Heredity (2014) 112, 469–470

www.nature.com/hdy

NEWS AND COMMENTARY

Co-transmission, co-evolution, and conflict

Sex linkage of nuclear-encoded mitochondrial genes

GE Hill

Heredity (2014) **112,** 469–470; doi:10.1038/hdy.2013.125; published online 18 December 2013

There is growing appreciation among evolutionary biologists for the central role of mitochondria and oxidative phosphorylation (OXPHOS) in the rise of metazoans (Lane and Martin, 2010). The result is an expanding focus on the integration of mitochondrial and nuclear genomes and the implications of such integration for topics as disparate as sex, aging, cancer and flight (Lane, 2005). In the transition from free-living organism to organelle, mitochondria transferred the great majority of their genes to the nucleus, retaining in vertebrates only 13 genes that code for proteins along with two genes that code for rRNA and 22 genes that code for tRNA (Bar-Yaacov *et al.*, 2012). Mitochondria depend on about 1500 nuclear genes whose products function in the mitochondria (N-mt genes). A subset of these N-mt genes forms complexes with mitochondrial genes (mt genes), and these mitonuclear constructs function as key translational and OXPHOS machinery within mitochondria (Bar-Yaacov *et al.*, 2012).

The interplay of mitochondrial and nuclear genes means that mitonuclear genetic compatibility is essential to life processes (Lane, 2011). Theoretically, coordination of interacting N-mt and mt genes is facilitated by having mt genes and N-mt genes inherited as a unit, a process known as co-transmission (Rand *et al.*, 2001). In animals with XY sex determination, in which males are heterogametic (XY) and females are homogametic (XX), genes on the X chromosome are maternally transmitted 67% of the time. Mitochondria are, with few exceptions, maternally transmitted. Thus, positioning N-mt genes on the X chromosome promotes co-transmission of N-mt and mt genes, which is predicted to result in more stable coadaptation (Rand *et al.*, 2004) because the interdependent sets of mt and N-mt genes tend to be inherited together. In a recent paper, Drown *et al.* (2012) tested this prediction that N-mt genes should be positioned on the X chromosome by using online genome databases to assign chromosomal position to genes in 14 species of mammals. They tallied the fraction of all annotated genes that were N-mt genes and the total number of genes on each chromosome to determine whether or not N-mt genes were overrepresented on the X chromosome.

The results were unexpected. Not only were N-mt genes not overrepresented on the X chromosome as theory predicted—in all mammals examined N-mt genes were significantly underrepresented on the X. These data suggested that N-mt genes had been selectively excluded from the X, the opposite pattern to that predicted by the co-transmission hypothesis.

The advantages of coadapted mitonuclear complexes are undeniable (Lane, 2011), so how can the exclusion of N-mt genes from the X be explained? Drown *et al.* (2012) suggested that the answer might lie in the conflicts that can arise between genes when they are disproportionately transmitted by one sex (Rice, 1984; Partridge and Hurst, 1998). If a mutant gene arises that benefits females to the detriment of males, it can spread in a population if the gene is maternally transmitted (Partridge and Hurst, 1998). Indeed the higher prevalence of mitochondrial diseases in males versus females is evidence that such conflicts do arise with maternally inherited mt genes. Drown *et al.* (2012) speculated that once upon a time N-mt genes were on the X in a mammalian ancestor but that X-linkage led to genomic conflict benefiting females but lowering the fitness of males. To resolve this genomic conflict, N-mt genes were relocated on autosomes instead of the X, giving us the pattern in extant mammals. (See Gallach and Betran (2011) and Gallach *et al.* (2010) for mechanisms of repositioning genes on chromosomes to avoid genomic conflict).

Genomic conflict involving N-mt genes on X chromosomes is hypothetical in mammals. Are there alternative explanations that might explain the underrepresentation of N-mt genes on the X? The simplest explanation is that, by chance, the ancestral autosome that evolved into the mammalian X chromosome had few N-mt genes. A more interesting, if more speculative, alternative explanation is that selection for enhanced mitonuclear coevolution resulted in the migration of N-mt genes off the X chromosome. The flip side of increased co-transmission is reduced efficacy for independent selection on the co-transmitted genes. Such effects are best known from the limitations imposed on selection by the position of genes on chromosomes when there is no recombination (Charlesworth and Charlesworth, 2000). When sex chromosomes and the mitochondrion are co-transmitted, sex linked N-mt genes and mt genes face the same restrictions on independent evolution as genes on chromosomes with limited recombination (Marais, 2007). There is growing evidence for coordinated evolution of mt and N-mt genes, both as a means for N-mt genes to rescue deleterious mutations in mt genes (Burton *et al.*, 2006) and in response to environmental changes (Dowling *et al.*, 2008). Paradoxically, for such coevolution to occur, mt and N-mt genes must be free to evolve independently. Co-transmission inhibits coevolution, so perhaps N-mt genes are positioned on autosomes in XY species to facilitate coevolution.

Not all animals have XY sex determination; some taxa such as birds are ZW, with males

Professor GE Hill is at the Department of Biological Sciences, 331 Funchess Hall, Auburn University, Auburn, AL 36849-5414, USA
E-mail: ghill@auburn.edu

homogametic (ZZ) and females heterogametic (ZW). In these systems, there is essentially no potential for maternally driven genomic conflict involving N-mt genes because N-mt genes cannot be positioned on the W and the Z is 67% paternally controlled. For the two bird species investigated, Drown *et al.* (2012) found that N-mt genes are located on Z chromosomes in the proportion expected if they are randomly distributed across chromosomes. Because the hypothesized pressure to relieve genomic conflict does not exist in ZW systems, Drown *et al.* (2012) interpreted the random distribution of N-mt genes on the Z as consistent with the genomic conflict hypothesis. Indeed, given that they occur no more frequently than expected by chance, there may be no need to invoke any adaptive explanation for N-mt genes on the Z. However, Z-linkage of N-mt genes in birds disrupts mt/N-mt co-transmission—Z-linked/mt genes are inherited with greater independence than autosomal/mt genes. Given the benefits of coadaptation, one could wonder why N-mt genes are not positioned on autosomes. A potential explanation is that N-mt genes have migrated to or remained on the Z chromosome to promote coevolution of N-mt and mt genes.

Z-linkage could promote coevolution not only in allowing independent evolution of mt and N-mt genes, but also because Z-linked genes evolve faster than autosomal genes (Mank *et al.*, 2007). Capacity for rapid evolution may be important if N-mt genes are to keep pace with the evolution of mt genes (Burton *et al.*, 2006). By putting N-mt genes in a chromosomal position where they are able to evolve rapidly and independently, animals may be better able to either compensate for the accumulation of deleterious mt genes or adapt mitonuclear processes to changing environments.

Clearly, ancestral gene location and movement of mammalian and avian N-mt genes needs is deserving of more study. Different hypotheses to explain the pattern of sex linkage of N-mt genes in birds and mammals will be resolved as the N-mt genes of more taxa with XY and ZW sex determination are mapped onto chromosomes and especially as the functions of N-mt genes and the extent to which they interact with mt genes are included in analyses (Gershoni *et al.*, 2010). Only a subset of N-mt genes produce products that form complexes with mt genes, and a further subset of such genes engages in key interactions with mt genes. Mitonuclear complexes function not only in the electron transport system but also in the transcription and translation of mitochondrial genes. Genomic conflict can involve any genes that are X-linked, but restrictions on coevolution will apply only to N-mt genes whose products function in mitonuclear complexes and particularly to those N-mt genes that are most closely coordinated with mt genes (Gershoni *et al.*, 2010). A key prediction is that N-mt genes on Z chromosomes in birds should evolve faster and be better coadapted with mt genes than N-mt genes on autosomes. Growing genomic data resources will soon permit testing such predictions.

CONFLICT OF INTEREST

The author declares no conflict of interest.

Bar-Yaacov D, Blumberg A, Mishmar D (2012). Mitochondrial-nuclear co-evolution and its effects on OXPHOS activity and regulation. *BBA-Gene Regul Mech* **1819**: 1107–1111.

Burton RS, Ellison CK, Harrison JS (2006). The sorry state of F-2 hybrids: consequences of rapid mitochondrial DNA evolution in allopatric populations. *Am Nat* **168**: S14–S24.

Charlesworth B, Charlesworth D (2000). The degeneration of Y chromosomes. *Phil Trans Royl Soc Lond B* **355**: 1563–1572.

Dowling DK, Friberg U, Lindell J (2008). Evolutionary implications of non-neutral mitochondrial genetic variation. *Trends Ecol Evol* **23**: 546–554.

Drown DM, Preuss KM, Wade MJ (2012). Evidence of a paucity of genes that interact with the mitochondrion on the x in mammals. *Genome Biol Evol* **4**: 875–880.

Gallach M, Betran E (2011). Intralocus sexual conflict resolved through gene duplication. *Trends Ecol Evol* **26**: 222–228.

Gallach M, Chandrasekaran C, Betran E (2010). Analyses of nuclearly encoded mitochondrial genes suggest gene duplication as a mechanism for resolving intralocus sexually antagonistic conflict in *Drosophila*. *Genome Biol Evol* **2**: 835–850.

Gershoni M, Fuchs A, Shani N, Fridman Y, Corral-Debrinski M, Aharoni A *et al.* (2010). Coevolution predicts direct interactions between mtDNA-encoded and nDNA-encoded subunits of oxidative phosphorylation complex I. *J Mol Biol* **404**: 158–171.

Lane N (2005). *Power, sex, suicide: mitochondria and the meaning of life*. Oxford University Press: Oxford, UK.

Lane N (2011). Mitonuclear match: optimizing fitness and fertility over generations drives ageing within generations. *Bioessays* **33**: 860–869.

Lane N, Martin W (2010). The energetics of genome complexity. *Nature* **467**: 929–934.

Mank JE, Axelsson E, Ellegren H (2007). Fast-X on the Z: rapid evolution of sex-linked genes in birds. *Genome Res* **17**: 618–624.

Marais GAB (2007). Sex chromosomes and mitochondrial DNA polymorphism in birds: the Hill-Robertson effects extend from nucleus to mitochondria. *Heredity* **99**: 357–358.

Partridge L, Hurst LD (1998). Sex and conflict. *Science* **281**: 2003–2008.

Rand DM, Clark AG, Kann LM (2001). Sexually antagonistic cytonuclear fitness interactions in *Drosophila melanogaster*. *Genetics* **159**: 173–187.

Rand DM, Haney RA, Fry AJ (2004). Cytonuclear coevolution: the genomics of cooperation. *Trends Ecol Evol* **19**: 645–653.

Rice WR (1984). Sex-chromosomes and the evolution of sexual dimorphism. *Evolution* **38**: 735–742.