Heredity (2011) 106, 535–536

www.nature.com/hdy

NEWS AND COMMENTARY

Population genetics of mutations

The fuel of evolution

C López-Fanjul and A García-Dorado

Heredity (2011) **106,** 535–536; doi:10.1038/hdy.2010.110; published online 25 August 2010

Volume 365 of the *Philosophical Transactions of the Royal Society B* includes a collection of 15 papers written to honour Brian Charlesworth on the occasion of his 65th birthday, which are presented under the general heading of 'The population genetics of mutations: good, bad and indifferent' (here referred to as GBI) edited by Loewe and Hill (2010). At first sight, this title might suggest just a simplistic way to classify mutations, as it seems obvious today that their effects on fitness follow a continuous distribution ranging from lethal to highly advantageous, albeit the mere existence of quasi-neutral 'indifferent' genetic variation was hotly debated a few decades ago. However, in spite of historical attacks on 'bean-bag genetics', the essence of the evolutionary process can be described in terms of the fate of these three different types of mutations in populations subjected to the forces of natural selection and genetic drift. The issue, beginning with a comprehensive introduction (Loewe and Hill, 2010), addresses topics such as the magnitude of spontaneous mutation rates (Kondrashov and Kondrashov), the distribution of mutational effects on fitness (Keightley and Eyre-Walker, Orr, Trindade *et al*.), the specific selective forces affecting different types of mutations (Lee and Langley, McVean, Sharp *et al*.), the consequences of mutation for the genetic architecture of quantitative traits (Crow, Mackay), and the evolutionary role of mutation in broader biological phenomena such as recombination (Barton), adaptation (Sniegowski and Gerrish, Stephan), aging (Hughes) and speciation (McDermott and Noor).

In this review, we concentrate on those contributions that focus on the evolutionary properties of the variability generated by mutation. Huge efforts have been devoted to obtaining estimates of the overall fitness mutation rate and the distribution of the corresponding mutational effects, following two experimental approaches that differ in the way in which those effects are defined.

One approach allows the description of those properties through the assay of lines in which mutations have been allowed to drift by relaxing selection as much as possible (mutation accumulation lines, denoted MA), mostly using *Drosophila* or microorganisms (such as those of *Escherichia coli* reported by Trindade *et al*. (2010) in GBI). Pertinent inferences obviously refer to those mutations with cumulative effects on fitness or its component traits that are within the experimental power, implying effects above 0.1%, and the data allow an estimate of the distribution of those mutational effects by assuming a known family distribution, usually a gamma one, a choice that imposes some limitations on the results obtained. The analysis of MA data is not simple and its outcome seems to be dependent on both the genetic and the environmental backgrounds considered, but some consensus has been reached indicating that, for deleterious cumulative effects within the experimental power of resolution, the rate of spontaneous mutation is small, probably below 0.05 per gamete and generation in *Drosophila*. Furthermore, the corresponding average homozygous effect s is around 10% or larger, and a considerable proportion of mutations have moderate-to-severe deleterious effects, say above 20% (Halligan and Keightley, 2009). In the heterozygous state, the expression of these latter mutations tends to be weak and, therefore, they are expected to contribute a large fraction of the mutational load concealed in large populations, which is responsible for their inbreeding depression rate after bottlenecking and also determines the extent to which this load could be purged by selection (García-Dorado, 2008).

Alternatively, deleterious mutations can be defined as those whose evolution can be constrained by natural selection. This involves values of the selection coefficient s that are large relative to the inverse of the effective population size N, say above some value between 10^{-3} and 10^{-7} depending on the species considered. In the case of *Drosophila*, where, on the whole, about one new mutation occurs per gamete and generation (Haag-Liautard *et al*., 2007), the analysis of the divergence between closely related species showed that about 58% of the spontaneous mutations per nucleotide belong to that deleterious class (Halligan and Keightley, 2009).

Putting all results together, a rough overall view can be reached. In *Drosophila*, this implies that the rate of 'indifferent' mutations is about 0.4 per gamete and generation. The remaining ones are mostly 'bad', those with minor deleterious effects—which escape detection in MA experiments—occurring at a rate of about 0.55, and those with deleterious effects above 0.1%—which are exposed in MA experiments—appearing at a rate of 0.05 at most and showing a leptokurtic distribution. In addition, information on the distribution of the product Ns for all new mutations can be obtained from the frequency distribution of single-nucleotide polymorphisms segregating in natural populations. This would translate to the distribution of s if precise estimates of N were available, although, as shown by Keightley and Eyre-Walker (2010) in their GBI paper, almost all the information could be captured by using distributions with only three classes. What remains to be established is the range of effects that is relevant for different phenomena. Obviously, the mutation rate for the 'bad' class as a whole applies to molecular evolution, but the genetic architecture of fitness determining short- to medium-term evolutionary processes, such as the magnitude of inbreeding depression or the extinction risk of small endangered populations, is likely to be governed by mutations that can be studied in MA experiments. Deleterious mutation may also have a role in the evolution of breeding systems, such as anisogamy or selfing, but its effectiveness depends on the genome degradation rate (Kondrashov, 1985), and the range of pertinent deleterious effects remains to be studied.

Positive natural selection, however, depends upon 'good' beneficial mutations, which occur at such a small rate that empirical information on their distribution is very scarce. In this case, theoretical treatments precede experimental data and, as explained in the GBI paper by Barton (2010), some insight can be gained by using the 'extreme value' theory. This requires that wild-type alleles are well adapted and also that the tail of the distribution of fitness values for all possible alleles falls in some 'ordinary way' (for example, it is not truncated). In this

situation, theory shows that the fitness effects of new beneficial mutations should be exponentially distributed, that is, 'good' effects are usually slight and rarely large. However, stronger empirical confirmation is needed.

The description of the 'good', 'bad' or 'indifferent' effects of spontaneous mutation determines how natural selection operates on its direct target trait, that is, on fitness. However, the adaptation of organisms occurs through indirect responses for genetically correlated traits, whose genetic variances and covariances are also generated by mutation. For metric traits, the per-generation input of variance due to mutation is usually scaled by the environmental variance to give the mutational heritability, a parameter ranging from 10^{-2} to 10^{-4} and clustering around an average value of 10^{-3} for a number of different traits and species. Thus, in an initially invariant population, a few hundred generations will be enough for mutation to regenerate the level of genetic variability for metric traits usually observed in standing populations of similar effective size (Amador *et al*., 2010). The distribution of effects of new spontaneous mutations on metric traits can only be assessed from MA studies, subjected to the limitations mentioned above. In general, both the asymmetry and leptokurtosis of those distributions increase with the closeness of the relationship between the pertinent trait and fitness.

The genetic properties of metric traits in populations depend not only on the joint distribution of mutational effects on the trait and fitness, but also on the nature of the relationship between them. To account for the fact that the genetic variance of such traits does not increase linearly with N, as well as for the temporal stability of their means, weak causal stabilizing selection should be invoked, implying that extreme values of the trait induce some fitness disadvantage. In addition, some apparent stabilizing selection can be expected from the segregation of rare alleles showing both a large effect on the trait and deleterious pleiotropic side effects. Thus, most of the variation in metric traits should be due to alleles with no deleterious side effects, those with the largest effects on the trait segregating at the lowest frequencies. This means that single loci are only likely to explain a very small fraction of the additive variance of a trait, in agreement with the results from quantitative trait locus analysis discussed in GBI by Mackay (2010). Such genetic architecture can account for the long-term sustained response observed in some artificial selection experiments, because the additive variance of the selected trait is continuously depleted as common favourable alleles are fixed, but is also incessantly fuelled as rare favourable alleles are promoted to higher frequencies. Epistatic interactions, relevant to the understanding of developmental patterns, can also be important in specific cases, but they are not generally expected to make large contributions to the genetic parameters and the evolution of quantitative traits (Pérez-Figueroa *et al*., 2009). Therefore, the response to natural or artificial selection can usually be predicted in terms of additive variances and covariances, the epistatic components of the variance usually being small (Hill *et al*., 2008). As noted by Crow (2010) in his contribution to GBI, the details of individual genes are usually not needed, in the same way that 'to measure temperature, one does not average the kinetic energy of individual molecules, but instead uses a thermometer'.

Although our knowledge is still incomplete, this GBI issue represents a significant contribution to the understanding of the genetic change in populations due to the continuous flux of mutations affecting fitness, and deserves to be widely read. In this brief report it has not been possible to address all topics covered in GBI, but we decidedly encourage our readers to complete the job.

Conflict of interest

The authors declare no conflict of interest.

Dr C López-Fanjul and Dr A García-Dorado are at the Departamento de Genética, Facultad de Biología, Universidad Complutense, Madrid 28040, Spain.

e-mail: clfanjul@bio.ucm.es or augardo@bio.ucm.es

Amador C, García-Dorado A, Bersabé D, López-Fanjul C (2010). Regeneration of the variance of metric traits by spontaneous mutation in a *Drosophila* population. *Genet Res* **92**: 91–102.

Barton NH (2010). Mutation and the evolution of recombination. *Philos Trans R Soc B* **365**: 1281–1294.

Crow JF (2010). On epistasis: why it is unimportant in polygenic directional selection. *Philos Trans R Soc B* **365**: 1241–1244.

García-Dorado A (2008). A simple method to account for natural selection when predicting inbreeding depression. *Genetics* **180**: 1559–1566.

Haag-Liautard C, Dorris M, Maside X, Macaskill S, Halligan DL, Houle D *et al*. (2007). Direct estimation of per nucleotide and genomic deleterious mutation rates in *Drosophila*. *Nature* **445**: 82–85.

Halligan DL, Keightley PD (2009). Spontaneous mutation accumulation studies in evolutionary genetics. *Ann Rev Ecol Syst* **40**: 151–172.

Hill WG, Goddard ME, Visscher PM (2008). Data and theory point to mainly additive genetic variance for complex traits. *PLoS Genet* **4**: e1000008.

Keightley PD, Eyre-Walker A (2010). What can we learn about the distribution of fitness effects of new mutations from DNA sequence data? *Philos Trans R Soc B* **365**: 1187–1193.

Kondrashov AS (1985). Deleterious mutations as an evolutionary factor. II. Facultative apomixis and selfing. *Genetics* **111**: 635–653.

Loewe L, Hill WG (eds) (2010). The population genetics of mutations: good, bad and indifferent. *Philos Trans R Soc B* **365**: 1149–1294.

Mackay TFC (2010). Mutations and quantitative genetic variation: lessons from *Drosophila*. *Philos Trans R Soc B* **365**: 1229–1239.

Pérez-Figueroa A, Caballero A, García-Dorado A, López-Fanjul C (2009). The action of purifying selection, mutation and drift on fitness epistatic systems. *Genetics* **183**: 299–313.

Trindade S, Perfeito L, Gordo I (2010). Rate and effects of spontaneous mutations that affect fitness in mutator *Escherichia coli*. *Philos Trans R Soc B* **365**: 1177–1186.

Editor's suggested reading

Colegrave N, Collins S (2008). Experimental evolution: experimental evolution and evolvability. *Heredity* **100**: 464–470.

Fox CW, Stillwell RC (2009). Environmental effects on sex differences in the genetic load for adult lifespan in a seed-feeding beetle. *Heredity* **103**: 62–72.

Chandler CH (2010). Cryptic intraspecific variation in sex determination in Caenorhabditis elegans revealed by mutations. *Heredity* **105**: 473–482.