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Editorial commentary: Is LRRTM1 the gene for handedness?

In this issue of *Laterality* we are publishing a paper by Tim Crow and his colleagues which is a critical response to the study that Clyde Francks and 41 colleagues published in July 2007 in *Molecular Psychiatry* (Francks et al., 2007), and we are also publishing a reply by Francks. The 2007 Francks et al. paper received world-wide publicity, most notably on the BBC website, where it was proclaimed, "Gene for left-handedness is found" (news.bbc.co.uk/1/hi/health/6923577.stm). The story was then picked up by a range of international and internet news media (see www.well.ox.ac.uk/monaco/handedness/handednesspressrelease.shtml).

Crow et al. originally submitted their critical comments on the Francks paper to *Molecular Psychiatry* itself, but the editor rejected the critical comments without external review, although Clyde Francks was asked by the editor to comment on them. The editor of *Molecular Psychiatry* has commented to us, "What is missing is the fact that we have a very low acceptance rate, a back log and have been accepting very, very few submissions, including letters and the necessary response."

The commentary by Crow et al., which has been seen by two peer-reviewers, is published here essentially unchanged, apart from minor alterations in format, from the version originally submitted to *Molecular Psychiatry*. We have also provided Francks with the opportunity to reply, and his response is essentially that provided to the editor of *Molecular Psychiatry*, again only with minor formatting changes.

Laterality, along with other journals from the Taylor and Francis group, has recently joined the Committee on Publication Ethics (COPE; see www.publicationethics.org.uk), whose members include the editors of 3500 biomedical journals, and whose primary mission "is to discuss issues related to the integrity of the scientific record". A part of the accepted process is the provision for the publication of pieces critical of published research, because of "the importance of peer review after publication" (www.publicationethics.org.uk/reports/2005/code). *Molecular Psychiatry* is not a member of COPE, and nor is the Nature group of journals of which it is a part (and *Nature* itself has a particular reputation for almost never publishing comments that are critical of the papers it publishes).

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Papers on left-handedness are well known for attracting media attention, with perhaps the most notorious example being the paper published in *Nature* by Halpern and Coren (1988), which claimed that left-handers had shorter life-spans than right-handers—a conclusion that most researchers nowadays accept is probably wrong, although the idea maintains a strong foothold in popular mythology. Whether or not LRRTM1 on chromosome 2p12 is indeed the genetic basis of handedness is still unclear, although the controversy of the claim seems indisputable. The two papers published here help to illuminate the issues, and the strengths and weaknesses of both sides. Ultimately most scientific issues are resolved by further data, and we therefore look forward to the possibility of publishing data from further studies on LRRTM1 that provide a resolution one way or the other.

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REFERENCES

Francks, C., Maegawa, S., Lauren, J., Abrahams, B. S., Velayos-Baeza, A., Medland, S. E., et al. (2007). LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Molecular Psychiatry*, *12*, 1129–1139.

Halpern, D. F., & Coren, S. (1988). Do right-handers live longer? *Nature*, *333*, 213.

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Where and what is the right shift factor or cerebral dominance gene? A critique of Francks et al. (2007)

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Francks et al. (2007, p. 1129) claim to have identified "The first potential genetic influence on human handedness ... and the first putative genetic effect on variability in human brain asymmetry" and a gene "that underlies much of human cognition, behaviour and emotion" (p. 1129). We criticise this claim on the basis that the authors have made unjustified assumptions concerning mode of transmission both of psychosis and relative hand skill, that they have failed to establish a parent of origin effect, and have overlooked previous findings concerning the genetic basis of handedness and asymmetry. We suggest that some of these errors relate to the application of linkage disequilibrium to detect variation that is common in the population and relates to the characteristic that defines the species. While we agree (and indeed first proposed) that the variation underlying psychosis is intrinsically related to the cerebral torque, which we take to be the anatomical basis of language, we are unconvinced by the data for LRRTM1 presented by Francks et al. We consider that a stronger case can be mounted for the Protocadherin11X/Y gene pair located in the hominid specific Xq21.3/Yp11.2 region of homology that was generated by a duplication from the X between 6 and 5 million years ago and that has been subject to a number of chromosomal and sequence changes. This gene pair can account for relationships between relative hand skill and verbal and non-verbal ability that are sex dependent, and morphological changes in the brain in psychosis that reflect interactions between sex and laterality, which are already established in the literature.

Keywords: Handedness; Protocadherin11X/Y gene pair; X-Y homology; LRRTM1; Xq21.3/Yp11.2.

One of us (Crow, 1995, 1997, 2000) has argued that the genetic variation relating to psychosis arose in the transition from a prior hominid to *Homo sapiens* and relates to cerebral asymmetry or the "torque", arguably the feature that is characteristic of the human brain. Where is this "right shift factor" or "cerebral dominance gene"? We have argued that it is on the X and Y chromosomes, and specifically that it is the gene pair ProtocadherinX

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and ProtocadherinY that was created in the course of hominid evolution (Crow, 2002a; Williams, Close, Giouzeli, & Crow, 2006).

In studies including our collected material (DeLisi et al., 2002; Laval et al., 1998) and adopting a traditional linkage and linkage disequilibrium approach Francks et al. (2007) have presented a case that the gene LRRTM1 on chromosome 2 is associated with directional handedness in *Homo sapiens* and contributes variation to common developmental disorders including schizophrenia and dyslexia. They make bold claims that "This is the first potential genetic influence on human handedness to be identified, and the first putative genetic effect on variability in human brain asymmetry" (p. 1129), and that the gene "underlies much of human cognition, behaviour and emotion" and is particularly associated with "cerebral cortical areas related to language perception and production" (p. 1130). We believe these claims to be unjustified by the evidence presented. In particular, the paper illustrates the difficulties faced by linkage and linkage disequilibrium approaches to common human psychological disorders.

The problems are:

1. Francks et al. claim that there is linkage for schizophrenia on 2p12, on the basis of their own ad hoc analysis allowing parent of origin effects (Francks et al., 2003). However, the authors of the original paper, DeLisi et al. (2002), had concluded that the evidence for linkage might well be a chance finding, as it was not replicated in three other studies each with sample sizes in excess of 300 sibling pairs (Crow, 2007).
2. By testing for a maternally imprinted allele in the absence of a prior argument Francks et al. have introduced a new layer of multiple testing. Specifically there is no justification for the assumption that schizophrenia is selectively inherited from the father (Penrose, 1991); in fact, the ratio in favour of maternal transmission is 2:1.
3. The problem with respect to relative hand skill is the same. While Francks et al. have made the assumption that their gene is maternally imprinted, i.e., there is preferential transmission from the father, this is in conflict with the well-known finding that handedness is influenced more by the mother (Annett, 2002).
4. Having "identified" ($p = .00002$!) the gene that they suggest "Underlies much of human cognition, behaviour and emotion" (p. 1129) in a set of siblings with dyslexia, Francks et al. were then unable to find this effect in a set of twins from Australia. Such a gross discrepancy should surely have given the authors cause to pause and think. Is handedness in Australia based on some different genetic mechanism? Or are Australians human in a different way?
5. As primary evidence of differential transmission, Francks et al. relied on hybrid cell lines, which they admit have "certain limitations ... in the

context of imprinting studies'' (p. 1132–1133). Moreover, expression in man was mono-allelic in only 3 out of 18 cases (data not presented) and expression was bi-allelic in both chimps and mice. The authors could find no evidence of differential epigenetic modification between the maternal/paternal alleles. The case for imprinting therefore collapses.

6. Given that the authors found maternal expression in the majority of samples (84%), why did they not predict maternal linkage? The fact that it was not found suggests that, by the authors' logic, variation in LRRTM1 is unrelated to the traits in question.
7. The title says ''LRRTM1 on chromosome 2p12 is a maternally suppressed gene . . .'': the results show the opposite—that the gene is normally expressed bi-allelicly.

In summary, the parent of origin analysis is not only unjustified by the facts of schizophrenia and handedness, but also unsupported by findings in the authors' own data. The authors have extended the boundaries of what is imprinted to include ''relatively inactive'' (by their own calculations 3/18 = 16%) genes (p. 1133) and by the assertion that epigenetic regulation may be present at ''certain locations and time points'' (p. 1136). By these criteria many more genes will be classified as imprinted than the 1 in 1000 that they cite as evidence against the possibility that theirs is a false positive. Elasticity of definition here renders hypothesis testing a joyous prospect as exploited by Francks, 41 co-authors, and the Public Relations group of the Wellcome Trust Centre for Human Genetics.

Francks et al.'s claims with respect to the existing literature are questionable.

1. They claim (p. 1129) their report is ''The first potential genetic influence on human handedness . . . and the first putative genetic effect on variability of human brain asymmetry'' but they have overlooked the papers of Corballis, Lee, McManus, and Crow (1996) and Sun et al. (2005), and indeed the background literature (Annett, 1985, 2002; Corballis, 1997; McManus, 1985) on the genetic transmission of handedness.
2. They omit to note that a weak linkage finding for handedness close to the Xq21.3 region reported by ourselves (Laval et al., 1998) was also seen in their own survey (Francks et al., 2002). Thus the Xq21.3 locus is the only one that has been found by independent groups, although we remain cautious about the interpretation of linkage findings in this field (see below).
3. Their claim that variability in human brain asymmetry ''underlies much of human cognition, behaviour and emotion'' (p. 1129) is unreferenced to relevant work (Crow, Crow, Done, & Leask, 1998;

Peters, Reimers, & Manning, 2006) that reveals interactions between laterality, sex, and verbal and non-verbal ability unexplained by autosomal imprinting.

The authors have overlooked evidence in handedness and cerebral asymmetry suggesting linkage to the sex chromosomes:

1. McKeever (2000) has summarised a body of evidence consistent with X linkage, Corballis et al. (1996) have presented evidence for X and Y linkage in 15,000 families, and concordant evidence has been discussed by Jones and Martin (2000, 2001).
2. The incidence of left-handedness is greater in males (Crow et al., 1998; Peters et al., 2006).
3. There is evidence from sex chromosome aneuploidies for reciprocal deviations in cerebral asymmetry consistent with an X/Y linked gene (Crow, 1993). These syndromes have been shown to have anatomical deviations in structural asymmetry (Rezaie et al., 2004), which suggests an influence across the antero-posterior axis from right frontal to left occipital, and handedness.
4. Bishop et al. (2000) have shown that verbal and spatial memory deficits in Turner's syndrome depend on the sex of the parent. This again suggests that a gene for lateralisation is present on the X chromosome and is subject to epigenetic effects.
5. The structural changes in the brain in psychosis have been found to reflect anomalies of asymmetry (Crow et al., 1989), and in several cases (Highley et al., 1998, 1999, 2003; McDonald et al., 2000) prominent interactions with sex have been recorded. It seems unlikely that these can be explained by any simple parent-of-origin effects.

Francks et al have hedged their bets by postulating that handedness is a complex trait "with several, or many, genetic ... influences" (p. 1137). However, all authorities on the familial transmission of handedness (Annett, 1985; Corballis, 1997, 2001; Klar, 1999; McManus, 1985) are agreed that a single gene will account for the facts. Moreover if, as some evidence in primates suggests (Buxhoeveden, Switala, Litaker, Roy, & Casanova, 2001; McGrew & Marchant, 1997), directional asymmetry on a population basis is simply absent in the chimpanzee and rhesus monkey but present in man, there are a relatively small number of species transitions at which this characteristic might have entered the hominid lineage. Given that asymmetry is an improbable feature, it seems highly unlikely that more than one such gene entered the hominid lineage in the past 6 million years.

Thus on Occam's principle one should consider either that the gene is one of those (Table 1) that have been so far suggested as related to language/

TABLE 1
Characteristics of putative cerebral dominance genes in hominid evolution

Gene	*Will account for a sex difference*	*Expressed in germinal cell layer*	*Cytogenetic change at 6MYA*	*Subsequent change*	*Selective pressure*	*No. of amino acid changes in hominid evolution*	*Radical change in protein structure*
FOXP2 Enard et al. (2002)	no	no	no	no	+ve	2	none
PCDHXY gene pair Crow (2002b); Williams et al. (2006)	yes	yes	Xq21.3 > Yp duplication	3 deletions within the homologous block on Y & a paracentric inversion (undated)	accelerated evolution	PCDHX 5 PCDHY 16	2 new cysteine residues added to PCDHX, 1 closely related to 2 other changes in ectodomain 5
LM04 Sun et al. (2005)	no	yes	no	no	no	0	none
LRRTM1 Francks et al. (2007)	no	n/k	no	no	no	0	none

asymmetry, or that a single gene of major effect remains to be identified. Of the four genes listed, all are expressed in foetal brain. Only LMO4 has been demonstrated, in the strategy by which it was identified, to be asymmetrically expressed. FOXP2 is apparently subject to positive selection and has accumulated two amino acid changes in the hominid lineage. Only the *ProtocadherinX/Y* gene pair will account for a sex difference, through sex linkage. This gene pair has also been subject to radical changes in hominid evolution, with a duplication (giving rise to the gene pair) from Xq21.3-Yp now dated at between 6 and 5 million years ago, with a number of subsequent deletions in the Y transposed region and a paracentric inversion that could be relevant to epigenetic regulation of gene expression. This gene-pair has been subject to 16 amino acid changes in the PCDHY sequence and, critically, to five amino acid changes in PCDHX which had previously been stable in hominid evolution.

We continue to believe that the search for the right shift factor and cerebral dominance gene is important and relevant to both schizophrenia and other psychoses and dyslexia, but are unconvinced by the case that Francks et al. have presented for LRRTM1. Indeed we suggest that the problems they have encountered cast some light on the inconsistencies of linkage studies of psychosis (Crow, 2007) and reading ability (Gayan et al., 2005) in general. In this context we note the curious fact that Francks et al have adopted an approach through linkage disequilibrium, which depends on transmission of sequence variations as founder effects within populations over many generations to detect what they describe (p. 1137) as "epigenetic misregulation" that presumably has a half-life of two or at most three generations before being lost in any population. While it can be argued that genetic linkage is relevant to detecting such variation, linkage disequilibrium clearly is not—it is on a different timescale.

Finally, we urge that the media coverage the authors have solicited should facilitate critical scrutiny of their evidence and of the linkage disequilibrium strategy in general. We believe the errors include (i) the assumption of heterogeneity without independent justification, (ii) inappropriate application of a technique designed to detect rare sequence variants to a problem relating to the population as a whole, (iii) neglect of what is already known about the anatomical and physiological correlates of the disorder in question, and (iv) failure to recognise that psychosis relates to the characteristic that defines *Homo sapiens* as a species and therefore must have been subject to significant change in the course of hominid evolution.

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REFERENCES

Annett, M. (1985). *Left, right, hand and brain: The right shift theory*. Hove, UK: Lawrence Erlbaum Associates Ltd.

Annett, M. (2002). *Handedness and brain asymmetry: The right shift theory*. Hove, UK: Psychology Press.

Bishop, D. V. M., Canning, E., Elgar, K., Morris, E., Jacobs, P. A., & Skuse, D. H. (2000). Distinctive patterns of memory function in subgroups with Turner syndrome: Evidence for imprinted loci on the X-chromosome affecting neurodevelopment. *Neuropsychologia*, *38*, 712–721.

Buxhoeveden, D., Switala, A. E., Litaker, M., Roy, E., & Casanova, M. F. (2001). Lateralization of minicolumns in human planum temporale is absent in nonhuman primate cortex. *Brain Behavior & Evolution*, *57*, 349–358.

Corballis, M. C. (1997). The genetics and evolution of handedness. *Psychological Review*, *104*, 714–727.

Corballis, M. C. (2001). Is the handedness gene on the X chromosome? Comment on Jones and Martin (2000). *Psychological Review*, *108*, 805–810.

Corballis, M. C., Lee, K., McManus, I. C., & Crow, T. J. (1996). Location of the handedness gene on the X and Y chromosomes. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *67*, 50–52.

Crow, T. J. (1993). Sexual selection, Machiavellian intelligence and the origins of psychosis. *Lancet*, *342*, 594–598.

Crow, T. J. (1995). Constraints on concepts of pathogenesis: Language and the speciation process as the key to the etiology of schizophrenia. *Archives of General Psychiatry*, *52*, 1011–1014.

Crow, T. J. (1997). Is schizophrenia the price that Homo sapiens pays for language? *Schizophrenia Research*, *28*, 127–141.

Crow, T. J. (2000). Schizophrenia as the price that Homo sapiens pays for language: A resolution of the central paradox in the origin of the species. *Brain Research Reviews*, *31*, 118–129.

Crow, T. J. (2002a). Handedness, language lateralisation and anatomical asymmetry: Relevance of protocadherinXY to hominid speciation and the aetiology of psychosis. *British Journal of Psychiatry*, *181*, 295–297.

Crow, T. J. (2002b). *The speciation of modern Homo sapiens*. Oxford, UK: Oxford University Press.

Crow, T. J. (2007). How and why genetic linkage has not solved the problem of psychosis: Review and hypothesis. *American Journal of Psychiatry*, *164*, 13–21.

Crow, T. J., Ball, J., Bloom, S. R., Brown, R., Bruton, C. J., Colter, N., et al. (1989). Schizophrenia as an anomaly of development of cerebral asymmetry. A postmortem study and a proposal concerning the genetic basis of the disease. *Archives of General Psychiatry*, *46*, 1145–1150.

Crow, T. J., Crow, L. R., Done, D. J., & Leask, S. J. (1998). Relative hand skill predicts academic ability: Global deficits at the point of hemispheric indecision. *Neuropsychologia*, *36*(12), 1275–1282.

DeLisi, L. E., Shaw, S., Crow, T. J., Shields, G., Smith, A. B., Larach, V. W., et al. (2002). A genome-wide scan for linkage to chromosomal regions in 382 sibling pairs with schizophrenia or schizoaffective disorder. *American Journal of Psychiatry*, *159*, 803–812.

Enard, W., Przeworski, M., Fisher, S. E., Lai, C. S. L., Wiebe, V., Kitano, T., et al. (2002). Molecular evolution of FOXP2, a gene involved in speech and language. *Nature*, *418*, 869–872.

Francks, C., DeLisi, L. E., Shaw, S. H., Fisher, S. E., Richardson, A. J., Stein, J. F., et al. (2003). Parent of origin effects on handedness and schizophrenia susceptibility on chromosome 2p12-q11. *Human Molecular Genetics*, *12*(24), 3225–3230.

Francks, C., Fisher, E. S., McPhie, I. L., Richardson, A. J., Marlow, A. J., Stein, J. F., et al. (2002). Erratum. *American Journal of Medical Genetics*, *70*.

Francks, C., Maegawa, S., Lauren, J., Abrahams, B. S., Velayos-Baeza, A., Medland, S. E., et al. (2007). LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Molecular Psychiatry*, *12*(8), 1–11.

Gayan, J., Willcutt, E. G., Fisher, S. E., Francks, C., Cardon, L. R., Olson, R. K., et al. (2005). Bivariate linkage scan for reading disability and attention-deficit/hyperactivity disorder localises pleitropic loci. *Journal of Child Psychology & Psychiatry*, *46*(10), 1045–1056.

Highley, J. R., DeLisi, L. E., Roberts, N., Webb, J., Relja, M., Razi, K., et al. (2003). Sex-dependent effects of schizophrenia: An MRI study of gyral folding, and cortical and white matter volume. *Psychiatry Research Neuroimaging*, *124*, 11–23.

Highley, J. R., Esiri, M. M., Cortina-Borja, M., McDonald, B., Cooper, S. J., Herron, B., et al. (1998). Anomalies of cerebral asymmetry in schizophrenia interact with gender and age of onset: A post mortem study. *Schizophrenia Research*, *34*, 13–25.

Highley, J. R., Esiri, M. M., McDonald, B., Cortina-Borja, M., Herron, B., Cooper, S. J., et al. (1999). The size and fibre composition of the corpus callosum with respect to gender and schizophrenia: A post mortem study. *Brain*, *122*, 99–110.

Jones, G. V., & Martin, M. (2001). Confirming the X-linked handedness gene as recessive, not additive: Reply to Corballis (2001). *Psychological Review*, *108*, 811–813.

Jones, G. V., & Martin, M. (2000). A note on Corballis (1997) and the genetics and evolution of handedness: Developing a unified distribution model from the sex-chromosomes gene hypothesis. *Psychological Review*, *107*, 213–218.

Klar, A. J. S. (1999). Genetic models for handedness, brain lateralization, schizophrenia and manic-depression. *Schizophrenia Research*, *39*, 207–218.

Laval, S. H., Dann, J., Butler, R. J., Loftus, J., Rue, J., Leask, S. J., et al. (1998). Evidence for linkage to psychosis and cerebral asymmetry (relative hand skill) on the X chromosome. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *81*, 420–427.

McDonald, B., Highley, J. R., Walker, M. A., Herron, B., Cooper, S. J., Esiri, M. M., et al. (2000). Anomalous asymmetry of fusiform and parahippocampal gyrus grey matter in schizophrenia: A post-mortem study. *American Journal of Psychiatry*, *157*(1), 40–47.

McGrew, W. C., & Marchant, L. F. (1997). On the other hand: Current issues in and meta-analysis of the behavioral laterality of hand function in nonhuman primates. *Yearbook of Physical Anthropology*, *40*, 201–232.

McKeever, W. F. (2000). A new family handedness sample with findings consistent with X-linked transmission. *British Journal of Psychology*, *91*, 21–39.

McManus, I. C. (1985). Handedness, language dominance and aphasia: A genetic model. Psychological Medicine. *Monograph Supplement*, *8*, 1–40.

Penrose, L. S. (1991). Survey of cases of familial mental illness. *European Archives of Psychiatry and Neurological Science*, *240*, 314–324.

Peters, M., Reimers, S., & Manning, J. T. (2006). Hand preference for writing and associations with selected demographic and behavioral variables in 255,100 subjects: The BBC Internet study. *Brain & Cognition*, *62*, 177–189.

Rezaie, R., Roberts, N., Cutter, W. J., Murphy, D. C. M., Robertson, D. M. W., Daly, E. M., et al. (2004). Anomalous asymmetry in Turner's and Klinefelter's syndromes: Further evidence for X-Y linkage of the cerebral dominance gene. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *130B*(1), 102–103.

Sun, T., Patoine, C., Abu-Khalil, A., Visvader, J., Sum, E., Cherry, T. J., et al. (2005). Early asymmetry of gene transcription in embryonic human left and right cerebral cortex. *Science*, *308*(5729), 1794–1798.

Williams, N. A., Close, J., Giouzeli, M., & Crow, T. J. (2006). Accelerated evolution of Protocadherin11X/Y: A candidate gene-pair for cerebral asymmetry and language. *American Journal of Medical Genetics (Neuropsychiatric Genetics)*, *141B*, 623–633.

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

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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

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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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REFERENCES

Burmeister, M., McInnis, M. G., & Zollner, S. (2008). Psychiatric genetics: Progress amid controversy. *Nature Reviews Genetics*, *9*, 527–540.

Crow, T. J., Close, J. P., Dagnall, A. M., & Priddle, T. H. (2009). Where and what is the right shift factor or cerebral dominance gene? A critique of Francks et al. (2009). *Laterality*, *14*, 3–10.

Francks, C., DeLisi, L. E., Fisher, S. E., Laval, S. H., Rue, J. E., Stein, J. F., et al. (2003a). Confirmatory evidence for linkage of relative hand skill to 2p12-q11. *American Journal of Human Genetics*, *72*, 499–502.

Francks, C., DeLisi, L. E., Shaw, S. H., Fisher, S. E., Richardson, A. J., Stein, J. F., et al. (2003b). Parent-of-origin effects on handedness and schizophrenia susceptibility on chromosome 2p12-q11. *Human Molecular Genetics*, *12*, 3225–3230.

Francks, C., Fisher, S. E., MacPhie, I. L., Richardson, A. J., Marlow, A. J., Stein, J. F., et al. (2002). A genomewide linkage screen for relative hand skill in sibling pairs. *American Journal of Human Genetics*, *70*, 800–805.

Francks, C., Maegawa, S., Lauren, J., Abrahams, B. S., Velayos-Baeza, A., Medland, S. E., et al. (2007). LRRTM1 on chromosome 2p12 is a maternally suppressed gene that is associated paternally with handedness and schizophrenia. *Molecular Psychiatry*, *12*, 1129–1139.

International Schizophrenia Consortium. (2008). Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature*, *455*(7210), 237–241.

Rakyan, V. K., Down, T. A., Thorne, N. P., Flicek, P., Kulesha, E., Graf, S., et al. (2008). An integrated resource for genome-wide identification and analysis of human tissue-specific differentially methylated regions (tDMRs). *Genome Research*, *18*, 1518–1529.

Stefansson, H., Rujescu, D., Cichon, S., Pietilinen, O. P. H., Ingason, A., Steinberg, S., et al. (2008). Large recurrent microdeletions associated with schizophrenia. *Nature*, *455*(7210), 232–236.

Voight, B. F., Kudaravalli, S., Wen, X., & Pritchard, J. K. (2006). A map of recent positive selection in the human genome. *PLoS Biology*, *4*, e72.

Walsh, T., McClellan, J. M., McCarthy, S. E., Addington, A. M., Pierce, S. B., Cooper, G. M., et al. (2008). Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science*, *320*, 539–543.