

The article by Kyaga *et al*¹ is an important contribution to the understanding of the selective advantage and disadvantage of common behavioural phenotypes. The accompanying editorial by Jamison puts this work in context and points out that the overlap between creativity and mental disorder is partial.² The proportion of persons in creative professions in Sweden is about 1.1% (based on the 1990 Swedish census, ages 15–64, and excluding scientific professions). The figure for the USA is similar: 1.4%.³ Our report in the neurological literature proposes that polymorphisms in the alpha-1-antitrypsin (A1AT) gene are a common genetic factor for both creativity and mental disorder.⁴ The proportion of people in creative professions observed in 1537 consecutive patients was 3.7%. A highly significant 38% of people in creative professions carried one or more polymorphisms of the A1AT gene compared with the 13% carrier rate observed in the other participants in this study,⁴ and similar to reported rates in European populations. When the larger proportion (20–30%) of the population that pursue creative avocations (acting, dancing, music, photography, visual arts, writing) are considered, the same relationship of A1AT carriers and creativity and ‘intense mental energy’, including clinical anxiety or bipolar disorder, is observed.⁴ An extension of these previous clinical series now totals 3176 consecutive patients and confirms the original findings⁴ (details available from the author on request). This means that creativity and mental disorder can overlap and one instance for many such cases may be the genetic and environmentally modulated interactions of A1AT liver protein and serum acute phase reactant. It is important to emphasise that not all artists are A1AT carriers and not all artists have intense goal-directed energy or even mood disorder, underlining the point of Jamison’s editorial. Nevertheless, it is likely that many people carrying A1AT polymorphisms trade the selective advantage of intense creative energy (blessing) for the disadvantage of susceptibility to lung and liver disease, and potentially significant recurrent mood disorder (curse). Pulmonary disease is associated with bipolar disorder (see Schmechel⁴), and A1AT polymorphisms would provide a genetic basis.

Declaration of interest

D.E.S. is principal inventor on a US patent in preliminary examination with regard to the use of A1AT as a therapeutic target in Alzheimer’s disease.

- 1 Kyaga S, Lichtenstein P, Boman M, Hultman C, Långström N, Landén M. Creativity and mental disorder: family study of 300 000 people with severe mental disorder. *Br J Psychiatry* 2011; **199**: 373–9.
- 2 Jamison KR. Great wits and madness: more near allied? *Br J Psychiatry* 2011; **199**: 351–2.
- 3 National Endowment for the Arts. *Artists in the Workforce: 1990–2005. Research Report #48*. National Endowment for the Arts, 2008 (<http://www.nea.gov/research/ArtistsInWorkforce.pdf>).
- 4 Schmechel DE. Art, alpha-1-antitrypsin polymorphisms and intense creative energy: blessing or curse? *Neurotoxicology* 2007; **28**: 899–914.

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Kyaga *et al*¹ have produced an excellent analysis based on the Swedish registers, which finds an increased rate of creativity in patients with schizophrenia or bipolar disorder, and their relatives. This lends support to the model for a correlation between schizophrenia, creativity and fitness that was developed jointly by one of us.² However, the authors claim that this finding supports the balancing selection hypothesis that aims to explain

why psychiatric disorders have persisted throughout evolution. The theory stipulates that if patients with such severe disorders have fewer children, then the genetic variants responsible for the illnesses should be filtered out from the general population, unless this effect is balanced by adaptive advantages harboured by these variants. Relatives of patients, who also carry such variants but are free from illness, might therefore have an increased fitness.

A higher level of creativity could indeed be advantageous and increase fitness, as outlined by the authors. However, there are many other qualities that can also increase fitness, for example being faster, stronger, having a higher cognitive ability, being more attractive or living longer. The only outcome that matters for evolution is how many children an individual will leave, because if one does not pass on his or her genetic variants, these variants will disappear from the population. However, a systematic review found that patients with schizophrenia have a fertility ratio of only 0.39 compared with the general population,³ and a more recent study of the Danish population also found strongly reduced rates for both schizophrenia and bipolar disorder.⁴ More importantly, any possible increased fertility among relatives is too small to compensate for the strongly reduced fertility of patients.^{3,5}

In contrast, the alternative mutation selection hypothesis, which the authors also discuss, can explain this apparent paradox, provided new (*de novo*) mutations replenish those that are lost because of reduced fitness. We found that about 5% of probands with schizophrenia had a *de novo* copy number variation (CNV), a twofold higher rate than in controls.⁵ A large proportion of these CNVs appear to be under strong selection pressure. In fact, the ten best supported CNV loci that increase risk to develop this disorder have high mutation rates (a *de novo* CNV occurring in between 1:3500 and 1:30 000 individuals), and are under strong selection pressure. This leads to the elimination from the general population of each new mutation at these loci in less than five generations on average.⁶ We anticipate that ongoing next-generation sequencing studies will also implicate the more numerous point mutations, and could help resolve this debate.

Increased creativity among individuals with severe psychiatric disorders is an advantage to them and their relatives and could cause increased fitness in relatives, but *de novo* mutations appear to be more relevant for the persistence of these disorders in the population.

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