Mayo, Oliver; Leach, Carolyn R.
Are common, harmful, heritable mental disorders common relative to other such non-mental disorders, and does their frequency require a special explanation?, Behavioral and Brain Sciences, 2006; 29 (4):415-416.

Copyright © 2006 Cambridge University Press

PERMISSIONS

http://journals.cambridge.org/action/stream?pageId=4088&level=2#4408

The right to post the definitive version of the contribution as published at Cambridge Journals Online (in PDF or HTML form) in the Institutional Repository of the institution in which they worked at the time the paper was first submitted, or (for appropriate journals) in PubMed Central or UK PubMed Central, no sooner than one year after first publication of the paper in the journal, subject to file availability and provided the posting includes a prominent statement of the full bibliographical details, a copyright notice in the name of the copyright holder (Cambridge University Press or the sponsoring Society, as appropriate), and a link to the online edition of the journal at Cambridge Journals Online. Inclusion of this definitive version after one year in Institutional Repositories outside of the institution in which the contributor worked at the time the paper was first submitted will be subject to the additional permission of Cambridge University Press (not to be unreasonably withheld).

10th December 2010

http://hdl.handle.net/2440/35539
attention to the reduced reproductive fitness in schizophrenia, they do not discuss the evidence that individuals with ADHD tend to have more children than do controls (Weiss et al. 1985).

K&M point out the arbitrariness between classification of what is “normal” and what is “abnormal” because most mental disorders are extreme points along a continuum of symptom severity. From this viewpoint, the “normal” spectrum of symptoms may have adaptive functions, such that normal depressed mood may motivate avoidance of similar situations in the future. Unlike somatic disorders, there is rarely an objective gold standard for diagnosis: Severities range widely and wax and wane over time in a given individual; boundaries with normality are fuzzy and shifting, depending often on society’s own changing norms and expectations (Joan of Arc, a heroine in her day, would probably nowadays be committed to an institution); and boundaries between the disorders themselves are often fuzzy and arbitrary with much overlap, irrespective of questions of comorbidity, as if it all depends on which “joints” we happen to choose with which to “carve” nature. Cultural factors may influence the prevalence and severity of mental disorders, because cultural and societal tolerance for different behaviours vary (McArdle 2009). Using the same cut-off scores on a behaviour teacher rating scale for example, produces different rates of hyperactivity in children of different countries (e.g., in Scotland, 4.5% of children are classified hyperactive, whereas, in Spain, 16% of children are classified hyperactive using the same criteria; Gingerich et al. 1998).

Brown and Braithwaite (2004) found that, despite (and, initially in fact probably because of) variability in both groups, on average, fish introduced into high-predation environments in a very few generations tended to become more bold (showing a greater propensity to take risks and greater exploratory behaviour) than did fish (from the same original founder population) from low-predation sites. Presumably it is advantageous for fish in high-predation environments to explore a new environment thoroughly to become aware of escape routes and to ensure that no predators are present. Thus, “personality” or temperament traits appear to be selected for, often in a very short time period, if they are advantageous in a particular environment. Generally, what is genetically transmitted is perhaps not so much a disorder per se, but rather a particular kind of general personality bias which may then predispose an individual to morbidity in a certain sociocultural context – or perceived excellence in another. There certainly appears to be a connection between temperament, which is considered to be an early precursor to personality traits (Nigg et al. 2002), and psychiatric disorders, because difficult-temperament children are over-represented in psychiatric populations (Maziade et al. 1990a). However, difficult temperament predicts the presence of psychiatric conditions in preadolescence and adolescence only when family functioning is also taken into account (Maziade et al. 1990b). Thus, extreme temperament is not automatically equivalent to a psychiatric disorder, and reflects the importance of considering gene-environment interactions.

Inheritance of general personality factors may predispose an individual to the risk of developing one or more of a range or possible maladaptive (or even adaptive) behaviours, depending on the individual’s environment (Legrand et al. 2005). Thus, the same genes for externalising tendencies may be expressed differently under different environmental conditions, and predispose, on the one hand, both to antisocial behaviour and drug and alcohol problems, and, on the other, to otherwise useful, if risky or dangerous, occupations (e.g., test pilots, fire fighters). Similarly, impulsive people may be well placed to take advantage of unexpected opportunities, whereas others’ impulsive choice may lead to drug addiction in which addicts affect their health for the immediate rewards of the drug (Cardinal 2004; Evenden 1999).

Are common, harmful, heritable mental disorders common relative to other such non-mental disorders, and does their frequency require a special explanation?

Olivier Mayo and Carolyn Leach

Abstract: Keller & Miller’s (K&M’s) conclusion appears to be correct; namely, that common, harmful, heritable mental disorders are largely maintained at present frequencies by mutation-selection balance at many different loci. However, their “paradox” is questionable.

The “paradox,” which is largely set out in the first sentence of Keller & Miller’s (K&M’s) abstract, has two elements: the existence of common disorders agreed to be deleterious in present-day environments and shown by the authors to reduce reproductive performance (fitness) in many cases; and an effective mechanism for reduction of frequency of alleles predisposing persons to deleterious traits. The reality of the paradox requires consideration before assessment of K&M’s explanation for the prevalence of disorders agreed to be common.

Mental disorders as a special category. We first address the case of mental disorders (MDs), since they are considered at length by K&M. Table 1 lists a number of disorders well established as having high population prevalence and substantial heritability. Heritability ($h^2$) is used as an indicator of genetic importance in aetiology despite its well-known defects (mentioned by K&M), because for common diseases there is no problem of $h^2$ being misleading.

We see immediately that traits other than MDs which certainly reduce fitness, for example, type 1 diabetes and endometriosis, are also at high frequencies which require explanation on K&M’s argument. We also tentatively conclude that, however special and important human mental abilities and disturbances thereto be to humans living in society, there is no reason to separate them out for the purposes of assessing K&M’s paradox. We shall therefore consider them separately only after dealing with the two general propositions which constitute K&M’s paradox.

The existence of common deleterious traits. The majority of the traits shown in Table 1 are deleterious in present-day societies, in terms of reduction in reproductive fitness. The societies under discussion are for the most part characterized by large numbers of unrelated people living in close proximity, sustained by nutrition adequate to excessive for the low level of physical effort required normally to gain a living in employment and other activities which themselves differ greatly from those of the first 24,000 generations at least of the human species’ putative 25,000 generations of existence.

Some of these traits have increased substantially in frequency in recent centuries. In some cases, environmental factors have been identified as causal, for example, diet and exercise patterns for ischaemic heart disease. Of type 1 diabetes, Hyttinen et al. (2003) have written:

Type 1 diabetes among children ≤ 15 years has increased worldwide during [recent decades]. In light of population genetics, the rate of increase in the incidence . . . is too rapid to be caused by changes in the population gene pool. Despite harmful effects of diabetes-associated alleles, they are common in many populations. Environmental risk factors may directly trigger the process leading to type 1 diabetes or may interact with diabetes susceptibility genes that modify the penetrance. Heritability [in our study] was found to be higher than that discovered before. If the increase in heritability is real, it should be at least partly interpreted as a changed penetrance of the diabetes susceptibility genes. (p. 1054)
Hence, such a change must have been environmentally induced.

Other diseases, such as many infectious diseases, have declined in incidence and prevalence in recent centuries. In virtually all cases where explanations have been obtained, environmental factors have been shown to be causal, even where genetic susceptibility is implicated in causation of the disease. Environmental change has thus been important in changes in disease incidence and prevalence upwards and downwards; it would be of interest to know what diseases have remained unchanged in incidence or prevalence in recent centuries, but rare Mendelian recessive disorders could lie in this group. K&M present no evidence on constancy of frequency of their target category: "[M]ental disorders that are much more common than would be expected from a single-gene mutation-selection balance; roughly, this corresponds to mental disorders with lifetime prevalence rates above 0.05% in reproductively aged adults" (sect. 1.3, para. 6). In the absence of evidence, one cannot reject the simple hypothesis that some changes in the human environment in the last thousand generations have contributed to an increase in the frequency of disorders that are particularly deleterious in large, organised societies not engaged in essential, risky, strenuous physical work. K&M address "ancestral neutrality" of causal alleles of relevant genes in sections 3.3 and 4 but reject it because of population-genetic considerations. Their argument concerning environmental change is brief and based on the implausibility of large G×E interactions and the rarity of strict neutrality (sect. 4.2). Leaving aside discussion of such strict neutrality, we simply note that very large G×E interactions are inherent in the increase in frequency of diabetes and various cancers; they are not inherently implausible. Indeed, K&M accept in section 4.4 that G×E interactions and nearly neutral variation could be important in the very high incidence of depression, where simple environmental change in incidence of change in incidence has indeed been invoked from time to time (e.g., Hibbeln 1998).

In the absence of evidence of constancy of frequency of MDs over time, one cannot reject the hypothesis that environmental factors have increased their frequency, making highly deleterious alleles that were previously neutral, advantageous or slightly deleterious. Neutrality is a second-order question until the hypothesis stated has been tested. **Depletion of genetic variation by natural selection.** Much of K&M’s argument is based on the Fisherian concept that a population will, other things being equal, increase in fitness at a rate given by the additive genetic variance in fitness (see Ewens 2001). On K&M’s argument, natural selection will therefore deplete variance in fitness rapidly, apart from that generated afresh by mutation. However, this conclusion ignores two matters: First, the environment is never constant and indeed may be viewed from the organism’s perspective as constantly deteriorating (Fisher 1930/1999); and, second, variance in fitness and associated metrics (e.g., heritability) are not simply reduced rapidly to zero for “fitness traits” and left as they are for “non-fitness traits” (see Bürger et al. 1989; Keightley & Hill 1987; Mayo et al. 1990). Traits which may be substantially influenced by the environment, such as all those listed in Table 1, should be considered in the light of the cautious just expressed; environmental change, potentially so much more rapid and far-reaching, should always be evaluated before considering genetic change. Indeed, Kirk et al. (2001) have drawn much the same conclusion from a very thorough direct study of the heritability of fitness in one human population.

**Genetic contributions to causation of mental disorders.** We argue that K&M have not made their case in regard to either the overall causation of MDs or the genetic evidence for mutation-selection balance as the prime source of genetic variance in MDs. However, as set out in the previous section, we consider such balance as the major source of genetic variance in many traits, among which could be MDs.

It is possible that those who hold the belief a priori that the genetic basis of multifactorial traits is oligogenic may still find this conclusion paradoxical in some way. However, we should note that evidence from experimental organisms shows that many traits are controlled by many – frequently hundreds – of genes, and that there are scores of interactions among these genes, even for simple quantitative traits in plants such as rice (for discussion, see Mayo 2004). For truly complex traits such as human mental development and function, influenced perhaps by thousands of genes, as noted by K&M, it should not be surprising that causation of variation is not oligogenic.

We note further that K&M have not made a convincing special case for MDs as against other common familial diseases, and conclude by quoting Bodmer (1999, p. 103), who has applied the same arguments to common cancers:

> These types of variants [rare variant alleles at many different loci] may thus represent a major new facet of the study of multifactorial disease inheritance, representing effects that lie between those of severe clearly inherited susceptibilities and relatively common multifactorial low-penetrance effects, such as are characterised by the many associations between polymorphic HLA variants and autoimmune diseases.