Behavioral and Brain Sciences

Is genomics bad for you?

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Abstract:	The plasticity of the genome complicates genetic causation, but should be investigated from a functional perspective. Specific adaptive hypotheses are referenced in the target article, but it is also necessary to explain how the integrity of the genome is maintained despite processes that tend towards its diversification and degradation. These include the accumulation of deleterious changes and intra-genomic conflict.

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10: Abstract

The plasticity of the genome complicates genetic causation, but should be investigated from a functional perspective. Specific adaptive hypotheses are referenced in the target article, but it is also necessary to explain how the integrity of the genome is maintained despite processes that tend towards its diversification and degradation. These include the accumulation of deleterious changes and intra-genomic conflict.

11. Main text

Most of the phenomena Charney terms “neo-genetic” entail changes to the genetic substrate and are therefore classifiable as kinds of mutation. Epigenetic marks differ because they influence gene expression, not sequence. Somatic mutations during development can lead to genetic mosaicism while epigenetic modifications presumably underlie cellular differentiation (Ng and Gurdon, 2008). Mutations in the germline can lead to non-Mendelian inheritance of portions of the genome (reviewed in Burt and Trivers, 2006), while epigenetic changes can create unusual patterns of expression such as polar overdominance (Cockett et al., 1996). Charney argues that these peculiarities undermine genotype to phenotype maps implicit in the statistical frameworks of behavior genetics. Rather than venture criticism, I here expand on the theoretical challenge presented by one aspect of mutation, simply that of its ubiquity.

Mutations can be understood as products either of necessity or chance. Charney’s emphasis on adaptive phenotypic plasticity is apposite. To the extent that mutations are functional they are instances of adaptedness *per se*, rather than drivers of adaptation (for an explanation of this perspective see Dickins and Dickins, 2008). Charney also describes well the manner in which adventitious changes are harnessed through somatic hypermutation in the immune system. But he says “stochasticity continually threatens to undermine the order imposed by biological systems”. This is surely so: severe and multifarious mutations affecting the genome within lineages (at least some of which are associated with behavioural dysfunction: e.g., Stewart et al., 2011) would seem to threaten extinction. How, for example, does a brain maintain its function or a population of organisms preserve its genomic integrity, despite frequent aneuploidy?

Let us consider only “conventional” mutations, viz. single nucleotide changes or

indels (insertions and deletions), of the kind that can be associated with Mendelian disorders. Many such mutations are deleterious, and even mildly deleterious mutations can lead to extinction when they accumulate under the influence of genetic drift (Muller, 1964). Even assuming an infinite population size, mutation accumulation can lead to population extinction with a probability that depends not on the average effect size of mutations but upon their rate of occurrence and on the intrinsic fecundity of individuals (Bull et al., 2007). Humans have slow life histories (Robson and Wood, 2008), a low effective population size (Yu et al., 2004) and a relatively high mutation rate (Kondrashov, 2003; Lynch, 2010) although they benefit from recombination. Given the proportion of *de novo* mutations expected to be deleterious, and with advances in medical care that plausibly entail a relaxation of negative selection, these parameters have led to concerns about population fitness in the medium term (Lynch, 2010; but see Keightley, 2012). Low frequency alleles with relatively large effect sizes may also underlie at least some of the missing heritability in genome wide association studies (Manolio et al., 2009), thereby contributing to the burden of disease at this time.

The reduction in the mean fitness of a population caused by mutations (the mutation load) is attenuated when the fitness of an individual depends on others around it; this is so-called soft selection (Wallace, 1975). Alternatively germline viability selection can expurgate deleterious alleles, an observation made plausible in humans by the seemingly high rate of "occult" pregnancies (Edmonds et al., 1982), with many aborted concepti manifesting aneuploidies (Macklon et al., 2002). The occurrence of mitotic and meiotic cell divisions in the germline of "sexual" species has significant population genetic consequences (Hastings, 1991). For example, when germline selection is soft this can favour the evolution of "anti-robustness" in which genotypes readily suffer reduced fitness when mutated (Archetti, 2009). Anti-robust genotypes are also expected in regenerative tissues for theoretical reasons (Krakauer and Plotkin, 2002) paradoxically contributing to robustness at the level of the organism.

Emerging evidence supports purifying selection in the mammalian mitochondrial genome (Fan et al., 2008; Stewart et al., 2008), which is probably facilitated by a germline bottleneck in copy number. We are beginning to understand how cell lineages behave in mammalian oogenesis (Reizel et al., 2012), but important details are unresolved. In the male germline, recent evidence suggests positive selection *for* specific genetic disorders (Goriely et al., 2003; Choi et al., 2012). One response to these preliminary data is to conceive of 'disease' as an outcome of a breakdown in the regulation and control of deleterious mutations. Focussing on the regulation of mitochondrial function one colourful review elaborates such a "quality-control" perspective (Braschi and McBride, 2010). Although Charney suggests that transposon activation in the brain might be positively associated with neural plasticity and flexibility, it may prove necessary to consider how neural networks buffer themselves from the deleterious effects of mutations or even how behaviour itself might modulate mutational effects.

Some of the phenomena Charney describes might threaten stability, not because of their passive accumulation, but because they are selected for independently of their effect on the rest of the genome. For example transposons active in the germline increase their contribution to posterity by over-replication, but can damage genes if they "jump" close by or into them. When intragenomic conflict occurs, and a component of the genome acts against the wider coalition, the evolution of repressors is favoured by natural selection (Burt and Trivers, 2006). Aspects of meiosis such as reduction division and recombination may have evolved to restrain selfish genetic elements.

Many forms of epigenetic regulation were revealed during research into genomic imprinting. Imprinted gene expression can be explained by conflict between paternally and maternally derived alleles within offspring (Haig and Westoby, 1989) or as a consequence of maternal-foetal co-adaptation (Keverne and Curly, 2008). From the conflict perspective imprinted gene expression does not benefit the organism, but potentially creates problems in the event of epigenetic dsyregulation or mutation (due to haploinsufficiency at the expressing allele). Aberrant patterns of imprinted gene expression are implicated in intrauterine growth restriction (Tycko, 2006), but recent screens (reviewed in Kelsey, 2011) have suggested abundant imprinted expression in the brain. Trivers (2000) has also outlined ways in which intragenomic conflict can manifest itself in the behaviour of individuals.

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