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Commentary

Mutation versus polymorphism in evolution

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These terms, mutation and polymorphism, can be used to describe the same sequence variant, but in relation to evolution there is a critical distinction. Whereas, *mutation* implies a change from the ancestral sequence at some time, *polymorphism* refers to inherited differences between individuals. Some mutations persist to become polymorphisms but others are repaired or further mutated and become irrelevant as agents of continuing evolution.

Unfortunately, there are many casual usages which create cross-discipline confusion. Some imply that clinically important variants are mutations whereas other variants are "just" inconsequential polymorphisms. Others, like transplantation geneticists, imply the reverse. To some *mutation* brings to mind a change from one particular "wild type" or original sequence as for example in a bacterium. This change may result in some consequence like drug resistance giving credence to the common assertion that evolution requires mutation followed by selection.

Complex genomes require different concepts [1]. For example, there is greater redundancy, no doubt reflecting whole genome duplication in vertebrates [2]. Some genomic regions are represented by four distinct versions. Which of the four could be regarded as the "wild type"? In addition, whole segments are duplicated and often inverted. Which is the mutant? Although apparently derived from a single sequence in invertebrates, copy numbers differ in vertebrate genomes [3]. Retroviral like elements are abundant and can be classified into groups based on sequence differences [4].

In some regions of vertebrate genomes, referred to as polymorphic blocks, there may be hundreds of alternative sequences, all equally "wild" or "original". In fact, many of these sequences have been conserved without detectable change for thousands of generations. Mutations, when they can be detected as recent changes, are generally inconsequential. For example, it is the conserved *polymorphisms* rather than the recent *mutations* which determine the outcome of transplantation.

As recently emphasised by Klein, some polymorphisms are so conserved as to be TRANSPECIES. For example, they are shared between for example humans and chimpanzees [5]. Contrary to common assertions, polymorphisms are not necessarily generated at speciation. In fact, sequences may be conserved rather than mutated.

These features of vertebrate genomics have been known and periodically rediscovered for decades but have been ignored by those who see mutation as the essential prerequisite for evolution.

How then do vertebrates evolve? In humans at least, it is now certain that the important differences between individuals are not due to recent changes but to different mixtures of conserved polymorphisms. There are sufficient combinations of such polymorphisms to account for the individuality of all alive today as well as all ancestors. Some may say, in their defence, that remixing conserved polymorphism is a form of *genomic mutation* even though the component sequences have NOT changed. Other forms of *genomic mutation* might include duplication, insertion, deletion and even integration of retrovirus but, the field is already confused enough! Fortunately, most use *mutation* to describe a demonstrable change in nucleotide sequence which can then be qualified depending upon its persistence, function and relevance.

In practice, we use *polymorphism* to refer to multiallelic inherited differences in a population, species or other group. It should not be restricted to those which occur in more or less than some percentage of the population, those occurring in single nucleotide positions or those which are regarded as neutral. These idiosyncratic uses of the term by sectional interests have created as much confusion as the misuse of mutation.

The two terms, defined in terms of either sequence change or difference, can then be used to contrast different concepts underlying evolution. Taking human evolution as an example, we refer to monogenic traits and diseases as due to mutations when it is reasonable to deduce that a change occurred in one particular ancestor. Examples include a form of porphyria where the mutation seems to have appeared de novo in a particular family several centuries ago [6,7]. Some monogenic traits are older and deeper so that the likely mutation is at best inferred rather than demonstrable [7].

Most inherited traits and diseases are polygenic and extremely complex suggesting dependence on multiple polymorphisms. Some of these may affect coding regions and therefore protein products but many are regulatory thereby explaining degrees of penetrance and severity. It is neither possible nor logical to implicate specific unidentifiable changes in sequence or "mutations". It appears more productive to seek the particular mix of conserved polymorphisms, in all their forms, irrespective of when these were generated.

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What are the generators of diversity? How are polymorphisms created? Why are they concentrated in some regions or blocks? Duplication is one of the major preconditions for the generation of polymorphism. Retroviral elements are enriched in the same regions [8] and appear to the principal drivers of the observed rearrangements of sequences [9–12].

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