The Sex Chromosome Hypothesis of Schizophrenia: Alive, Dead, or Forgotten? A Commentary and Review

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Abstract

The X chromosome has long been an intriguing site for harboring genes that have importance in brain development and function. It has received the most attention for having specific genes underlying the X-linked inherited intellectual disabilities, but has also been associated with schizophrenia in a number of early studies. An X chromosome hypothesis for a genetic predisposition for schizophrenia initially came from the X chromosome anomaly population data showing an excess of schizophrenia in Klinefelter's (XXY) males and triple X (XXX) females. Crow and colleagues later expanded the X chromosome hypothesis to include the possibility of a locus on the Y chromosome and, specifically, genes on X that escaped inactivation and are X-Y homologous loci. Some new information about possible risk loci on these chromosomes has come from the current large genetic consortia genome-wide association studies, suggesting that perhaps this hypothesis needs to be revisited for some schizophrenias. The following commentary reviews the early and more

recent literature supporting or refuting this dormant hypothesis and emphasizes the possible candidate genes still of interest that could be explored in further studies.

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Introduction

Several years ago, the literature was populated with reports that sex chromosome anomalies were more frequent in people with schizophrenia, and case reports were published, particularly on X chromosome anomalies and schizophrenia [1–3]. These were published in years prior to the field having the technology for examining DNA sequences and genes directly. The main source of genetic data came from chromosome karyotypes and, particularly, some high-resolution ones. However, the early large population studies specifically screening for X chromosomes were reports based on buccal smear findings of the so-called “bar bodies” in cells indicating extra X chromosomes (e.g., more than 1; [4–7]). It was generally recognized that having Klinefelter's syndrome put one at an increased risk for a major psychiatric disorder, particularly psychotic in nature [2, 8].

At the same time, observations also existed of many sex differences in the clinical aspects of schizophrenia, such as the timing of onset, specific symptom clusters, and outcome of the disorder (reviewed in [9–12]), as well as sex differences in familial risk for schizophrenia (reviewed in [13]). The combination of these 2 lines of evidence led DeLisi and Crow in a series of papers in the 1980s and 1990s to postulate that a gene for schizophrenia must exist on the sex chromosomes, not just on X but also on Y [3, 14–17]. Since the illness was transmitted to females and males from both mothers and fathers and, thus, did not follow the typical X-linked pattern of inheritance, the hypothesis led to emphasizing the regions of homology between both X and Y and also loci where recombination between X and Y chromosomes is known to occur [3, 14] (reviewed in [18]). The hypothesis was further supported by the observations that many genes expressed in the brain responsible for cognitive development are derived from the X chromosome and that approximately 50% of all intellectual disabilities have a defect in a gene on the X chromosome as its underlying basis (reviewed in [19, 20]).

Nevertheless, although initially promising [21–23], early molecular studies were never able to show a linkage or association with schizophrenia for any region of the sex chromosomes or variants in the genes located there, despite the existence of some good candidates [24–31]. Although there continued to be lack of data to support this hypothesis and interest waned among most investigators in pursuing it further, the sex chromosome hypothesis has never been clearly negated. Gene expression on the sex chromosomes is difficult to study because of the complexity of X inactivation, its possible skewness in some situations, the various genes that escape inactivation fully or at least partially, and finally the fact that inactivation of X chromosome genes may be occurring in some cells but not others. Given these problems, knowledge is limited about the most appropriate ways in which population data on sex chromosome genes can be evaluated. Nevertheless, there are some indications that factors on these chromosomes do confer at minimum a small risk [32, 33].

Goldstein and colleagues [4] recently published a review of sex differences in the genetics of schizophrenia and also described a study from their group [34] which demonstrated that psychosis rates for offspring of ill individuals were similar when sex of the progeny was not considered. But, if the sex of both the ill parent and the affected offspring were taken into account, then a sex-dependent pattern of transmission appeared. Sons of

mothers with psychosis had a higher rate of illness than daughters of women with the disorder (18.8 vs. 9.5%). Additionally, daughters of men with psychosis had an increased incidence of psychosis when compared to male progeny of other psychotic males (15.2 vs. 3.2%; Goldstein et al. [34]). These results, along with a review of other studies involving both schizophrenia and bipolar disorder, led these authors to suggest that a sex chromosome gene for psychosis still remains viable and that reduced penetrance or X inactivation may be occurring when mothers transmit the X chromosome gene to daughters. In the case of transmission from fathers, these authors suggest that an X chromosome gene is more likely involved than one on Y, given excess father-to-daughter transmission. This study contrasts with the much earlier report of Crow et al. [14] finding evidence for X and Y inheritance for schizophrenia from family data of multiplex families with affected sibling pairs. In these families, those individuals who had paternal inheritance of illness were more likely to be siblings of the same sex than those affected siblings with a maternal line of inheritance of illness. Since fathers pass on their X to daughters and their Y to sons, if the gene for illness were on either X or Y, it is likely that those siblings affected would be the same sex. Whereas, since mothers pass on 1 of their 2 Xs to their children (sons or daughters), it would be unlikely that with maternal inheritance, same-sex concordance would occur any more than by chance. Nevertheless, this study may not be inconsistent with the Goldstein et al. [34] report, since it did not address whether fathers transmitted illness more often to daughters than sons. Neither of these studies has yet been replicated in other populations.

The Candidate Gene Approach

Examples of candidate sex chromosome genes that have specifically been studied and implicated in schizophrenia are currently weak and inconsistent. These are listed in Table 1.

1. The MAOB (monoamine oxidase B gene) located on Xp11, which is associated with deamination of certain amines in food along with neurotransmitters, including dopamine. Studies have shown a male-specific haplotype associated with psychosis and polymorphisms that have been associated with psychotic symptoms, such as delusions [35–38].
2. The protocadherin 11X and Y (PCDH11XY) gene pair. Crow (reviewed in [18, 39]) hypothesized in-

Table 1. Summary of loci on the sex chromosomes found to be candidates or genes of interest for increased risk of schizophrenia

Locus	Chromosomal location	Known function
CNKSR2 ^a	Xp22.12	A scaffolding protein. Plays a role in assembling synaptic complexes. Loss of function is associated with X-linked mental disability [33].
NLGN4X ^a	Xp21.33-32	A neuroligin, may modulate the presynaptic calcium channel by interaction with neurexins. Mutations found in autism [33].
DMD ^c	Xp21.2	Connects the cytoskeleton of skeletal muscle to the basal lamina. Loss leads to dysfunction in mitochondrial permeability, and subsequent increase of stress-induced reactive oxygen species leads to damage and cell death [64].
MAOB	Xp11.3	Produces enzyme involved in oxidation of monoamines including 5-HT and DA as well as other neuro- and vasoactive amines in the central nervous system [65].
KDM5C ^b	Xp11.22	Involved in encoding a chromatin-modifying enzyme that acts on the amino acid on histone H3. Mutations in histone H3 methylation have been shown to be involved in several disorders of intellectual disability. Additionally, it has been found to be involved in the transcription of genes related to neural plasticity and neural maturation [66].
SYP/ CACNA1F	Xp11	SYP: Encodes a membrane protein of small synaptic vesicles in brain and endocrine cells. Involved in early neurogenesis and synaptogenesis. Also involved in the regulation of neurotransmitter release, synaptoplasticity, and production/recycling of vesicles in synapses [67]. CACNA1F: Involved in the production of Ca channels. In particular, this gene provides instructions on making a portion of the alpha subunit for these channels [68, 69].
HOPA	Xq13	Belongs to the thyroid receptor-associated proteins (TRAP) that serve as co-activators for thyroid hormone receptor. Also codes proteins critical in the regulation of transcription via the Wnt and receptor tyrosine kinase pathways, both of which are involved in cell differentiation and growth [70].
PCDH11XY	Xq21.3/Yp11.2	Cell-surface adhesion molecules expressed predominantly in the brain [18, 39, 71].
MAGEA11 ^c	Xq28	Involved in the androgen and progesterone receptor signaling pathway. Involved in migration and differentiation of cells in embryos and germ cells [72].
ARHGAP4 ^a	Xq28	Produces RHO GTPase-activating protein that plays a part in growth of axons and mobility of cells during embryonic development [40, 48].
MECP2 ^a	Xq28	Involved in the expression of DNA sequences that have been methylated. An epigenetic factor that participates in chromatin folding and transcriptional regulation [40, 44].
GPR50	Xq28	Encodes a protein that can disrupt melatonin signaling. Also associated with neural development. May be connected to neurotransmitter signaling and response to stress [73, 74].
IRAK1	Xq28	Crucial to the IL-1 receptor signaling pathway [40, 49, 50].
SRY	Y	May be involved in dopamine regulation [53].
RENBP ^a	Xq28	Involved in the renin angiotensin system with production of angiotensin II, a neurotransmitter that communicates with dopaminergic systems. Hypothesized to be important for normal thought processes [40, 54, 55].

^a Candidate genes found through a genome-wide association study. ^b Candidates from genome-wide exome sequencing studies.
^c Candidate genes from a genome-wide copy number variation analysis.

volvement of these genes in schizophrenia. They are part of a small class of genes that have homologies on both X and Y. These are cell surface adhesion molecules expressed predominantly in the brain.

3. MECP2, a gene that is involved in the expression of DNA sequences that have been methylated. This gene is expressed in greater amounts in the brain than in other tissues in the body, and mutations in the gene

have been associated with many neurodevelopmental disorders, including autism and schizophrenia [40–42]. It is also associated with decreased brain cortical area in at least 2 studies [43, 44]. Additionally, MECP2 has recently been shown in animal models to be an integral component for GABA release from neurons [45]. Of note, GABAergic dysfunction has been long thought to be involved in the pathogenesis of schizophrenia [46, 47].

4. ARHGAP4 gene, specifically involved in producing the RHO GTPase activating protein. This protein plays a role in growth of axons and mobility of cells during development in utero. It is heavily present in the central nervous system during this period and was found to be a gene of interest for schizophrenia within the Xq28 region [40, 48].
5. IRAK1, another gene of interest, plays a role in the IL-1 receptor signaling pathway. Specific IL-1 β receptor gene polymorphisms have been associated with an increased risk of schizophrenia [40, 49, 50]. IL-1 β is also hypothesized to participate in immunological reactions involving infections in utero, which may then lead to deleterious effects on a developing neurological system [40, 51].
6. The SRY gene on the Y chromosome [52]. The gene is present on a limited number of dopaminergic neurons in the midbrain area and has been suggested to be involved in important processes involving dopamine regulation, i.e., catecholamine synthesis, in the midbrain in animal models [53]. Few, if any, studies have looked at this particular gene in psychosis or schizophrenia.

The Unbiased Screening of the Genome

Beginning in approximately 2007, a new concept became the major focus of the field of psychiatric genetics, that is, to perform large genome-wide association studies (GWAS) with very densely packed marker sets to find risk genes for all the major psychiatric disorders, including schizophrenia. One of the largest international research collaborations in psychiatry was formed during this time, the Psychiatric Genomics Consortium (PGC), and, ultimately, it has been able to perform GWAS of schizophrenia on over 100,000 individuals with the published results showing several risk variants of small effect, including some on the sex chromosomes [32, 33]. The markers used to screen in GWAS generally cover the X chromosome, but not the Y chromosome, in a dense enough pattern to be able to perform a meaningful GWAS.

However, the first smaller GWAS of schizophrenia performed demonstrated some evidence of SNPs associated with the X chromosome in their top results [13, 30, 31]. Wong et al. [40] performed a GWAS of schizophrenia in the Han Chinese population and also examined a group of selected candidate genes from prior studies and plausible biological pathways. In this series of studies, they found genome-wide significance for SNPs in the gene RENBP as well as in 2 other genes that have previously been associated with schizophrenia, ARHGAP4 and MECP2, all 3 of which are located on Xq28.

RENPB, renin-binding protein, is involved in the renin-angiotensin system. This system has previously been thought to be involved in schizophrenia as well as other disorders [40, 54, 55]. Angiotensin II is a neurotransmitter that communicates with dopaminergic systems in the brain and is hypothesized to be important for normal thought processes [56, 57].

The first publication from the International Schizophrenia Consortium [32], later incorporated within the larger PGC (<http://www.med.unc.edu/pgc/about-us/about-the-pgc>), interestingly, out of the SNP associations with $p < 0.0001$, found 2 mapped to the X chromosome, one of which was XY homologous. In a later publication from this consortium [33], some loci on the X chromosome reached genome-wide significance and included 2 genes of interest involved in synaptic plasticity and function: NLGN4X on Xp21.3 and CNKSR2 on Xp22.12.

There are also some other intriguing recently published studies that suggest focusing back on examining the sex chromosomes. One is a large Swedish exome sequencing study on over 12,000 individuals, 4,877 with schizophrenia [58]. These authors, focusing on the presence of ultra-rare variants, found them to be significantly more frequent in people with schizophrenia than in the rest of the population. Most of the rare variants were concentrated in brain-expressed genes, disrupting the gene sequence, presumably altering protein structure. Most relevant is that the elevation in damaging ultra-rare mutations appeared to be mostly within X-linked genes for intellectual disability, including KDM5C (an H3K4 methylation eraser gene variant). There are other exome sequencing studies of schizophrenia showing an excess of variants in genes whose mRNAs are bound by the fragile X mental retardation protein (FMRP; [58–60]).

Similarly, the recently published large-scale copy number variation (CNV) analysis of the PGC data [61] also found some X chromosome associations. In this report of over 21,000 cases, CNVs were found in various locations throughout the genome, but also included 2

significant duplications on Xq28 (one of which was in MAGEA11) and suggestive, although not significant, deletions on Xp21.2 (DMD). It is also interesting that a study of CNVs in Klinefelter's individuals [62] showed an overall increase in CNVs when compared with normal males or females, and half of the X-linked CNVs fell within regions encompassing genes. Most of these genes (90%) escape X inactivation and are within the regions of X-Y homology, particularly the pseudoautosomal region 1 (PAR1) and Xq21.31.

In summary, the role variants in genes on the sex chromosomes play in abnormal brain development, and thus in the risk for mental illnesses, is yet to be determined. The challenges that have prevented progress in understanding the effects of these genes are many and include the complex role X inactivation plays in gene expression and the manner in which homologous genes on both X and Y chromosomes contribute to gene expression. Future studies might clarify the significance of the sex chromosomes in schizophrenia by examining sequencing data on the sex chromosomes in multiplex families to identify loci shared by all affecteds within families [63], exploring

these abnormalities across diagnoses and further exploring the candidate genes that have thus far been observed, particularly as they have emerged from the unbiased GWAS and CNV whole-genome screens. A combination of new sequencing techniques in multiplex families with a focus on sex chromosomes may ultimately move this notion from the "sex chromosome hypothesis" to the finding of genes of risk for schizophrenia and other disorders, as well as lead to a further understanding of the role of the sex chromosomes in brain development and maldevelopment at the molecular level.

Statement of Ethics

There are no ethical issues with the data reviewed in this article.

Disclosure Statement

The authors have no conflicts of interest for any of the information in this article.

References

- DeLisi LE, Reiss AL, White BJ, Gershon ES: Chromosomal aberrations in schizophrenia. *Schizophr Res* 1988;1:277–281.
- DeLisi LE, Friedrich U, Wahlstrom J, Boccio-Smith A, Forsman A, Eklund K, Crow TJ: Schizophrenia and sex chromosome anomalies. *Schizophr Bull* 1994;20:495–505.
- DeLisi LE, Crow TJ: Evidence for an X chromosome locus for schizophrenia. *Schizophr Bull* 1989;15:431–440.
- Nielsen J, Fischer M: Sex-chromatin and sex-chromosome abnormalities in male hypogonadal mental patients. *Br J Psychiatry* 1965; 111:641–647.
- Trixler M, Kosztolányi G, Méhes K: Sex chromosome aberration screening among male psychiatric patients (author's transl). *Arch Psychiatr Nervenkr* (1970) 1976;221:273–282.
- Polani PE: Abnormal sex chromosomes and mental disorders. *Nature* 1969;223:680–686.
- Kaplan AR: Sex-chromatin variations in institutionalized females. I. Sex chromosome anomalies in hospitalized schizophrenics, adult prisoners, confined juvenile offenders, and noninstitutionalized volunteers. *Recent Adv Biol Psychiatry* 1966;9:21–27.
- DeLisi LE, Maurizio AM, Svetina C, Ardekani B, Nierenberg J, Szulc K, Leonard J, Harvey P: Klinefelter's syndrome (XXY) as a genetic model for psychotic disorders. *Am J Med Genet B Neuropsychiatr Genet* 2005;135B:15–23.
- Seeman MV: Gender differences in schizophrenia. *Can J Psychiatry* 1982;27:107–112.
- Seeman MV: Sex and schizophrenia. *Can J Psychiatry* 1985;30:313–315.
- Seeman MV: Women and schizophrenia. *Medscape Womens Health* 2000;5:2.
- Abel KM, Drake R, Goldstein JM: Sex differences in schizophrenia. *Int Rev Psychiatry* 2010;22:417–428.
- Goldstein JM, Cherkerzian S, Tsuang MT, Petryshen TL: Sex differences in the genetic risk for schizophrenia: history of the evidence for sex-specific and sex-dependent effects. *Am J Med Genet B Neuropsychiatr Genet* 2013;162B:698–710.
- Crow TJ, DeLisi LE, Johnstone EC: Concordance by sex for psychosis is paternally inherited: evidence for a pseudoautosomal locus. *Br J Psychiatry* 1989;155:92–97.
- Crow TJ: The continuum of psychosis and its genetic origins. The sixty-fifth Maudsley lecture. *Br J Psychiatry* 1990;156:788–797.
- Crow TJ: A continuum of psychosis, one human gene, and not much else – the case for homogeneity. *Schizophr Res* 1995;17:135–145.
- Crow TJ: A Darwinian approach to the origins of psychosis. *Br J Psychiatry* 1995;167: 12–25, erratum in *Br J Psychiatry* 1995;16: 414.
- Crow TJ: The XY gene hypothesis of psychosis: origins and current status. *Am J Med Genet B Neuropsychiatr Genet* 2013;162B:800–824.
- Skuse DH: X-linked genes and mental functioning. *Hum Mol Genet* 2005;14 Spec No 1:R27–R32.
- Xu J, Distech CM: Sex differences in brain expression of X- and Y-linked genes. *Brain Res* 2006;1126:50–55.
- Collinge J, DeLisi LE, Boccio A, Johnstone EC, Lane A, Larkin C, Leach M, Lofthouse R, Owen F, Poulter M, Crow TJ: A pseudoautosomal locus for schizophrenia: molecular evidence from an analysis of sib-pairs. *Br J Psychiatry* 1991;158:624–629.
- Laval S, Dann J, Butler RJ, Loftus J, Rue J, Leask SJ, Bass N, Comazzi M, Vita A, Nanko S, Shaw S, Peterson P, Shields G, Smith AB, Stewart J, DeLisi LE, Crow TJ: Evidence for linkage to psychosis and cerebral asymmetry (relative hand skill) on the X chromosome. *Am J Med Genet B Neuropsychiatr Genet* 1998;81:420–427.
- Crow TJ, Poulter M, Lofthouse R, Chen G, Shah T, Bass N, Morganti C, Vita A, Smith C, Boccio A, Shields G, DeLisi LE: Male siblings with schizophrenia share alleles at the androgen receptor above chance expectation. *Am J Med Genet B Neuropsychiatr Genet* 1993;48: 159–160.

- 24 Crow TJ, DeLisi LE, Lofthouse R, Poulter M, Lehner T, Bass N, Shah T, Walsh C, Boccio-Smith A, Shields G, Ott J: An examination of linkage of schizophrenia and schizoaffective disorder to the pseudoautosomal region (Xp22.3). *Br J Psychiatry* 1994;164:159–164.
- 25 DeLisi LE, Devoto M, Lofthouse R, Poulter M, Smith A, Shields G, Bass N, Chen G, Vita A, Morganti C, Ott J, Crow TJ: Search for linkage to schizophrenia on the X and Y chromosomes. *Am J Med Genet B Neuropsychiatr Genet* 1994;54:113–121.
- 26 Dann J, DeLisi LE, Devoto M, Laval S, Nancarrow DJ, Shields G, Smith A, Loftus J, Peterson P, Vita A, Comazzi M, Invernizzi G, Levinson DF, Wildenauer D, Mowry BJ, Collier D, Powell J, Crowe RR, Andreasen NC, Silverman JM, Mohs RC, Murray RM, Walters MK, Lennon DP, Hayward NK, Albus M, Lerer B, Maier W, Crow TJ: A linkage study of schizophrenia to markers within Xp11 near the MAOB gene. *Psychiatr Res* 1997;70:131–143.
- 27 DeLisi LE, Shaw S, Sherrington R, Nanthakumar B, Shields G, Smith AB, Wellman N, Larach VW, Loftus J, Razi K, Stewart J, Vita A, Comazzi M, De Hurt M, Crow TJ: Failure to establish linkage on the X chromosome in 301 families with schizophrenia or schizoaffective disorder. *Am J Med Genet B Neuropsychiatr Genet* 2000;96:335–241.
- 28 DeLisi LE, Crow TJ, Davies KE, Terwilliger JD, Ott J, Ram R, Flint T, Bock A: No genetic linkage detected for schizophrenia to Xq27–28. *Br J Psychiatry* 1991;158:630–634.
- 29 DeLisi LE, Wellman N, Stewart J, Smith AB, Churchman M, Crow TJ: A linkage disequilibrium study of markers within the pericentromeric region of the X chromosome. *Am J Med Genet B Neuropsychiatr Genet* 1999;88:588–589.
- 30 Barr CL, Kennedy JL, Pakstis AJ, Castiglione CM, Kidd JR, Wetterberg L, Kidd KK: Linkage study of a susceptibility locus for schizophrenia in the pseudoautosomal region. *Schizophr Bull* 1994;20:277–286.
- 31 Kalsi G, Curtis D, Brynjolfsson J, Butler R, Sharma T, Murphy P, Read T, Petursson H, Gurling HM: Investigation by linkage analysis of the XY pseudoautosomal region in the genetic susceptibility to schizophrenia. *Br J Psychiatry* 1995;167:390–393.
- 32 International Schizophrenia Consortium: Common polygenic variation contributes to risk of schizophrenia that overlaps with bipolar disorder. *Nature* 2009;460:748–752.
- 33 Schizophrenia Working Group of the Psychiatric Genomics Consortium: Biological insights from 108 schizophrenia-associated genetic loci. *Nature* 2014;511:421–427.
- 34 Goldstein JM, Cherkurian S, Seidman LJ, Petryshen TL, Fitzmaurice G, Tsuang MT, Buka SL: Sex-specific rates of transmission of psychosis in the New England high-risk family study. *Schizophr Res* 2011;128:150–155.
- 35 Bergen SE, Fanous AH and Walsh D, O'Neill FA, Kendler KS: Polymorphisms in SLC6A4, PAH, GABRB3, and MAOB and modification of psychotic disorder features. *Schizophr Res* 2009;109:94–97.
- 36 Carrera N, Sanjuan J, Molto MD, Carracedo A, Costas J: Recent adaptive selection at MAOB and ancestral susceptibility to schizophrenia. *Am J Med Genet B Neuropsychiatr Genet* 2009;150B:369–374.
- 37 Sun J, Jayatilake K, Zhao Z, Meltzer HY: Investigating association of four gene regions (GABRB3, MAOB, PAH, and SLC6A4) with five symptoms in schizophrenia. *Psychiatr Res* 2012;198:202–206.
- 38 Piton A, Gauthier J, Hamdan FF, Lafrenière RG, Yang Y, Henrion E, Laurent S, Noreau A, Thibodeau P, Karemera L, Spiegelman D, Kuku F, Dugay J, Destroismaisons L, Jolivet P, Côte M, Lachapelle K, Diallo O, Raymond A, Marineau C, Champagne N, Xiong L, Gaspar C, Rivière J-B, Tarabeux J, Cossette P, Krebs M-O, Rapoport JL, Addington A, De Lisi LE, Mottion L, Joobier R, Fombonne E, Drapeau P, Rouleau GA: Systematic resequencing of X-chromosome synaptic genes in autism spectrum disorder and schizophrenia. *Mol Psychiatry* 2011;16:867–880.
- 39 Crow TJ: Schizophrenia as variation in the sapiens-specific epigenetic instruction to the embryo. *Clin Genet* 2012;81:319–324.
- 40 Wong EH, So HC, Li M, Wang Q, Butler AW, Paul B, Wu HM, Hui TC, Choi SC, So MT, Garcia-Barcelo MM, McAlonan GM, Chen EY, Cheung EF, Chan RC, Purcell SM, Cherny SS, Chen RR, Li T, Sham PC: Common variants on Xq28 conferring risk of schizophrenia in Han Chinese. *Schizophr Bull* 2014;40:777–786.
- 41 Shibayama A, Cook EH Jr, Feng J, Glanzmann C, Yan J, Craddock N, Jones IR, Goldman D, Heston LL, Sommer SS: MECP2 structural and 3'-UTR variants in schizophrenia, autism and other psychiatric diseases: a possible association with autism. *Am J Med Genet B Neuropsychiatr Genet* 2004;128B:50–53.
- 42 Chahrour M, Jung SY, Shaw C, Zhou X, Wong ST, Qin J, Zoghbi HY: MeCP2, a key contributor to neurological disease, activates and represses transcription. *Science* 2008;320:1224–1229.
- 43 Joyner AH, J CR, Bloss CS, Bakken TE, Rimol LM, Melle I, Agartz I, Djurovic S, Topol EJ, Schork NJ, Andreassen OA, Dale AM: A common MECP2 haplotype associates with reduced cortical surface area in humans in two independent populations. *Proc Natl Acad Sci USA* 2009;106:15483–15488.
- 44 Colibazzi T, Wexler BE, Bansal R, Hao X, Liu J, Sanchez-Peña J, Corcoran C, Lieberman JA, Peterson BS: Anatomical abnormalities in gray and white matter of the cortical surface in persons with schizophrenia. *PLoS One* 2013;8:e55783.
- 45 Chao HT, Chen H, Samaco RC, Xue M, Chahrour M, Yoo J, Neul JL, Gong S, Lu HC, Heintz N, Ekker M, Rubenstein JL, Noebels JL, Rosenmund C, Zoghbi HY: Dysfunction in GABA signaling mediates autism-like stereotypies and Rett syndrome phenotypes. *Nature* 2010;468:263–269.
- 46 Costa E, Davis JM, Dong E, Grayson DR, Guidotti A, Tremolizzo L, Veldic M: A GABAergic cortical deficit dominates schizophrenia pathophysiology. *Crit Rev Neurobiol* 2004;16:1–23.
- 47 Nakazawa K, Zsiros V, Jiang Z, Nakao K, Kolata S, Zhang S, Zhang S, Belforte JE: GABAergic interneuron origin of schizophrenia pathophysiology. *Neuropharmacology* 2012;62:1574–1583.
- 48 Vogt DL, Gray CD, Young W: ARHGAP4 is a novel RhoGAP that mediates inhibition of cell motility and axon outgrowth. *Mol Cell Neurosci* 2007;36:332–342.
- 49 Sasayama D, Hori H, Teraishi T, Hattori K, Ota M, Iijima Y, Tatsumi M, Higuchi T, Amano N, Kunugi H: Possible association between interleukin-1 β gene and schizophrenia in a Japanese population. *Behav Brain Funct* 2011;7:35.
- 50 Söderlund J, Schröder J, Nordin C, Samuelsson M, Walther-Jallow L, Karlsson H, Erhardt S, Engberg G: Activation of brain interleukin-1 β in schizophrenia. *Mol Psychiatry* 2009;14:1069–1071.
- 51 Marx CE, Jarskog LF, Lauder JM, Lieberman JA, Gilmore JH: Cytokine effects on cortical neuron MAP-2 immunoreactivity: implications for schizophrenia. *Biol Psychiatry* 2001;50:743–749.
- 52 Gillies GE, Virdee K, McArthur S, Dalley JW: Sex-dependent diversity in ventral tegmental dopaminergic neurons and developmental programming: a molecular, cellular and behavioral analysis. *Neuroscience* 2014;282:69–85.
- 53 Czech DP, Lee J, Sim H, Parish CL, Vilain E, Harley VR: The human testis determining factor SRY localizes in midbrain dopamine neurons and regulates multiple components of catecholamine synthesis and metabolism. *J Neurochemistry* 2012;122:260–271.
- 54 Kucukali CI, Aydin M, Ozkok E, Bilge E, Zengin A, Cakir U, Kara I: Angiotensin-converting enzyme polymorphism in schizophrenia, bipolar disorders, and their first-degree relatives. *Psychiatr Genet* 2010;20:14–19.
- 55 Crescenti A, Gassó P, Mas S, Abellana R, Deulofeu R, Parellada E, Bernardo M, Lafuente A: Insertion/deletion polymorphism of the angiotensin-converting enzyme gene is associated with schizophrenia in a Spanish population. *Psychiatry Res* 2009;165:175–180.
- 56 Jenkins TA, Allen AM, Chai SY, MacGregor DP, Paxinos G, Mendelsohn FA: Interactions of angiotensin II with central dopamine. *Adv Exp Med Biol* 1996;396:93–103.
- 57 Jenkins TA, Mendelsohn FA, Chai SY: Angiotensin-converting enzyme modulates dopamine turnover in the striatum. *J Neurochem* 1997;68:1304–1311.

- 58 Genovese G, Fromer M, Stahl EA, Ruderfer DM, Chambert K, Landén M, Moran JL, Purcell SM, Sklar P, Sullivan PF, Hultman CM, McCarroll SA: Increased burden of ultra-rare protein-altering variants among 4,877 individuals with schizophrenia. *Nat Neurosci* 2016;19:1433–1441.
- 59 Purcell SM, Moran JL, Fromer M, Ruderfer D, Solovieff N, Roussos P, O'Dushlaine C, Chambert K, Bergen SE, Kahler A, Duncan L, Stahl E, Genovese G, Fernandez E, Collins MO, Komiyama NH, Choudhary JS, Magnusson PK, Banks E, Shakir K, Garimella K, Fennell T, DePristo M, Grant SG, Haggarty SJ, Gabriel S, Scolnick EM, Lander ES, Hultman CM, Sullivan PF, McCarroll SA, Sklar P: A polygenic burden of rare disruptive mutations in schizophrenia. *Nature* 2014;506:185–190.
- 60 Fromer M, Pocklington AJ, Kavanagh DH, Williams HJ, Dwyer S, Gormley P, Georgieva L, Rees E, Palta P, Ruderfer DM, Carrera N, Humphreys I, Johnson JS, Roussos P, Barker DD, Banks E, Milanova V, Grant SG, Hannon E, Rose SA, Chambert K, Mahajan M, Scolnick EM, Moran JL, Kirov G, Palotie A, McCarroll SA, Holmans P, Sklar P, Owen MJ, Purcell SM, O'Donovan MC: De novo mutations in schizophrenia implicate synaptic networks. *Nature* 2014;506:179–184.
- 61 CNV and Schizophrenia Working Groups of the Psychiatric Genomics Consortium: Contribution of copy number variants to schizophrenia from a genome-wide study of 41,321 subjects. *Nat Genet* 2017;49:27–35.
- 62 Rocca MS, Pecile V, Cleva L, Speltra E, Selice R, Di Mambro A, Foresta C, Ferlin A: The Klinefelter syndrome is associated with high recurrence of copy number variations on the X chromosome with a potential role in the clinical phenotype. *Andrology* 2016;4:328–334.
- 63 DeLisi LE: A case for returning to multiplex families for further understanding the heritability of schizophrenia: a psychiatrist's perspective. *Mol Neuropsychiatry* 2016;2:15–19.
- 64 Gao Q, McNally EM: The dystrophin complex: structure, function and implications for therapy. *Compr Physiol* 2015;5:1223–1239.
- 65 Wei YL, Li CX, Li SB, Liu Y, Hu L: Association study of monoamine oxidase A/B genes and schizophrenia in Han Chinese. *Behav Brain Funct* 2011;7:42.
- 66 Scandaglia M, Lopez-Atalaya JP, Medrano-Fernandez A, Lopez-Cascales MT, Del Blanco B, Lipinski M, Benito E, Olivares R, Iwase S, Shi Y, Barco A: Loss of Kdm5c causes spurious transcription and prevents the fine-tuning of activity-regulated enhancers in neurons. *Cell Rep* 2017;21:47–59.
- 67 Shen YC, Tsai HM, Ruan JW, Liao YC, Chen SF, Chen CH: Genetic and functional analyses of the gene encoding synaptophysin in schizophrenia. *Schizophr Res* 2012;137:14–19.
- 68 Wei J, Hemmings GP: A further study of a possible locus for schizophrenia on the X chromosome. *Biochem Biophys Res Commun* 2006;344:1241–1245.
- 69 Wei J, Hemmings GP: Searching for a locus for schizophrenia within chromosome Xp11. *Am J Med Genet* 2000;96:4–7.
- 70 Sandhu HK, Sarkar M, Turner BM, Wassink TH, Philibert RA: Polymorphism analysis of HOPA: a candidate gene for schizophrenia. *Am J Med Genet* 2003;123B:33–38.
- 71 Giouze M, Williams NA, Lonie LJ, DeLisi LE, Crow TJ: Protocadherin X/Y, a candidate gene-pair for schizophrenia and schizoaffective disorder: a DHPLC investigation of genomic sequence. *Am J Med Genet B Neuro-psychiatr Genet* 2004;129B:1–9.
- 72 Park S, Sung Y, Jeong J, Choi M, Lee J, Kwon W, Jang S, Park SJ, Kim JY, Kim SH, Yoon D, Ryoo ZY, Kim MO: Critical roles of hMAGEA2 in induced pluripotent stem cell pluripotency, proliferation, and differentiation. *Cell Biochem Funct* 2017;35:392–400.
- 73 Ryan J, Carrière I, Ritchie K, Ancelin ML: Involvement of GPR50 polymorphisms in depression: independent replication in a prospective elderly cohort. *Brain Behav* 2015;5:e00313.
- 74 Grunewald E, Kinnell HL, Porteous DJ, Thomson PA: GPR50 interacts with neuronal NOGO-A and affects neurite outgrowth. *Mol Cell Neurosci* 2009;42:363–371.