Meiotic Error-Correction

How sexual reproduction may facilitate a trans-generational repair mechanism that can bias meiotic gene conversion against new mutations and in favor of ancestral alleles[1]

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Finding Mutations

Highly conserved DNA (where selection has most consistently punished variation) is comprised of elements of life's code where mutations pose an especially highly risk.

Thus, any difference between homologous chromosomes in these regions can warn of a potentially dangerous mutation; yet this warning is of little use to an organism, unless it can find some way to discern which of the two strands (paternal or maternal) harbors the mutation.

Sexual reproduction may be addressing this challenge.

If a sexual organism can just pass on to its offspring the suspicion that a particular DNA variant has a 50% chance of being a mutation, this offspring's separately derived homologous chromosome can serve as both an independent check, and a correction template.

*This **Meiotic Error-Correction** process could work as follows -*

During the close association of homologous chromosomes in synapsis, primordial germ cells create a trans-generational epigenetic signature at (or near) an isolated DNA variant, thereby marking as 'suspect' both [mutant and normal] alleles.

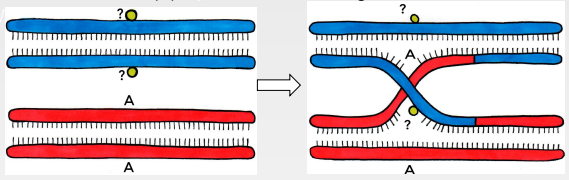
After fertilization, when one of these two 'suspect-alleles' is paired with a new homolog (in the subsequent meiosis) any persisting heterozygosity will again indicate a potential mutation; but now the marked suspect-allele can be recognized as the likely culprit.

If this suspect-allele acts to promote meiotic homologous strand exchange, the ensuing mismatch can be resolved by gene conversion biased in favor of the less-suspect allele from the new chromosome, ***thus removing this mutation from the new organism's germline***.

Applying the Fix

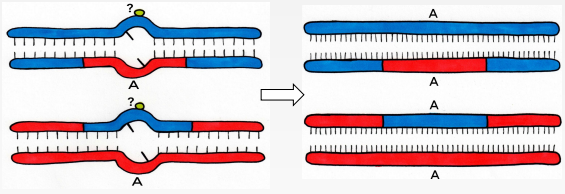
In meiosis an allele (**?**) marked as suspect (**o**) in the prior generation aligns with new homolog containing the ancestral allele (**A**)

The 'suspect-allele' mark then induces non-crossing over branch migration i.e. single strand exchange.



A suspect-allele that is a mutation will generate heteroduplex DNA with a base pair mismatch on each of the two chromosomes.

The mismatch is resolved by gene conversion biased against this initiating strand, thus replacing the mutation by its ancestral allele.



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A Core Prediction

Even if *Meiotic Error-Correction* removes just a small fraction of existing mutations per generation, it must generate inheritance patterns contrary to current expectations. Its most essential prediction is that -

In highly conserved DNA, isolated SNPs will be inherited at lower rates than expected under strictly mendelian models.

Emerging Evidence

From **Sohail et.al.**[2] *"we detected underdispersion of the number of rare loss-of-function (LoF) alleles in eight independent datasets from modern human and Drosophila melanogaster populations. Thus, ongoing selection against deleterious alleles is characterized by synergistic epistasis, which can explain how human and fly populations persist despite very high genomic deleterious mutation rates."*

Alternatively, this "underdispersion" (i.e. gradual disappearance from the lineage) of mutations, is consistent with their removal (over many generations) by *Meiotic Error-Correction*. Their removal by selection was not directly observed, it was just inferred from a presumed absence of any other plausible explanation.

From "***B V Halldorsson et.al.***[3] *"gene conversions are biased towards GC base-pairs, while mutations are biased towards AT base-pairs… On average, the number of gene conversions per generation is comparable to that of mutations. Intriguingly, this means that the nucleotide composition of the human genome represents an equilibrium that is maintained by an unwitting battle between the sexes, where male driven AT-biased mutations are offset by female driven GC-biased gene conversion events."*

That the cumulative effect of gene conversion on genome base composition is to precisely counter the changes that mutations would otherwise impose, can be described as a state of equilibrium, but this is not an explanation. Meiotic Error-Correction could explain why such an equilibrium would arise, and why it would persist. It could also explain why gene conversion and mutation rates should be comparable.

Cellular Processes – which might function mainly as tools to find & remove mutations?

The cell's DNA repair machinery, it's first line of defense against mutations, is able to remove many forms of 'recognizable' DNA damage. But point mutations, once completed, leave no obvious 'damage' signature, so DNA repair cannot prevent their accumulation. Nor can even selection halt their initial spread, as most mutations are harmless as heterozygotes.

Sexual reproduction is thought to distribute mutations to offspring unevenly so that selective deaths can remove a greater number per generation.[4] Yet this benefit must be weighed against both the two fold reproductive cost of meiosis, and the high mutational cost of male germ cell production. Moreover, this putative benefit of sex is weak compared what it would confer if it is assisting the direct removal of mutations via *Meiotic Error-Correction.*

Synapsis (the close association between homologous chromosomes in meiosis) is more extensive than needed to instruct crossing-over.[5] Its sensitivity to any non-homology is consistent with its primary role being to find potential mutations.

Concerted Evolution (where multi-copy genes are homogenized via inter-copy gene conversions) is an apparent a gene maintenance strategy, used for instance by polyploid asexual bdelloid rotifers[6] and in multi-copy palindromic Y chromosome genes in mammals.[7] The prevalence of polyploidy where sexual recombination is not possible, hints that it might also serve as a means for cells to distinguish between common and rare variants, so as to bias gene conversion against the latter.

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