REVIEW ARTICLE

Search for missing schizophrenia genes will require a new developmental neurogenomic perspective

H. B. KIRAN KUMAR, CHRISTINA CASTELLANI, SUJIT MAITI, RICHARD O'REILLY and SHIVA M. SINGH*

Molecular Genetics Unit, Department of Biology and Psychiatry, University of Western Ontario, London, Ontario, Canada N6A 5B7

Abstract

Even the most powerful experimental designs in search of genetic causes of schizophrenia have not met the desired goal. It is imperative to review the reasons for such an outcome and to formulate novel strategies for the future direction of this research in the new era of individual genomes. Here, we will review aspects of neurodevelopmental hypothesis of schizophrenia in the light of novel genomic and epigenomic insights. Specifically, we will argue for the involvement of *de novo* mutations and epigenetic modifications during neurodevelopment that may result in schizophrenia. Our conclusion is that the successful elucidation of hereditary mechanisms in neuropsychiatric disorders must begin with attention to discrete endophenotypes; consideration of ontogeny, forethought of genome structure including temporal and spatial patterns of (epi) mutations and the use of judicious techniques that go beyond association studies.

[Kiran Kumar H. B., Castellani C., Maiti S., O'Reilly R. and Singh S. M. 2013 Search for missing schizophrenia genes will require a new developmental neurogenomic perspective. *J. Genet.* **92**, 335–340]

Introduction

Schizophrenia is one of the most devastating mental disorders. Its diagnosis relies on the diagnostic and statistical manual of mental disorders (DSM), which combines a set of distinguishing features, some distinct and others subjective. Although there is no biological marker, in most cases diagnosis is fairly reliable, particularly when there is evidence of a family history. In fact, family history of schizophrenia is the strongest single indicator of an individual's risk for schizophrenia (Mortensen *et al.* 2010). For example, an identical twin of a patient with schizophrenia has the greatest risk, 40–50% concordance (Gottesman 1991) and a child whose parent has schizophrenia has about a 10% chance as compared to the risk in the general population of about 1% (Perala *et al.* 2007). This realization has rationalized the extensive focus on genetics in schizophrenia research. The emphasis on genetic research on this disease has been further fueled by advances in genomic technologies and their celebrated successes with ever increasing number of diseases and disorders. Unfortunately, despite extensive efforts, the outcome of genetic research on schizophrenia has been less than satisfactory, even though the published results have identified a number of critical genomic regions and importance of epigenetic as well as environmental factors in the development of schizophrenia. Despite these, two questions remain paramount. First, what gene(s) or environmental factor(s) cause schizophrenia? Second, why have we not succeeded in the identification of any genes or environmental causes of this common mental disease? We may add that this disappointment is not because of lack of resources, worldwide interest and attempt. The schizophrenia genetic research community has tried almost all experimental methods and approaches available and a chronological assessment of this research points to a pattern. One way to describe this pattern is to quote Yogi Berra, 'when you come to a fork in the road, take it!'

We also realize that such perceptions are often in the eye of the beholder. Genetic studies on schizophrenia over the years have for the most part followed the developments made in single gene diseases. These have included research involving association (Bergen and Petryshen 2012), linkage (Kohn and Lerer 2002), candidate gene (Schwab and Wildenauer 2009), chromosomal aberration (Bassett 1992), fragile site (Garofalo *et al.* 1993), anticipation (Bassett and Husted 1997), triplet repeat expansions (O'Donovan *et al.* 1995), positional cloning (Karayiorgou and Gogos 2006), epigenetics (Petronis *et al.* 1999), genomewide scan (Levinson

*For correspondence. E-mail: ssingh@uwo.ca.

Keywords. schizophrenia; neurodevelopment; differentiation; *de novo* mutations and epimutations (DNM/DNeM).

et al. 1998) and copy number variation (Kirov 2010) studies interspersed with reports of naturally occurring and genetically modified animal models. It is natural to recall the excitement associated with a number of these publications in very high impact journals with fan fare over the past four decades. Clearly, they were viewed as major breakthroughs and each provided new hope for the future. Unfortunately most of these hopes have not yielded desired advances and the question 'why have we not succeeded in identification of any of the genes or environmental causes of this disease?' must take priority. It is not only logical, but also timely. Consequently we will address three questions. What do we know about the genetic causes of schizophrenia? Why have we not seen any significant breakthrough? And finally, what is needed to make progress?

What do we know?

Over 40 years of research has established that a number of genomic regions and genes (http://www.schizophreniaforum.org/res/sczgene/default.asp), most with relatively small effects, may be involved in schizophrenia (Allen *et al.* 2008). Further, a number of rare variants of major effect (ISC 2008, International schizophrenia consortium pngu.mgh.harvard.edu/isc/; Walsh *et al*. 2008) may be responsible for a relatively small proportion of cases. Also, results of a meta-analysis that included genome-wide association study (GWAS) results from over 8000 cases of SCZ and 19,000 controls have identified an association between SCZ and (single nucleotide polymorphism) SNPs in or close to the major histocompatibility complex (MHC) on chromosome 6. The results have offered further speculation that SCZ may be a response to infection (O'Reilly and Singh 1996) which provides a foundation for the role of gene–environment interactions. Such results follow Deb-Rinker *et al.* (1999, 2002) who isolated and identified human endogenous retrovirus (HERV) sequences from the DNA of affected members of monozygotic twin pairs discordant for SCZ, and Karlsson *et al.* (2001) who reported the presence of the HERV-W family of endogenous retroviruses in the cerebrospinal fluid from patients with schizophrenia. Further, a recent study has independently shown an association of rs1051788, an exonic polymorphism of the MHC class I polypeptide-related sequence B (*MICB*) gene, with herpes simplex virus (HSV1) seropositivity, *Toxoplasma gondii* (Nimgaonkar and Yolken 2012) as well as risk for schizophrenia (Prasad *et al.* 2010).

An overall conclusion from these results is that a large number of genes belonging to different pathways, each with relatively small effects are involved in the aetiology of schizophrenia. Some of the primary pathways involved include neurodevelopment, neurogenesis, neurophysiology including signalling, apoptosis and stress responses. They suggest heterogeneity of causation even within a single family, a finding that poses complication for genetic analysis. Further, some but not all of these genes may either offer protection or sensitivity to environmental conditions including viruses that may affect neurodevelopment or neurophysiology. Involvement of viruses, particularly retroviruses may be attractive in expediting new mutations by insertional mutagenesis, given the preponderance of repetitive retroviral related sequences in the human genome (Beck *et al.* 2010; Huang *et al.* 2010; Iskow *et al.* 2010). Low copy repeats at the human *VIPR2* gene predispose to recurrent and nonrecurrent rearrangements (Beri *et al.* 2013). Besides, a number of other environmental factors that may contribute to the development of schizophrenia include maternal malnutrition (Markham and Koenig 2011), trauma (Alvarez *et al.* 2011), oxidative stresses (Gawryluk *et al.* 2011) and xenobiotics (Dutheil *et al.* 2008). Most of these point to abnormalities during neurodevelopment and function among other upstream effects. Study by Talkowski *et al.* (2012) suggest that some neurodevelopmental genes are sensitive to perturbation by multiple mutational mechanisms, leading to variable pheno-typic outcomes that manifest at different life stages. Further, parent-of-origin specific genetic factors associated with brain morphology may provide yet another important variable in schizophrenia (Pidsley *et al.* 2012).

Why have we not identified any schizophrenia causal gene(s)?

The successful search for disease genes is based on a number of prerequisites. These include reliable diagnostic methods, an appropriate genetic model, suitable biological material, informative technology and an insight in the biological system affected. We suggest that most research on the search for schizophrenia causing gene(s) has not met most/all such prerequisites. For example, most DNA collections used in schizophrenia research represent diagnosis by a number of clinicians over time. Even small family collections may vary in diagnostic heterogeneity including age of onset and potential for phenocopy (Lescai and Franceschi 2010). The result is that the patients studied in most studies do not represent a homogeneous group. This heterogeneity is complicated by unrealistic or less than satisfactory genetic models. For example, most genetic models tested do not accommodate for the reduced (48%) discordance of monozygotic twins or gene × environment interactions. Not surprisingly, there is an ongoing debate over whether the functional variation carried by an individual is likely to be comprised of a large number of common variants interacting with each other and the environment or a smaller number of rare variants with more dramatic effects (Bodmer and Bonilla 2008), with no consensus. Given the complexity of causations, one may argue that an effective approach to identify causal genes may be based on the analysis of transcriptome and epigenome. Unfortunately, suitable samples of human brain needed for such studies are not available, forcing researchers to use indirect approaches. These may include RNA and DNA from blood, transformed lines and postmortal

brain tissues. The assumption is that the DNA from any tissue source including transformed cell lines will be identical to the affected brain and brain regions. However, this may or may not be the case, as the development of the human neural system is poorly understood. Availability of suitable brain regions will go a long way in alternative studies. This lack of biological material among the other issues noted here adds unreliability at every step and has likely contributed to lack of success in research on schizophrenia genetics. Additional complications to the genetic model include a number of recent reports. First, allele-biased expression in differentiating human neurons has been implicated in the aetiology of many neuropsychiatric disorders (Lin *et al.* 2012). Second, there is increasing evidence for the importance of father's age to disease risk and the rate of *de novo* mutations (Kong *et al.* 2012). Third, cerebral asymmetry in shown to play an important role in the organization of the brain and its possible implication in neurodevelopmental and psychiatric conditions (Rentería 2012). Also, runs of homozygosity implicate autozygosity as a schizophrenia risk factor. Such a bias towards recessivity suggests that alleles that increase the risk of schizophrenia have been selected against over evolutionary time (Keller *et al.* 2012). Finally, mRNA editing in schizophrenia or bipolar disorder can add further noise to the gene hunting exercise.

What do we need to move forward?

Schizophrenia is a neurodevelopmental disorder (Altamura *et al.* 2013) or collection of neurodevelopmental disorders (Insel 2010). This is supported by epidemiological (Jablensky 2010; Stilo and Murray 2010); imaging (Fitzsimmons *et al.* 2013) and psychological results (Cannon *et al.* 2000). This demands that we understand normal developmental processes in order to identify any underlying causes. What is also known is that changes at different stages including early insults may affect brain development and cause schizophrenia (Andreasen 2010). However, the assumption that brain development is similar to other developmental systems may not be true. In fact, there are reasons to argue that brain development and differentiation may involve unusual cellular processes. For example, there is some evidence for genomic mosaicism in the proliferating cerebellum. It may involve nondisjunction leading to aneuploidy and a significant proportion (20%) of neural and glial cells may be aneuploids as a result (Westra *et al.* 2008). Further, neural progenitor cells may preferentially undergo transpositions in the hippocampus and other regions of brain (Coufal *et al.* 2009). Needless to say, these alterations will have a direct effect on gene expression and directly affect the pathway involved. Further, such processes appear to be brain specific and programmed, and not just accidental, making neurodevelopment a special and unusual case as compared to the development of most other organ systems. Also important in this context are genomic *de novo* mechanisms that may lead to mosaicism. One such mechanism is copy number variation (CNVs). Maiti *et al.* (2011) have established that *de novo* CNVs are common during ontogeny. CNV events, if operational during preimplantation development, may make resulting monozygotic twins discordant (Christin Catellani, Richard O'Reilly, Suhith Maiti, Kiran Kumar H.B. and Shiva M. Singh, unpublished observations). Genomic exploration of monozygotic twins discordant (MZD) for schizophrenia uncovers *de novo* mutations (DNM) and reveals candidate genes (Christin Catelllani, Richard O'Reilly, Suhith Maiti, Kiran Kumar H.B. and Shiva M. Singh, unpublished observations). Further, if operational during foetal development, they may generate mosaics at the level of the individual or within a given organ system. In conclusion, there is enough evidence to argue that genetic changes in the form of *de novo* mutations resulting in genomic discordance in monozygotic twins or variable mosaicism across individuals may be common during neurodevelopment.

Also significant in the context of brain development is the phenomenon of epigenetics. To this end, some of the genetic alterations discussed above may cause changes in epigenetic status. This variation will contribute to increased variability for a phenotype (Feinberg and Irizarry 2010), including phenotypic extremes. Indeed epigenetic changes, such as DNA methylation and histone modifications that control higher order DNA structure and gene expression are involved in several neurodevelopmental disorders including Rett syndrome (Shahbazian and Zoghbi 2001) and fragile-X syndrome (Warren 2007). In fact epigenetics, CNVs and other molecular mechanisms underlying neurodevelopment have been implicated in a number of neurodevelopmental disabilities (Gropman and Batshaw 2010). A special feature of the epigenetic changes is that they are prone to a variety of environmental factors. These may include infection (Depino 2006), stress (Grizenko *et al.* 2008), drugs and chemicals including alcohol, diet and nutrition among others (Wade and Archer 2006; Zhang and Meaney 2010). The emerging research on the subject is captivating. For example, Weaver *et al*. (2004) showed that maternal care has a direct effect on the methylation of the promoter of the glucocorticoid receptor gene in rat pups. Here the neglect of pups by the mother causes changes in DNA methylation of the gene promoter leading to its silencing and directly affecting the hypothalamus–pituitary–adrenal (HPA) axis. Ultimately, this change is reflected in behavioural abnormalities, which could be reversed by altering histone acetylation using an inhibitor trichostatin A (TSA), a histone deacetylase (HDAC). Such results argue for a direct effect of environmental factors on neurodevelopment. Further, these changes are stable over the lifetime and may be passed on transgenerationally (Youngson and Whitelaw 2008). Interestingly, comparable results on humans have begun to emerge and implicate epigenetic mechanisms in brain and behaviours. Given that most of these effects are complex and involve multiple genes and pathways, individuals are expected to vary in resilience due to genetic as well as nongenetic factors. Indeed a number of researchers have begun to

explore epigenetic mechanisms in schizophrenia and related disorders. What is needed is to include aspects of epigenetics in ongoing studies on genomics.

Conclusion

The search for genetic determinants of most brain disorders including schizophrenia remains a major scientific challenge. Taking short cuts in genetic models, mutational mechanisms, epigenetic features, biological material, clinical homogeneity and a better understanding of neurodevelopment may not yield desired results. Undertaking more of the same with ever increasing number alone will not assure success. A real success will require a new thinking. Here, clearly defined longitudinal endophenotype(s) would offer a unique 'window' into the aberrant trajectory and an opportunity to track the pathway(s) involved. Towards this end, several endophenotypes have been suggested for schizophrenia that reflect the neurodevelopment paradigm, including minor physical anomalies (Compton *et al.* 2011), visual masking (Chkonia *et al.* 2010); antisaccades and smooth pursuit eye movements (Schmechtig *et al.* 2010). Finally, the genetic, epigenetic and phenotypic features are best assessed in the context of evolutionary adaptation of the brain that may favour variation beyond what is inherent in genes. Consequently, it may incorporate additional programmed *de novo* changes involving the genome and epigenome. Logically, *de novo* genomic changes of immediate effect will involve structural variations including transpositions while epigenomic changes may begin with DNA methylation. Both mechanisms will directly affect gene expression and participate in phenotypic outcomes that will respond to adaptive pressures. As it stands, current models of genetic analysis assume stability of the genome. They do not accommodate common and programmed *de novo* changes that may be a special feature of neurodevelopment.

We recognize that it is one thing to identify a problem, but developing solutions(s) that are practical and feasible are a different matter altogether. We may add that some but not all issues presented here could be at least partially accommodated by focussing on monozygotic twins that are concordant and discordant for such disorders including schizophrenia. The use of monozygotic twins will reduce the extensive genetic as well as phenotypic heterogeneity. Also, they often have similar trajectories, environment and the complexity of causation. It will enable consideration of the role of ontogeny and offer the opportunity to make genotype–phenotype correlations as well as gene-by-environment interactions. Also, a well-planned experiment with twins will allow the potential to trace epigenetic features as well as *de novo* mutations. Such studies however will require a strategic change in our experimental design. Rather than assessment of restricted number of genetic and epigenetic markers and the averaging their effect on ever increasing number of heterogeneous patients and controls, we will have to focus on exhaustive longitudinal assessment of development, complete genome sequence, complete epigenomics, environment and phenotype on a relatively small number of judiciously selected twins that are concordant and discordant for the disorders. Recent results on CNVs on monozygotic twins discordant for schizophrenia support this strategy (Singh *et al.* 2009; Maiti *et al.* 2011). This will provide a new approach to the understanding of the role of stable as well as dynamic (including random) changes during neurodevelopment of near identical genotypes that may offer differential predisposition to the development of mental disorders including schizophrenia. The results will be twin or individual specific and will not apply to all patients. However, follow up studies with a proven approach could be applied to increasing number of twin pairs towards a more comprehensive understanding of causations of such highly heterogeneous disorders.

Acknowledgements

This research was supported by grants from Canadian Institute of Health Research, Ontario Mental Health Foundation and Schizophrenia Society of Ontario to Prof. Shiva Singh and Dr Richard O'Reilly.

References

Allen N. C., Bagade S., McQueen M. B., Ioannidis J. P., Kavvoura F. K., Khoury M. J. *et al.* 2008 Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the SzGene database. *Nat. Genet.* **40**, 827–834.

Altamura A. C., Pozzoli S., Fiorentini A. and Dell'osso B. 2013 Neurodevelopment and inflammatory patterns in schizophrenia in relation to pathophysiology. Prog Neuropsychopharmacol. *Biol. Psychiatr.* **42**, 63–70.

Alvarez M. J., Roura P., Osés A., Foguet Q., Solà J. and Arrufat F. X. 2011 Prevalence and clinical impact of childhood trauma in patients with severe mental disorders. *J. Nerv. Ment. Dis.* **199**, 156–161.

Andreasen N. C. 2010 The lifetime trajectory of schizophrenia and the concept of neurodevelopment. *Dialogues Clin. Neurosci.* **12**, 409–415.

Bassett A. S. 1992 Chromosomal aberrations and schizophrenia. *Autosomes. Br. J. Psychiatr.* **161**, 323–334.

Bassett A. S. and Husted J. 1997 Anticipation or ascertainment bias in schizophrenia? Penrose's familial mental illness sample. *Am. J. Hum. Genet.* **60**, 630–637.

Beck C. R., Collier P., Macfarlane C., Malig M., Kidd J. M., Eichler E. E. *et al.* 2010 LINE-1 retrotransposition activity in human genomes. *Cell* **141**, 1159–1170.

Bergen S. E. and Petryshen T. L. 2012 Genome-wide association studies of schizophrenia: does bigger lead to better results? *Curr. Opin. Psychiatr.* **25**, 76–82.

Beri S., Bonaglia M. C. and Giorda R. 2013 Low-copy repeats at the human VIPR2 gene predispose to recurrent and nonrecurrent rearrangements. *Eur. J. Hum. Genet.* **21**, 757–761.

Bodmer W. and Bonilla C. 2008 Common and rare variants in multifactorial susceptibility to common diseases. *Nat. Genet.* **40**, 695–701.

Cannon T. D., Huttunen M. O., Lonnqvist J., Tuulio-Henriksson A., Pirkola T., Glahn D. *et al.* 2000 The inheritance of neuropsychological dysfunction in twins discordant for schizophrenia. *Am. J. Hum. Genet.* **67**, 369–382.

Chkonia E., Roinishvili M., Makhatadze N., Tsverava L., Stroux A., Neumann K. *et al.* 2010 The shine-through masking paradigm is a potential endophenotype of schizophrenia. *PLoS ONE* **5**, e14268.

Compton M. T., Chan R. C., Walker E. F. and Buckley P. F. 2011 Minor physical anomalies: potentially informative vestiges of fetal developmental disruptions in schizophrenia. *Int. J. Dev. Neurosci.* **29**, 245–250.

Coufal N. G., Garcia-Perez J. L., Peng G. E., Yeo G. W., Mu Y., Lovci M. T. *et al.* 2009 L1 retrotransposition in human neural progenitor cells. *Nature* **460**, 1127–1131.

Deb-Rinker P., Klempan T. A., O'Reilly R. L., Torrey E. F. and Singh S. M. 1999 Molecular characterization of a MSRV-like sequence identified by RDA from monozygotic twin pairs discordant for schizophrenia. *Genomics* **61**, 133–144.

Deb-Rinker P., O'Reilly R. L., Torrey E. F. and Singh S. M. 2002 Molecular characterization of a 2.7-kb, 12q13-specific, retroviral-related sequence isolated by RDA from monozygotic twin pairs discordant for schizophrenia. *Genome* **45**, 381–390.

Depino A. M. 2006 Maternal infection and the offspring brain. *J. Neurosci.* **26**, 7777–7778.

Dutheil F., Beaune P. and Loriot M. A. 2008 Xenobiotic metabolizing enzymes in the central nervous system: Contribution of cytochrome P450 enzymes in normal and pathological human brain. *Biochimie* **90**, 426–436.

Feinberg A. P. and Irizarry R. A. 2010 Evolution in health and medicine Sackler colloquium: Stochastic epigenetic variation as a driving force of development, evolutionary adaptation, and disease. *Proc. Natl. Acad. Sci. USA* **1**, 1757–1764.

Fitzsimmons J., Kubicki M. and Shenton M. E. 2013 Review of functional and anatomical brain connectivity findings in schizophrenia. *Curr. Opin. Psychiatr.* **26**, 172–187.

Garofalo G., Ragusa R. M., Argiolas A., Scavuzzo C., Spina E. and Barletta C. 1993 Evidence of chromosomal fragile sites in schizophrenic patients. *Ann. Genet.* **36**, 132–135.

Gawryluk J. W., Wang J. F., Andreazza A. C., Shao L. and Young L. T. 2011 Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int. J. Neuropsychopharmacol.* **14**, 123–130.

Gottesman I. 1991 *Schizophrenia genesis: the origins of madness*. W. H. Freeman, New York, USA.

Grizenko N., Shayan Y. R., Polotskaia A., Ter-Stepanian M. and Joober R. 2008 Relation of maternal stress during pregnancy to symptom severity and response to treatment in children with ADHD. *J. Psychiatr. Neurosci.* **33**, 10–16.

Gropman A. L. and Batshaw M. L. 2010 Epigenetics, copy number variation, and other molecular mechanisms underlying neurodevelopmental disabilities: new insights and diagnostic approaches. *J. Dev. Behav. Pediatr.* **31**, 582–591.

Huang C. R., Schneider A. M., Lu Y., Niranjan T., Shen P., Robinson M. A. *et al.* 2010 Mobile interspersed repeats are major structural variants in the human genome. *Cell* **141**, 1171–1182.

Insel T. R. 2010 Rethinking schizophrenia. *Nature* **468**, 187–193.

Iskow R. C., McCabe M. T., Mills R. E., Torene S., Pittard W. S., Neuwald A. F. *et al.* 2010 Natural mutagenesis of human genomes by endogenous retrotransposons. *Cell* **141**, 1253–1261.

Jablensky A. 2010 The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues Clin. Neurosci.* **12**, 271–287.

Karayiorgou M. and Gogos J. A. 2006 Schizophrenia genetics: uncovering positional candidate genes. *Eur. J. Hum. Genet.* **14**, 512–519.

Karlsson H., Bachmann S., Schröder J., McArthur J., Torrey E. F. and Yolken R. H. 2001 Retroviral RNA identified in the cerebrospinal fluids and brains of individuals with schizophrenia. *Proc. Natl. Acad. Sci. USA* **98**, 4634–4639.

Keller M. C., Simonson M. A., Ripke S., Neale B. M., Gejman P. V., Howrigan D. P. *et al.* 2012 Schizophrenia psychiatric genome-wide association study Consortium. Runs of homozygosity implicate autozygosity as a schizophrenia risk factor. *PLoS Genet.* **4**, e1002656.

Kirov G. 2010 The role of copy number variation in schizophrenia. *Expert. Rev. Neurother.* **10**, 25–32.

Kohn Y. and Lerer B. 2002 Genetics of schizophrenia: a review of linkage findings. *Isr. J. Psychiatry Relat. Sci.* **39**, 340–351.

Kong A., Frigge M. L. and Masson G. 2012 Rate of de novo mutations and the importance of father's age to disease risk. *Nature* **488**, 471–571.

Lescai F. and Franceschi C. 2010 The impact of phenocopy on the genetic analysis of complex traits. *PLoS ONE* **5**, e11876.

Levinson D. F., Mahtani M. M., Nancarrow D. J., Brown D. M., Kruglyak L., Kirby A. *et al.* 1998 Genome scan of schizophrenia. *Am. J. Psychiatr.* **155**, 741–750.

Lin M., Hrabovsky A., Pedrosa E., Wang T., Zheng D. and Lachman H. M. 2012 Allele-biased expression in differentiating human neurons: implications for neuropsychiatric disorders. *PLoS ONE* **7**, e44017.

Maiti S., Kumar K. H., Castellani C. A., O'Reilly R. and Singh S. M. 2011 Ontogenetic de novo copy number variations (CNVs) as a source of genetic individuality: studies on two families with MZD twins for schizophrenia. *PLoS ONE* **6**, e17125.

Markham J. A. and Koenig J. I. 2011 Prenatal stress: role in psychotic and depressive diseases. *Psychopharmacology* **214**, 89–106.

Mortensen P. B., Pedersen M. G. and Pedersen C. B. 2010 Psychiatric family history and schizophrenia risk in Denmark: which mental disorders are relevant? *Psychol. Med.* **40**, 201–210.

Nimgaonkar V. L. and Yolken R. H. 2012 Neurotropic infectious agents and cognitive impairment in schizophrenia. *Schizophr. Bull.* **38**, 1135–1136.

O'Donovan M. C., Guy C., Craddock N., Murphy K. C., Cardno A. G. and Jones L. A. *et al.* 1995 Expanded CAG repeats in schizophrenia and bipolar disorder. *Nat. Genet.* **10**, 380–381.

O'Reilly R. L. and Singh S. M. 1996 Retroviruses and schizophrenia revisited. *Am. J. Med. Genet.* **67**, 19–24.

Perala J., Suvisaari J., Saarni S. I., Kuoppasalmi K., Isometsa E., Pirkola S. *et al.* 2007 Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch. Gen. Psychiatr.* **64**, 19–28.

Petronis A., Paterson A. D. and Kennedy J. L. 1999 Schizophrenia: an epigenetic puzzle? *Schizophr. Bull.* **25**, 639–655.

Pidsley R., Dempster E., Troakes C., Al-Sarraj S. and Mill J. 2012 Epigenetic and genetic variation at the IGF2/H19 imprinting control region on 11p15.5 is associated with cerebellum weight. *Epigenetics* **7**, 155–163.

Prasad K. M., Bamne M. N., Shirts B. H., Goradia D., Mannali V., Pancholi K. M. *et al.* 2010 Grey matter changes associated with host genetic variation and exposure to herpes simplex virus 1 (HSV1) in first episode schizophrenia. *Schizophr Res.* **118**, 232–239.

Rentería M. E. 2012 Cerebral asymmetry: a quantitative, multifactorial, and plastic brain phenotype. *Twin Res. Hum. Genet.* **15**, 401–413.

Schmechtig A., Vassos E., Kumari V., Hutton S. B., Collier D. A., Morris R. G. *et al.* 2010 Association of Neuregulin 1 rs3924999 genotype with antisaccades and smooth pursuit eye movements. *Genes Brain Behav.* **9**, 621–627.

Schwab S. G. and Wildenauer D. B. 2009 Update on key previously proposed candidate genes for schizophrenia. *Curr. Opin. Psychiatr.* **22**, 147–153.

Shahbazian M. D. and Zoghbi H. Y. 2001 Molecular genetics of Rett syndrome and clinical spectrum of MECP2 mutations. *Curr. Opin. Neurol.* **14**, 171–176.

Singh S. M., Castellani C. A. and O'Reilly R. L. 2009 Copy number variation showers in schizophrenia: an emerging hypothesis. *Mol. Psychiatr.* **14**, 356–358.

Stilo S. A. and Murray R. M. 2010 The epidemiology of schizophrenia: replacing dogma with knowledge. *Dialogues Clin. Neurosci.* **12**, 305–315.

Talkowski M. E., Rosenfeld J. A., Blumenthal I., Pillalamarri V., Chiang C., Heilbut A. *et al.* 2012 Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries. *Cell* **149**, 525–537.

Wade P. A. and Archer T. K. 2006 Epigenetics: environmental instructions for the genome. *Environ. Health Perspect.* **114**, 140–141.

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.

Warren S. T. 2007 The epigenetics of fragile X syndrome. *Cell Stem Cell* **1**, 488–489.

Weaver I. C., Cervoni N., Champagne F. A., D'Alessio A. C., Sharma S., Seckl J. R. *et al*. 2004 Epigenetic programming by maternal behavior. *Nat. Neurosci.* **7**, 847–854.

Westra J. W., Peterson S. E., Yung Y. C., Mutoh T., Barral S. and Chun J. 2008 Aneuploid mosaicism in the developing and adult cerebellar cortex. *J. Comp. Neurol.* **507**, 1944–1951.

Youngson N. A. and Whitelaw E. 2008 Transgenerational epigenetic effects. *Annu. Rev. Genomics Hum. Genet.* **9**, 233–257.

Zhang T. Y. and Meaney M. J. 2010 Epigenetics and the environmental regulation of the genome and its function. *Annu. Rev. Psychol.* **61**, 439–466.

Received 27 February 2013, in final revised form 23 April 2013; accepted 29 April 2013
Published on the Web: 6 August 2013