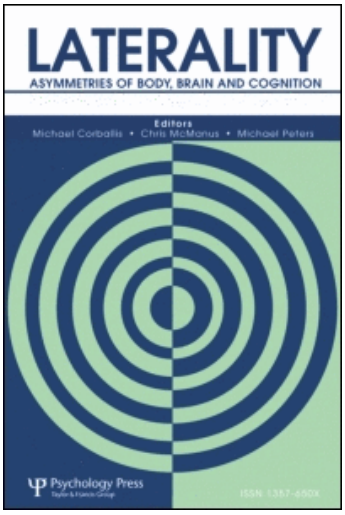

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Understanding the genetics of behavioural and psychiatric traits will only be achieved through a realistic assessment of their complexity

Clyde Francks[a]
[a] University of Oxford, UK

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Understanding the genetics of behavioural and psychiatric traits will only be achieved through a realistic assessment of their complexity

Clyde Francks
University of Oxford, UK

Francks et al. (2007) performed a recent study in which the first putative genetic effect on human handedness was identified (the imprinted locus LRRTM1 on human chromosome 2). In this issue of *Laterality*, Tim Crow and colleagues present a critique of that study. The present paper presents a personal response to that critique which argues that Francks et al. (2007) published a substantial body of evidence implicating LRRTM1 in handedness and schizophrenia. Progress will now be achieved by others trying to validate, refute, or extend those findings, rather than by further armchair discussion.

Keywords: Handedness; Genetics; LRRTM1; Candidate gene; Schizophrenia.

In their critique of the Francks et al. (2007) study, which presented evidence for an involvement of the gene LRRTM1 in handedness and schizophrenia, Crow et al. have re-stated a long-standing, pseudo-autosomal, single-gene hypothesis for handedness, schizophrenia, and brain asymmetry (Crow, Close, Dagnall, & Priddle, 2009 this issue). Single-gene theories have not found broad support among the psychiatric genetics community, as most researchers consider such models unrealistic for complex traits such as schizophrenia, and insufficient to explain genetic epidemiological, linkage, and association data, and data on environmental influences (Burmeister, McInnis, & Zollner, 2008). To the extent that LRRTM1 is not located on the pseudo-autosomes, the findings of Francks et al. (2007) are clearly not compatible with Crow's long-standing hypothesis. However, beyond this, the critique of Francks et al. (2007) that is offered by Crow et al. contains no new data, no suggestions for re-analysis, and no specific methodological critiques, and its value is therefore questionable. Francks et al. (2007) have published a body of evidence implicating LRRTM that now enables others

Address correspondence to: Clyde Francks, Wellcome Trust Centre for Human Genetics, University of Oxford, Roosevelt Drive, Oxford OX3 7BN, UK. E-mail: clyde@well.ox.ac.uk

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to try to validate, refute, or extend those findings. This will be achieved through scientific experimentation, not by further armchair discussion. The methods reported by Francks et al. (2007) were widely used and validated, and applied correctly. The results were described completely, whether supportive of LRRTM1's involvement or not.

DETAILED RESPONSES

In their critique, Crow et al. re-state Crow's single-gene theory for handedness, brain asymmetry, and psychosis. However, this is at odds with genetic epidemiological data, genomewide linkage data, genomewide association data, and data on environmental factors, which have failed to support a single major-gene model in schizophrenia determination in the general patient population (Burmeister et al., 2008). Indeed, in 2008 there has been a rapid accumulation of compelling new data implicating diverse genomic variations, some *de novo*, some inherited, in the pathogenesis of schizophrenia (International Schizophrenia Consortium, 2008; Stefansson et al., 2008; Walsh et al., 2008). These findings have once more underscored the complex and heterogeneous genetic contributions to schizophrenia. The genetic contribution to handedness may overlap to some extent with that of schizophrenia, but again I am unaware of any data to suggest that a single-gene model fits epidemiological data for handedness *better* than oligogenic or other complex-trait models, and the latter seem more likely from a developmental perspective.

There are no previously published data showing linkage or association of the pseudo-autosomal protocadherin gene PCDHXY with handedness, schizophrenia, or brain asymmetry. Neither are there published data to show an epigenetic association of PCDHXY with these traits. In other words, there are no published data, or unpublished data of which I am aware, that show a relationship, within human populations, between variation in PCHDXY and variation in handedness, schizophrenia risk, or brain asymmetry. Such evidence would be a minimum requirement in order to consider PCHDXY as a determining factor for these traits. In contrast, Francks et al. (2007) found such data at LRRTM1, and were therefore accurate in describing this gene as the "first potential genetic influence on human handedness to be identified" (p. 1129), and "the first putative genetic effect on variability in human brain asymmetry" (p. 1129). At the same time, these are cautious and measured statements.

Francks et al. (2007) did not claim that LRRTM1 underlies much of human cognition, behaviour, and emotion. This is misquoting by Crow et al. It was clear in their report that Francks et al. (2007) considered LRRTM1 to be only one potential effect of many on these complex traits. My own feeling

is that it is extremely unlikely that any single gene will be found to underlie all of the population variability in these traits.

The suggestion is made by Crow et al. that a maternally imprinted gene is inconsistent with data on transmission of handedness and schizophrenia in families. However, a maternally imprinted gene might only be inconsistent if one considers that handedness and schizophrenia are caused by variation in a single gene. If one is not bound to the single-gene hypothesis, then there is no reason that a maternally imprinted gene should not be one factor of several, or many, interacting factors. It was clear in Francks et al. (2007) that they considered LRRTM1 to be only one of many factors, and that they did not expect any individual gene to determine the overall pattern of inheritance that is observed for these traits.

The rationale for testing for association under a parent-of-origin model is questioned by Crow et al. However, Francks et al. (2007) made this choice prior to any association testing, on the basis of observations on the pattern of linkage data across the relevant genomic region. Francks et al. (2007) never claimed that the linkage data at 2p12-q11 were significant in a genome-wide context. They only demonstrated that the linkage across this region was driven overwhelmingly by the paternally inherited chromosome (Francks et al., 2003b). This gave a sound rationale for pursuing a putative susceptibility gene at this locus under an imprinted model.

Crow et al. suggest that data implicating LRRTM1 are invalidated by a lack of replication of association with handedness in an Australian sample (Francks et al., 2007). They suggest that Francks et al. (2007) consider Australians to be human in a different way from Europeans. However, one is led to this absurd position only in the narrow context of a single-gene hypothesis. In a multifactorial framework involving genes and environment, non-replication within all study samples of modest size cannot logically invalidate a result (although it does beg questions, as previously discussed in the paper).

The data for imprinting of LRRTM1 are questioned by Crow et al. However, they fail to account for the human lymphoblast cell lines that demonstrated mono-allelic paternal expression in all four informative cell lines tested. The imprinted expression was therefore observed in three independent experimental settings, albeit that it appears complex (as for many other known imprinted genes). Where expression was mono-allelic and the parental origin could be identified (in the cell hybrids and the human lymphoblast cell lines), it was always paternal, thus supporting the characterisation of LRRTM1 as a maternally suppressed gene. (This is the preferred terminology within the imprinting community, including for variably imprinted genes). The preliminary analysis of methylation by Francks et al. (2007) revealed nothing, but only two short candidate sequences within the entire LRRTM1 locus were analysed. In fact, new

data from the Human Epigenome Project (Rakyan et al., 2008) now indicate substantial and tissue-specific methylation within the promoter of LRRTM1, and also a particular profile of methylation in placental tissue, which may be supportive of the imprinting. I therefore recommend comprehensive methylation profiling of this locus as a high-priority experiment in schizophrenia patient and control DNA samples. This experiment has the potential to yield a biomarker of one subtype of schizophrenia that has predictive value.

Crow et al., suggest that a degree of maternal expression of LRRTM1 means that one should expect maternal linkage, though none was observed. However, no data are yet available on imprinting in the human developing brain, which would be necessary to make this judgement. Francks et al. (2007) had only post-mortem, adult brain samples. The key point is that the quantitative trait locus was mapped to LRRTM1 under a parent-of-origin model, then the prediction was made that LRRTM1 was imprinted, and finally this hypothesis was tested with three experimental approaches. The a priori chance that LRRTM1 would show any evidence for imprinting was less than 1 in 1000, based on best estimates of the frequency of imprinted genes in the human genome (and this is including both variably and completely imprinted genes). The maternal imprinting of LRRTM1 was therefore considered as supportive of the association data that led to this gene. There was no loosening of definitions or hypotheses involved.

Crow et al. are right to mention some weak evidence for linkage on chromosome X (although not within the pseudo-autosomal region, and therefore not supportive of Crow's hypothesis). We highlighted and commented on the X linkage in previous papers in our series (Francks et al., 2002, 2003a, 2003b). The evidence is less noteworthy in strength than several autosomal loci, and much weaker than at 2p12-q11.

Several indirect lines of evidence are outlined by Crow et al. in support of an X-Y linked locus in handedness and psychosis. However, nothing in Francks et al. (2007) excludes the possibility of an X-Y linked locus. The results are only inconsistent with such a locus if considered within the narrow context of a single-gene explanation for handedness and psychosis. If one accepts that handedness, brain asymmetry, and schizophrenia are likely to be multifactorial traits, then there is no conflict.

Crow et al. suggest that it is hedging one's bets to treat handedness and schizophrenia as complex, multifactorial traits. However, certainly as regards schizophrenia, this is the natural position that the majority community has come to, on the basis of the majority of genetic epidemiological, linkage, and association data, together with data on environmental influences (Burmeister et al., 2008). If one accepts this, then the core of the critique by Crow et al. melts away.

There is some confusion in Crow et al. about allelic association versus epigenetic variation. Allelic association was found by Francks et al. (2007) with common variation (9% frequency), which indicates an ancestral effect mediated by DNA variation. The paternal nature of this association indicated a maternally imprinted locus, which LRRTM1 turned out to be. Francks et al. (2007) did not claim to have direct evidence that epigenetic variability at this locus is also causally related to the traits, although this remains a plausible and intriguing possibility to pursue, as outlined above.

Crow et al. list a handful of genes that may be involved in human brain evolution, in order to compare them as candidates for causing brain asymmetry and psychosis in human evolution. The logic here is lost on me. FOXP2 was never proposed to be involved in cerebral dominance. The evolution of LRRTM1 has not been investigated thoroughly, and in fact there is evidence for positive selection favouring the disease-protective haplotypes at this locus (Voight, Kudaravalli, Wen, & Pritchard, 2006). Again, from a developmental perspective, it seems naive to think that a change in a single gene could determine all of these complex traits, and there is no compelling evidence for this from human evolutionary data.

In summary, an involvement of LRRTM1 in handedness and schizophrenia is supported by the data described by Francks et al. (2007), as agreed by the reviewers of the original manuscript, and the 40 international co-authors on the report. The LRRTM1 story is now open to the scientific community for further investigation, as is appropriate for any initial observations of this kind. In their critique Crow et al. offer little more than a repetition of a long-standing hypothesis that has failed to accumulate compelling supportive evidence, despite its longevity in the literature. It is time to abandon theoretical dogma and to embrace, with an open mind, the multiple opportunities now available for molecular genetic investigations of behavioural and psychiatric traits.

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