

## Correspondence

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## Intergenerational transmission of psychopathy

The conclusions drawn by Auty *et al*<sup>1</sup> – that the development and persistence of psychopathic personality characteristics is most likely down to both genetic and environmental factors – are well-judged, modest, and consistent with their results. Their report highlights a large and potentially important dataset, and the topic of intergenerational transmission of personality characteristics is underresearched.

Unfortunately, although it was not mentioned in the limitations, I am concerned that the results of the analysis remain open to confounding by genetic factors. For example, the mediation model involving disrupted employment as an intergenerational mediator of psychopathic trait from one generation to the next (male and female) was statistically significant. But, in finding that unemployment was a cause of psychopathic traits in the offspring, given that some genetic influence to psychopathy exists, and that correlation between genetic risk for psychopathy and unemployment is likely, the conclusions seem vulnerable to the alternative explanation that it is shared genetic material, not psychosocial risk factors, being measured in the models. This could be an important threat to inference. For example, in the study of intergenerational transmission of conduct problems by D'Onofrio *et al*,<sup>2</sup> the investigators identified evidence for complete confounding of environmental risk factors by shared genetic liability. Readers should be cautious, therefore; bringing about changes in personality structure in the offspring of psychopathic individuals by intervening in the parental psychosocial environment may be injudicious.

- 1 Auty KM, Farrington DP, Coid JW. Intergenerational transmission of psychopathy and mediation via psychosocial risk factors. *Br J Psychiatry* 2015; **206**: 26–31.
- 2 D'Onofrio BM, Slutske WS, Turkheimer E, Emery RE, Harden KP, Heath AC, *et al*. Intergenerational transmission of childhood conduct problems: a Children of Twins Study. *Arch Gen Psychiatry* 2007; **64**: 820–9.

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**Authors' reply:** We agree that the intergenerational transmission of psychopathy could be driven by genetic factors as well as by environmental factors. The degree of influence that environmental factors have on intergenerational transmission of personality features and the possible confounding by genetic features are of central importance in understanding the aetiology of psychopathology.

The Cambridge Study in Delinquent Development (CSDD) has not collected any genetic material. However, it has collected detailed information on environmental measures and can provide some insight into this issue. Current work involves comparing the

intergenerational transmission of psychopathy for offspring with resident fathers (up to age 16) with that for offspring with non-resident fathers. We would expect that, to the extent that the intergenerational relationship is driven by genetics, it would be just as strong for those with non-resident fathers as for those with resident fathers. To the extent that environment matters, the relationship should be stronger for those with resident fathers.

We have found that, for male offspring with a resident father, transmission of Hare Psychopathy Checklist: Screening Version (PCL:SV) Factor 1 and Factor 2 scores is strong and statistically significant ( $P < 0.001$ ). However, for males with a non-resident father, the transmission is weaker. It was significant only for the more behavioural Factor 2 scores ( $P = 0.021$ ) and not for the Factor 1 scores, which measure psychopathic personality features.

These results suggest that environmental factors might be important in the transmission of psychopathic personality features to male offspring. For female offspring with a resident father, the transmission of Factor 1 and Factor 2 scores was not significant. For female offspring with a non-resident father, the transmission of Factor 1 scores was not significant but, surprisingly, the transmission of Factor 2 scores was significant ( $P = 0.003$ ). Our results suggest that, for both male and female offspring, genetic factors may be important in the transmission of the more behavioural Factor 2 scores. However, it may be that environmental factors are more important for male offspring.

Our results agree with previous analyses of the CSDD dataset examining the intergenerational transmission of convictions. Farrington *et al*<sup>1</sup> found that the relationship between the convictions of same-gender intergenerational pairs was stronger than for opposite-gender pairs; father–son was stronger than father–daughter correlation, and mother–daughter was stronger than mother–son correlation.

- 1 Farrington DP, Barnes GC, Lambert S. The concentration of offending in families. *Legal Criminol Psychol* 1996; **1**: 47–63.

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Influences of schizophrenia risk variant rs7914558 at *CNNM2* on brain structure

A genome-wide significant variant at rs7914558, which is located in the intron of the cyclin M2 gene (*CNNM2*) on chromosome 10q24.32, has been identified in a meta-analysis of genome-wide association studies (GWAS) by the Schizophrenia Working Group of the Psychiatric Genomics Consortium (PGC).<sup>1</sup> Recently, the largest GWAS, combining all available schizophrenia samples in the PGC, has identified genomic loci, including the *CNNM2* gene where the genetic variant at rs11191419 ( $r^2 = 0.608$ ) was the most significant.<sup>2</sup> Major alleles of both variants were related to risk for schizophrenia (the major G allele at rs7914558 was a risk allele).

Using Irish and Italian cohorts of patients with schizophrenia and healthy controls, Rose *et al* examined the relationships between the genome-wide significant variant at rs7914558 and neurocognition, cognitive function and brain structure.<sup>3</sup> They reported that the *CNNM2* risk A variant was associated with reduced self-serving bias in 256 Irish patients and 131 controls. In addition, they found the risk A allele was associated with grey matter volume in putative social cognition-related regions, such as the temporal pole and anterior cingulate cortex. The A-allele carriers had greater grey matter volume in the right temporal pole and anterior cingulate cortex in 159 Irish healthy controls, reduced grey

matter volume in the left anterior cingulate cortex in 66 Italian patients with schizophrenia, and greater grey matter volume in the left anterior cingulate cortex in 37 Italian controls.

In terms of providing evidence that the *CNNM2* variant would contribute to social cognition and its neural underpinnings, it is a very interesting study. However, the study has a very important limitation. The reported risk allele was incorrect: the risk allele at rs7914558 is not minor 'A' but major 'G'. Therefore, interpretation of these associations was opposite.

At almost the same time, we reported that the rs7914558 variant was associated with grey matter volume in the orbital region of the bilateral inferior frontal gyri in 173 Japanese patients with schizophrenia and 449 healthy individuals.<sup>4</sup> Those with the risk G/G genotype of rs7914558 had reduced grey matter volume in the bilateral inferior frontal gyri compared with carriers of the non-risk A allele. Interestingly, the orbital region of the inferior frontal gyrus also plays an important role in social functioning. Taken together, the variant was associated with reduced grey matter volume in putative social cognition-related regions, including the temporal pole, anterior cingulate and inferior frontal cortices, which were reduced in patients with schizophrenia, although the detailed regions were not consistent among the different populations studied.

Furthermore, a recent study has indicated that mutations in the *CNNM2* gene are associated with intellectual disability, and the knockdown of *Cnnm2* isoforms in zebrafish has resulted in disturbed brain development.<sup>5</sup> These findings suggest that the *CNNM2* variant might play a role in the social cognition and social functioning impairments noted in patients with schizophrenia through the volumetric vulnerability of these grey matter regions.

- 1 Ripke S, Sanders AR, Kendler KS, Levinson DF, Sklar P, Holmans PA, et al. Genome-wide association study identifies five new schizophrenia loci. *Nat Genet* 2011; **43**: 969–76.
- 2 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**: 421–7.
- 3 Rose EJ, Hargreaves A, Morris D, Fahey C, Tropea D, Cummings E, et al. Effects of a novel schizophrenia risk variant rs7914558 at *CNNM2* on brain structure and attributional style. *Br J Psychiatry* 2014; **204**: 115–21.
- 4 Ohi K, Hashimoto R, Yamamori H, Yasuda Y, Fujimoto M, Umeda-Yano S, et al. The impact of the genome-wide supported variant in the cyclin M2 gene on gray matter morphology in schizophrenia. *Behav Brain Funct* 2013; **9**: 40.
- 5 Arjona FJ, de Baaij JH, Schlingmann KP, Lameris AL, van Wijk E, Flik G, et al. *CNNM2* mutations cause impaired brain development and seizures in patients with hypomagnesemia. *PLoS Genet* 2014; **10**: e1004267.

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**Authors' reply:** Dr Ohi is correct that the risk allele at the locus rs7914558 is the major G allele; throughout the paper we had incorrectly identified the risk allele as being the major A allele.<sup>1</sup> We have submitted a corrigendum to state that the G allele is both the major allele and the risk allele.

However, while the tables and text have incorrectly named the risk allele as the A allele, the analysis undertaken, and its interpretation, are correct, as we based our analysis on the major allele being the risk allele. As we state in our study, the risk allele was associated with reduced self-serving bias, and increased grey matter volume in regions relevant to social cognition in both the Irish and Italian samples. Dr Ohi, therefore, seems to be incorrect in asserting that the results are consistent with data from his group's study, in which the risk allele was associated with reduced grey matter volume in the orbitofrontal cortex. Although both regions are associated with social cognition, they are also implicated in other cognitive processes, which might explain the differences in results. While both sets of results will require replication in independent samples before firm conclusions are drawn, the availability of a replication sample in our study enabled us to provide additional support for our results, despite their counterintuitive nature.

We also take this opportunity to disagree with Dr Ohi's assertion that this variant rs7914558 is necessarily associated with *CNNM2*. Although the title of our paper notes that this variant is located at the same locus as *CNNM2*, and named as such in the PGC GWAS study, we highlight in our discussion that linkage disequilibrium from this variant extends to three other genes over a region of several hundred kb, any one of which could potentially be associated with this signal. In fact, the most recent study by the PGC<sup>2</sup> suggests, based on eQTL analysis, that the single-nucleotide polymorphism most strongly associated with schizophrenia in this region (rs11191419) is associated with altered expression of the *AS3MT* gene.

- 1 Rose EJ, Hargreaves A, Morris D, Fahey C, Tropea D, Cummings E, et al. Effects of a novel schizophrenia risk variant rs7914558 at *CNNM2* on brain structure and attributional style. *Br J Psychiatry* 2014; **204**: 115–21.
- 2 Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014; **511**: 421–7.

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