effects on life-history trajectories by affecting key life-history traits such as the age at first reproduction, and suggested that the trade-off between reproduction and self-maintenance might be mediated by the cumulative deleterious effect of ROS. Chicks were reared in enlarged or reduced broods, which implied low or high access to food during the first weeks of life, respectively (see also Alonso-Alvarez et al. 2007). Experimental broods were created by cross-fostering the chicks, thus disrupting the natural covariation between brood size and parental quality. This experimental design allows disentangling the contribution of genetic and environmental factors to the expression of adult phenotypic traits. Individual variability in red blood cell resistance to oxidative stress was analyzed just before the start of reproductive life (i.e., at the time of sexual maturity). In the present study, we took advantage of this experimental design to (1) estimate additive genetic and common environmental components of phenotypic variances of two key life-history traits (i.e., number of reproductive events during lifetime and age at last reproduction) and individuals' resistance to oxidative stress, and (2) determine the phenotypic and genetic correlations between these traits. We predict positive genetic correlations between resistance to oxidative stress at sexual maturity and reproductive life-history traits as genes encoding for an effective antioxidant machinery in early life would allow individuals to live longer and extend the duration of their reproductive life.

Methods

CROSS-FOSTERING PROTOCOL AND MEASUREMENT OF TRAITS

Wild zebra finches breed for the first time as early as two months of age, and reproduce one to six times per year (Zann 1996). Maximum life span varies among populations, ranging from 1–5 years (Zann 1996). Here, captive zebra finches without any breeding experience (all less than 1 year old) were obtained during October, 2002 from two French pet providers (Alonso-Alvarez et al. 2006; see also Forstmeier et al. 2007). A total of 52 pairs of zebra finches were randomly allocated to two experimental groups and allowed to raise either a two-chick or a six-chick brood in

indoor aviaries. Two-day-old chicks were cross-fostered among synchronous broods. Asynchrony in hatching time among breeding pairs limited cross-fostering combinations. Therefore, chicks were reared by either recipient parents or original parents, either in enlarged or reduced broods, until the age of 40 days. Initial clutch size did not differ between groups that further received two or six chicks (see Alonso-Alvarez et al. 2006 for further details on the cross-fostering protocol).

To assess blood resistance to oxidative stress before the first breeding event, birds were blood sampled at the age of 60 days (approximate age of sexual maturity; Zann 1996). Resistance to oxidative stress was assessed as the time needed to hemolyze 50% of erythrocytes exposed to a free-radical generator (2,2′-azobis-(amidinopropane)hydrochloride [i.e., AAPH]) in 118 birds ($N =$ 50 and 68, for birds reared in reduced and enlarged broods, respectively). We used the KRL test (Brevet Spiral V02023, Couternon, France) adapted to avian physiological parameters. AAPH acts mostly by producing peroxyl radicals, which induce lipid and protein peroxidation in the cell membrane (e.g., Zou et al. 2001) (see Alonso-Alvarez et al. 2004, 2006; Bertrand et al. 2006; Alonso-Alvarez et al. 2007; Bize et al. 2008 for details).

Birds were released at the age of 60 days into a large outdoor aviary (18 m length × 3 m wide × 2.5 m high) that contained water, food ad libitum, and 90 nest-boxes, and then allowed to breed freely until mortality. Reproduction and survival of each bird were monitored throughout lifetime. Therefore, we could obtain life-history data for the number of reproductive events during lifetime and the age at last reproduction for each bird (Alonso-Alvarez et al. 2006 for further details).

QUANTITATIVE GENETIC ANALYSES

All birds alive at the age of 60 days were used for statistical analyses ($N = 116$). A total of 13 birds without any original or recipient broodmate were included in the analyses for a better estimation of the total phenotypic variance although they cannot participate to the decomposition of the genetic and common environmental effects. Similar results were achieved when these birds were excluded from analyses (results not shown, but available by request). Genetic and common environmental components (V_{Origin} and $V_{\text{Recipient}}$) of total phenotypic variances (V_{P}) were estimated using REML univariate mixed-effect models, with original and recipient nests fitted as random effects. Phenotypic and genetic correlations (r_{P} and r_{G}) among traits were estimated by fitting a single REML multivariate mixed-effect model with original nest fitted as a random effect. Therefore, phenotypic and genetic correlations were estimated from full siblings that grew up in different broods. Environmental correlations could not be estimated due to zero $V_{\text{Recipient}}$ in the two life-history traits used for the analyses (see Results). By including the three traits in the single multivariate model, the correlation between the two life-history traits was controlled while testing for genetic and phenotypic correlations between the life-history traits and resistance to oxidative stress. Sex, experimental brood size (two vs. six), and whether a bird was raised by its original parents or recipient parents were fitted as fixed effects (categorical variables) in the models where significant (nonsignificant results are not shown).

Additive genetic (co)variances (V_{A} and Cov_{A}) were calculated as twice the (co)variance component of original nest (V_{Origin} and Cov_{Origin}) because full siblings share 50% of their genes (Lynch and Walsh 1998). Environmental variances (V_{E}) were equal to the recipient nest component ($V_{\text{Recipient}}$ in univariate models), and phenotypic (co)variances were calculated as the sum of the original nest, recipient nest, and residual variance components ($V_{\text{P}} = V_{\text{Origin}} + V_{\text{Recipient}} + V_{\text{R}}$). Narrow-sense heritability (h^2) and common environmental effect (c^2) were estimated as $h^2 = V_{\text{A}}/V_{\text{P}}$ and $c^2 = V_{\text{E}}/V_{\text{P}}$ for each trait. We also provide the coefficient of additive genetic variance CV_{A} (Houle 1992) in which the additive genetic variance is scaled by the trait mean ($\overline{X}$): $CV_{\text{A}} = 100 \times \sqrt{V_{\text{A}}}/\overline{X}$ to enable comparison with other traits and populations.

The statistical significance of each random effect was assessed using likelihood ratio tests that compare models based on −2 times the difference in REML log-likelihood scores distributed as χ^2 where the number of degrees of freedom equaled the number of variance terms removed. The significance of each variance component function was assessed using a *t*-test. ASReml version 2 (VSN International; Gilmour et al. 2006) was used to fit full-sibling univariate and multivariate models and calculate variance component functions and standard errors (see Lynch and Walsh 1998).

Results

In the univariate models, none of the fixed effects was significant. Considerable proportion of the total phenotypic variance was explained by additive genetic effects for life-history traits, number of reproductive events during lifetime, and age at last reproduction, although only the latter trait showed significant heritability (Table 1). Both life-history traits showed zero common environmental effects. In resistance to oxidative stress, small (and nonsignificant) proportions of phenotypic variance were explained by additive genetic and common environmental effects (Table 1).

Among fixed effects in the multivariate (trivariate) model, only experimental brood size was significant ($P = 0.01$). Birds from reduced broods showed higher blood resistance to oxidative stress at the age of 60 days (reduced broods: 61.33 ± 0.71 min; enlarged broods: 60.02 ± 0.52 min; see also Alonso-Alvarez et al. 2006), and reproduced more times throughout the life (reduced: 5.16 ± 0.49; enlarged: 4.23 ± 0.31; see also Alonso-Alvarez et al. 2006), yet with shorter life spans than those from enlarged broods (244.36 ± 16.21 days; 273.97 ± 11.41 days). Our results from

Table 1. Quantitative genetics on number of reproductive events during lifetime, age at last reproduction, and resistance to oxidative stress from REML univariate mixed-effect models. *$P<0.05$ for likelihood ratio tests and one-tailed t tests.

	Number of reproduction	Age at last reproduction (days)	Resistance to oxidative stress (min)
N	116	108	97
$V_{Origin}\pm$SE	0.801±0.930	2279±1248*	0.4209±1.985
$V_{Recipient}\pm$SE	0	0	2.661±2.202
$V_P\pm$SE	8.343±1.121	9573±1400	17.680±2.659
$h^2\pm$SE	0.192±0.217	0.4761±0.2278*	0.048±0.224
$c^2\pm$SE	0	0	0.151±0.117
Trait mean±SD	4.53±2.88	264.1±97.6	60.41±4.20
CV_A	27.95	25.56	1.52

the multivariate model showed positive phenotypic correlations between number of reproductions and age at last reproduction, and between the two life-history traits and resistance to oxidative stress, although only the first was significant (Table 2). All the genetic correlations between the three traits were positive and significant (Table 2).

Discussion

Our quantitative genetic analyses in the zebra finch showed that age of last reproduction had high narrow-sense heritability ($h^2 = 0.48$), suggesting high resemblance between related individuals in the reproductive life span. The number of reproductions had non-significant medium narrow-sense heritability ($h^2 = 0.19$), whereas the resistance of blood to oxidative stress measured before first reproduction (at age 60 days) had low narrow-sense heritability ($h^2 = 0.05$) due to high level of residual variance that possibly includes environmental influences during the post-natal development. Quality of parental care and brood competition experienced during the nestling period might have influenced variation in resistance to oxidative stress at maturity (Costantini et al. 2006), as revealed by the significant effect of brood size treatment (see also Alonso-Alvarez et al. 2007). Although physiological traits generally possess intermediate heritabilities (Mousseau and Roff 1987), the proportion of environmental components in the total phenotypic variances may increase as individuals grow older because different nutritional conditions and stress experienced during growth are likely to result in severe variations in physiological conditions at maturity among individuals. Because chicks were cross-fostered two days after hatching, environmental effects before age of two days could have been incorporated into genetic (co)variances. The precise assessment of oxidative stress is difficult (reviewed in Monaghan et al. 2009) because blood sample is prone to oxidation by any source such as solar radiation and high temperature during sampling. This may result in a part of unexplained interindividual variance in resistance to oxidative stress.

Table 2. Phenotypic and genetic correlation among number of reproductive events during lifetime, age at last reproduction, and resistance to oxidative stress (OxStress) from a REML multivariate (trivariate) mixed-effect model. *$P<0.05$, **$P<0.01$, ***$P<0.001$. Significant fixed effect (experimental brood size: $P=0.01$) was included in the multivariate mixed-effect model.

Traits	Phenotypic correlation±SE	Genetic correlation±SE
No. of reproductions–Age last reproduction	0.654±0.059***	0.722±0.261**
No. of reproductions–Resistance OxStress	0.077±0.110	0.949±0.513*
Age at last reproduction–Resistance OxStress	0.137±0.108	0.853±0.451*

Interestingly, despite low additive genetic variance in early resistance to oxidative stress, we detected positive genetic correlations between this physiological variable and the two life-history traits. Thus, families with higher resistance to oxidative stress were those with higher number of reproductive events during lifetime and delayed reproductive senescence. The highly significant phenotypic and genetic correlations between the number of reproduction and age at the last reproduction are possibly due to autocorrelation of the two traits as long-lived individuals are also likely to reproduce more times.

We measured early resistance to oxidative stress, which was genetically, but not phenotypically, correlated with the number of reproductions and reproductive life span. Thus, in our data, phenotypic correlations were poor surrogates for genetic architecture of life-history and physiological traits, advocating caution when inferring genetic patterns from phenotypic data (see Hadfield et al. 2007). Previous studies of zebra finches suggest that a high investment in reproduction lead to a subsequent decrease in resistance to oxidative stress (Alonso-Alvarez et al. 2004, 2006; Bertrand et al. 2006). On the other hand, Bize et al. (2008) have recently reported that female Alpine swifts *Apus melba* showing strong

resistance to oxidative stress (assessed after a breeding event by the same method) subsequently produced larger clutches than those that previously showed a low resistance. These experimental and correlational studies suggest, beyond any genetic level, that the antioxidant capacity before reproduction can positively influence subsequent reproductive investment, and, in turn, reproductive investment can impair resistance to oxidative stress after reproduction. In a similar way, our results of quantitative genetic analyses suggest that the efficiency of the antioxidant machinery before reproduction (i.e., at sexual maturity) is genetically related to individual reproductive investment throughout lifetime, and ultimately, influences evolutionary responses for reproductive life-history traits.

Our measurement of the hemolysis rate of red blood cells exposed to a controlled free-radical attack not only provides an assessment of total antioxidant defenses present in the blood but also indicates the rate of lipid peroxidation in the erythrocyte membrane, which would affect the cell capacity to resist free-radical aggressions (e.g., Zou et al. 2001). Recent molecular studies have suggested that the resistance to a ROS-induced hemolysis possibly has a genetic basis. In the particular case of blood cells, the gene *ATM* (ataxia telangiectasia mutated) is vital for regulating intracellular ROS levels into hematopoietic stem cells (HSC) (Ito et al. 2004). Similarly, HSC from mice lacking FoxO transcription factors showed high ROS levels (Tothova et al. 2007; see also Warren and Rossi 2009). Previous studies have shown that genes encoding FoxO may control the resistance to lipid peroxidation (Dansen et al. 2004) and lipid peroxidation, as previously mentioned, is linked to cell membrane integrity and hemolysis (Zou et al. 2001; Armutcu et al. 2005). Therefore, zebra finch families with red blood cells with high resistance to a free-radical attack may have oxidative-stress-related genes involved in high somatic maintenance.

Evolutionary studies of senescence have been mainly focused on age-related phenotypic changes in fitness-linked traits such as fecundity and survival (Monaghan et al. 2008). The role played by oxidative stress in evolutionary life-history trade-offs (Harman 1957) has only been highlighted during the last years, as intimately related with the general cost of vital and reproductive activities (Kirkwood and Austad 2000; Alonso-Alvarez et al. 2004; Dowling and Simmons 2009; Monaghan et al. 2009). In this context, the use of quantitative genetics as a tool to assess the genetic basis of senescence has been limited to analyze life-history and morphological traits in animal populations including humans (reviewed in Wilson et al. 2008). As far as we know, this is the first study supporting the presence of potential pleitropic effects of oxidative-stress-related genes on life-history traits. Oxidative stress induces damages on a variety of macromolecules, including lipids, proteins, and DNA, ultimately interfering with cell and tissue functions (Finkel and Holbrook 2000). These damages would be good candidates for explaining senescence, particularly in reproductive individuals. Genes promoting an increased investment in reproduction are likely to incur high levels of ROS production and oxidative damage, which could in turn constrain reproduction in later life and longevity, and thereby life-history trade-offs.

Here, we showed a genetic link between early somatic maintenance, in terms of oxidative stress resistance, and prolonged reproductive life span. The genetic covariance between early antioxidant status and reproductive life-history traits suggests that oxidative-stress-related genes may constrain reproductive senescence. Thus, individuals able to invest enough antioxidant resources for early self-maintenance will also live longer and ultimately reproduce more times. Although associations between oxidative stress and life-history traits are probably complex (Dowling and Simmons 2009), the positive genetic correlations between early resistance to oxidative stress and life-history traits shown in this study provide a genetic framework that links these traits.

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