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Genetics of schizophrenia from a clinical perspective

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Abstract

Schizophrenia (SZ) is a common disorder that runs in families. It has a relatively high heritability, i.e. inherited factors account for the major proportion of its etiology. The high heritability has motivated gene mapping studies that have improved in sophistication through the past two decades. Belying earlier expectations, it is now becoming increasingly clear that the cause of SZ does not reside in a single mutation, or even in a single gene. Rather, there are multiple DNA variants, not all of which have been identified. Additional risk may be conferred by interactions between individual DNA variants, as well as ‘gene-environment’ interactions. We review studies that have accounted for a fraction of the heritability. Their relevance to the practising clinician is discussed. We propose that continuing research in DNA variation, in conjunction with rapid ongoing advances in allied fields, will yield dividends from the perspective of diagnosis, treatment prediction through pharmacogenetics, and rational treatment through discoveries in pathogenesis.

Introduction

Schizophrenia (SZ) is a common, severe, and potentially fatal disorder for which treatment is empirical and unsatisfactory (Insel, 2010). The absence of satisfactory treatment compels etiological research to facilitate future rational therapeutic drug development. In view of ongoing, rapid advances in genetics and genomics, intensive gene mapping studies have been conducted over the past two decades. We review these studies below, with the perspective of the practising clinician in mind. First, we review principles of gene mapping. Next, we summarize the current status of SZ gene mapping studies (with a section describing ongoing work in India). Finally, we discuss the potential dividends from this field of research for the practising clinician, in conjunction with prospects for advances in the near future. This review is restricted to studies involving DNA variation, but we argue that major advances will occur only if the DNA variant research is placed in the context of genomics.

Principles of Gene Mapping

Linkage and association analysis

The human genome, encompassing 23 pairs of chromosomes, consists of approximately three billion base pairs. Any two individuals can potentially differ at more than 10 million sites ('loci') in the genome. While this number constitutes only a small fraction of the entirety of genomic sequences, it nevertheless represents a major multiple analysis challenge from the gene mapper's perspective. To make this challenge more tractable, early gene mappers evaluated multiply affected families in order to identify relatively large chromosomal segments that appeared to be inherited along with the disease of interest. This strategy is called 'linkage analysis'. By establishing that co-segregation of disease and the identified particular chromosomal segment is an unlikely chance occurrence, the disease-causing mutation(s) could be localized to the 'linked' chromosomal region. Further 'fine mapping' studies could then evaluate DNA variation in the linked region in order to identify the disease causing mutation. Linkage is an ideal method for disease gene identification in conditions with a clear mode of inheritance. As the inheritance of disorders such as SZ is not clear-cut, and as there are logistical limitations in recruiting large families, gene mappers have turned to population based, case-control analyses. This approach, called 'association analysis' seeks DNA variations that are more common among cases than among controls. It is based on the concept that members of a population are more likely to share a common ancestor; an ancestor with a disease causing mutation would transmit the mutation to members of the extant generations along with flanking chromosomal segments. DNA polymorphisms in these 'associated' chromosomal segments would all be differentially distributed between cases and controls. Further analysis of variations in this region could thus reveal disease causing mutation/s. It is important to emphasize that the linkage and association analyses are complementary approaches. The probability of false positive or false negative findings has to be considered for both methods. In particular, associations may also be detected due to numerous artifacts (Hunter & Kraft, 2007); therefore replication of association findings in independent cohorts is essential to confirm initial findings. Association analysis is generally carried out using case-control samples and to a lesser extent family-based (trio – parents and proband) samples. The latter is the preferred approach, given the limitations of population stratification in case-control studies. However, the difficulty in recruitment of trio families (including both parents) and the proportion of non-informative matings for particular polymorphisms means that the family-based effort is more time consuming and expensive from the perspective of participant recruitment. A combination of family-based transmission disequilibrium test (TDT) analysis and case-control association analysis may be the most informative strategy for genetic analysis of common complex traits.

Next generation sequencing, fine mapping and rare variants

When the complete sequence of the human genome was unavailable, investigators could only survey particular portions of the human genome. Therefore, many investigators selected particular genes for analysis based on prior knowledge of the disease of the interest. This selective approach was dubbed the 'candidate gene' approach. The completion of the human genome project and public availability of a catalogue of human DNA variants (e.g.

www.hapmap.org; www.ncbi.nih.gov) have enabled genome-wide association studies (GWAS). GWAS utilize statistical methods to minimize the risk of false positives and provide greater power to detect genotype-phenotype associations if sufficiently large samples are analysed. GWAS have been completed for numerous diseases, and hundreds of disease mutations have been identified (<http://www.genome.gov/gwastudies/>; Manolio, 2009a; Wellcome Trust Case Control Consortium, 2007). For many diseases, many more risk-enhancing variants remain to be discovered (Tang et al., 2011). Efforts to fine-map promising risk loci and detection of rare genetic variants using 'deep sequencing' technologies have emerged as powerful approaches to augment genetic association studies. Indeed, the availability of economical, highly accurate next generation sequencing techniques offer the promise of using whole genome sequencing (WGS) for association analyses (Girard et al., 2011). Another advance is the increasing availability and sophistication of high throughput techniques for the analyses of the 'epigenome' (i.e. heritable variation that is based not in nucleotide sequences but in other mechanisms such as DNA methylation) (Archer et al., 2010; Costa et al., 2002; Feng & Fan, 2009; Narayan & Draganow, 2010).

Current status of SZ gene mapping studies

SZ is diagnosed on the basis of a constellation of symptoms and has a multifactorial aetiology (Gottesman & Erlenmeyer-Kimling, 2001). It clusters in certain families, but the inheritance is complex and the possibility of genetic heterogeneity (i.e. different genetic mutations segregating in different families) cannot be excluded. Genetic factors and gene-environment interactions together contribute over 80% of the liability for developing SZ. Multiple studies have consistently demonstrated that the risk to relatives of a patient (proband) with SZ is higher than that to relatives of controls (Kendler & Diehl, 1985). There is a 48% risk of developing the disorder over the course of their lifetime in identical twins (Gottesman, 1994), who share virtually all their genetic variants. The risk varies from 6 to 17% in first degree relatives among whom there is 50% sharing of genetic variants, on average. SZ, along with several chronic non-communicable diseases such as asthma, diabetes, hypertension and stroke is estimated to have a relatively high heritability (Chakravarti & Little, 2003). The life time risk for SZ ranges from 0.4% (Gejman et al., 2010) to 0.7–0.8% (McGrath et al., 2008; Saha et al., 2005; Tandon et al., 2008a), with an aggregate lifetime morbid risk estimate of 1% (Gottesman & Shields, 1982). The genetic basis of SZ has been investigated for well over a century. The modern approaches include chromosomal analysis, linkage analysis, and association genetics using both candidate gene and genome-wide association strategies. Gene mapping studies have recently identified several common and rare DNA risk variants for SZ. These studies are summarized below.

SZ linkage analysis

As the pattern of inheritance of SZ is complex, it has been difficult to garner consistent evidence for linkage (Ng et al., 2009). In two separate meta-analyses (Badner & Gershon, 2002; Lewis et al., 2003) linkage was suggested at two chromosomal regions, namely 8p21–22 and 22q11–12. Linkage has also been reported at other chromosomal loci; e.g. 1p13–q23, 1q23–q31, 2p12–q22, 2q22–q23, 3p25–p22, 5q23–q34, 10pter–p14, 11q22–q24, 6p22–p21,

6q15–q23, 14pter–q13, 15q21–q26, 16p13–q12, 17q21–q24, 18q22–qter, 20p20–p11, 22pter–q12 (Lewis et al., 2003). Several putative genes have been identified in these regions and these genes have been evaluated further as candidates for association analysis.

SZ association analysis

In the years predating GWAS, only selected chromosomal regions could be analysed. Therefore, gene mappers focused on regions in which linkage was detected previously, and/or ‘candidate’ genes for which evidence was available through other avenues of research. For example, genes localized to chromosomes 1, 6, 8 and 22 were analysed as these regions initially provided evidence for linkage (Fallin et al., 2011; Hamshere et al., 2011; Riley & McGuffin, 2000). In relation to candidate genes in linked regions, Neuregulin-1 (*NRG1*) provides a typical example. Stefansson et al. (2002) first reported linkage of SZ to *NRG1* on chromosome 8 in the Icelandic population. The gene encoding catechol-methyltransferase (*COMT*) is another example. It was favoured because it is localized to a putative linked region (Hosak, 2007; Gao et al., 2010) and because of its known function in dopamine metabolism, which is thought to be dysfunctional in SZ.

Unlike genes identified through linkage analyses, other candidate genes were selected on the basis of biochemical and pharmacological studies; e.g. genes from the dopaminergic and serotonergic pathways as well as genes encoding proteins involved in hormonal pathways and membrane phospholipids (Arranz et al., 1998; Carlsson et al., 2001; Chowdari et al., 2001; Greenwood et al., 2011; Laruelle et al., 1999; Lieberman et al., 1998; Nielsen et al., 1998; Rotondo et al., 1999; Seeman, 2010; Semwal et al., 2002; Talkowski et al., 2006, 2008; Tandon et al., 2008b; Weinberger, 1987). Several meta-analyses were published (Allan et al., 2008; Chen et al., 2011a, 2011c); but consistent findings have been limited (Alkelai et al., 2009; Sanders et al., 2008; Sullivan et al., 2008).

Genome-wide association studies

With availability of cheaper and more accurate panels of DNA polymorphisms representing variants across the entire genome, the mapping strategy in SZ favoured GWAS. Large international consortia generated evidence for several common polymorphisms associated with SZ, such as the major histocompatibility complex region at 6p22–p21 (Kirov et al., 2009; Ripke et al., 2011; Sebat et al., 2009; Shi et al., 2009; Stefansson et al., 2009; International Schizophrenia Consortium, 2008; Williams et al., 2010). In addition, five novel loci were identified at chromosomes 1p21.3, 2q32.3, 8p23.2, 8q21.3, 10q24.32–q24.33. Associations were also reported at miR-137, a microRNA with intriguing functions (Ripke et al., 2011; Smrt et al., 2010). These alleles represent relatively modest odds ratios (OR) (~1.2–1.8) (Almoguera et al., 2012; Chen et al., 2011b; Kingsmore, et al., 2008; Li et al., 2011; Shi et al., 2011; Steinberg et al., 2011; Yi et al., 2012). While initial studies were restricted to Caucasian ancestry samples (Gershon et al., 2011) GWAS have been published also on Chinese and Japanese ancestry samples (Yamada et al., 2011; Yue et al., 2011). Several hundred SZ risk loci may be present (Purcell et al., 2009). It is conceivable that joint analysis of SNPs at genes that are functionally related may reveal more substantive risk. Such ‘pathway’ analysis could also reduce the burden of corrections for multiple comparisons during replicate analyses (Jia et al., 2010, 2012; Sun et al., 2010).

Copy number variations

A number of chromosomal abnormalities have been described among individuals with SZ, even before systematic gene mapping studies were launched (MacIntyre et al., 2003). The three most frequently observed chromosomal anomalies are deletions on chromosome 22q11, a balanced reciprocal translocation of 1q42/11q14, and another involving the X chromosome (Blackwood et al., 2001; DeLisi et al., 1994; Williams et al., 2006). Recent GWAS have revealed that large segments of DNA can be deleted or occur in more than two copies in the genomes of a minority of individuals with SZ, leading to dosage imbalances (Kirov et al., 2012; Rees et al., 2011, 2012; Zhao et al., 2012). These rare genetic lesions are nevertheless associated with relatively large risks for SZ (ORs ~7–12) (Kirov et al., 2009; Glessner et al., 2012; Grozeva et al., 2012; Stefansson et al., 2008). As the copy number variations (CNVs) have been identified through population-based studies, it remains to be seen whether they conform to classical Mendelian patterns. Genes involved in cell signalling, brain development and glutamate appear to be affected through the CNVs (McClellan & King, 2010; International Schizophrenia Consortium, 2008).

De novo variation

The CNV studies indicate that a portion of the risk may be due to variants that are not inherited (Girard et al., 2011; Rees et al., 2012; Rodriguez-Murillo et al., 2012; Xu et al., 2011). Though individually rare, the *de novo* events can ‘pile up’ in the same genes, thereby providing important etiologic evidence (Sanders et al., 2012). These intriguing possibilities have opened up yet another novel avenue in SZ genetics.

Ongoing work in India

India accounts for approximately one fifth of the world population and by extension a similar proportion of its disease burden. In India, 5.2 people per 1,000 adults are estimated to suffer from SZ at any given time (Ganguli, 2000) and more than 4.3 to 8.7 million people (<http://www.schizophrenia.com/szfacts.htm>) are affected. Though SZ continues to be a national health burden (Ganguli, 2000), only a few groups in the country have been investigating its genetic underpinnings in the last decade. Most groups focused on case-control studies and phenotype-genotype correlations. A few collected specific samples based on particular ancestral groups, family-based samples, or for pharmacogenetic studies. Some representative publications (Table 1) are described below.

A group in Kerala assayed SNPs in the serotonin transporter gene (*SLC6A4*) and reported several significant allelic and genotypic associations as well as a haplotype linking the three risk alleles, namely 5HTTLPR/S-rs2066713/C-STin2/12-repeat (Vijayan et al., 2009). The same group focused on pharmacogenomics of antipsychotic drugs as related to polymorphisms of *DRD2* and *SLC6A4* (Vijayan et al., 2007, 2009). A research group from north Bengal worked primarily on HLA-G and HLA Class I gene markers (Debnath & Chaudhuri, 2006; Singh et al., 2011). The same group also reported decreased serum levels of the interleukins IL-2 and IL-6 levels in SZ patients (Singh et al., 2009). A group from Delhi, working on the T928G (Ser310Ala) polymorphism of ionotropic glutamate receptor kainate 3 gene (*GRIK3*) reported a statistically significant difference in the genotype and

allelic distribution among cases and controls (Ahmad et al., 2009). A report from Hyderabad investigated the serotonin receptor polymorphism (Araga & Narasu, 2002).

A Chennai based group did not find association with dystrobrevin binding protein 1 (dysbindin) gene (*DTNBP1*) (Holliday et al., 2006), but linkage to 1p31.1 was reported in a caste-based pedigree from Tamil Nadu (Holliday et al., 2009). This group published several linkage and association studies in caste-based south Indian samples on dysbindin, phosphodiesterase 4B, tumour necrosis factor haplo-type analysis and prevalence of *DISC1* variants (Handoko et al., 2003; Holliday et al., 2006, 2009).

Of the two groups based in Delhi, the Institute of Genomics and Integrative Biology (IGIB) has investigated several candidate genes in case-control and family-based samples such as the potassium channel-coding gene, *KCNN3*, (Saleem et al., 2000), CAG-repeat polymorphisms in the *CLOCK* gene (Saleem et al., 2001a), a CAG repeat marker (22CH3) on chromosome 22q (Saleem et al., 2001b), a novel nonsense mutation (Trp27Ter) in exon 2 of the synaptogyrin 1 gene (*SYNGRI*) (Verma et al., 2004, 2005a) and the *MLC1* gene (putative cation-channel gene on 22q13) (Verma et al., 2005b). They also investigated the dopaminergic system for associations with synonymous polymorphisms (His313 and Pro319) of the dopamine D2 receptor (*DRD2*) (Kukreti et al., 2006), brain-derived neurotrophic factor (*BDNF*) and catechol-o-methyl transferase (*COMT*) (Gupta et al., 2009a, 2009b, 2011).

Our group has focused mainly on neurotransmitters and related signalling pathways. They include dopamine receptor D3 (Prasad et al., 1999, 2002), dopamine transporter and catechol-o-methyl transferase (Semwal et al., 2001, 2002; Srivastava et al., 2010) from the dopaminergic pathway; other candidates like membrane phospholipids such as *CPLA2* (cytosolic phospholipase A2) (Chowdari et al., 2001) and signalling pathway genes including regulator of G-protein signalling 4 (*RGS4*) (Chowdari et al., 2002); inositol polyphosphate 1 phosphatase (*INPP1*) (Semwal et al., 2002); cytosolic phospholipase A2 (*cPLA2*) (Chowdari et al., 2001; Semwal et al., 2002); *NOTCH4* (Prasad et al., 2004); and serotonergic pathway genes namely serotonin receptor 2A (*HTR2A*), serotonin receptor 2C (*HTR2C*) and tryptophan hydroxylase (*TPH*) (Semwal et al., 2001, 2002; Deshpande et al., 2005).

In sum, the studies from India represent an encouraging trend that could indicate novel risk bearing polymorphisms. As several groups have not attempted replicative analyses and genome-wide significance was not attained for any of the studies, much work remains.

How can gene mapping studies assist the practising clinician?

Diagnostics

SZ has been, and continues to be a syndromal concept. One of the most compelling motivations for gene mapping studies was the possibility that identification of disorder related mutations would not only establish aetiological factors convincingly (in contrast to some risk factors identified from epidemiological studies, for which causal links are difficult to establish), but the gene mapping effort would also enable us to ‘carve the disorder at the

‘joints’. Ideally, diagnostic groups could be redefined on the basis of genetic mutations; such mutations might even be of diagnostic assistance to the clinician. These goals have been tempered by the realization that SZ risk may be due to hundreds of risk variants, not all of which have been identified (unpublished). It has been argued that greater portions of the ‘missing heritability’ may be explained as we continue gene mapping studies (Manolio et al., 2009b). It has also been suggested that rare, highly penetrant mutations may lead to more detailed phenomenological research, diagnostic tests, and treatment based on biology rather than on a constellation of clinical symptoms (Corvin, 2011). Whether a more complete delineation would assist with the SZ diagnostic framework is debatable. Another line of investigations suggests the same genetic variants, or different variants at the same gene may confer risk for a range of psychiatric disorders. For example, certain CNVs confer not only high relative risk of SZ but also of other psychiatric disorders, most commonly bipolar disorder, autism, learning disability, ADHD, seizure disorder, obesity and dyslexia (Corvin, 2011; Girirajan et al., 2011; Levy et al., 2012; Malhotra & Sebat, 2012). If these results are extended to additional common variants, they may yet force a change in our diagnostic schema. It is also important to keep in mind that on-going studies are not only targeting the diagnostic entity of SZ, but also clinically relevant variables such as cognitive variation (Barch & Ceaser, 2012; Sugranyes et al., 2011; Taylor & MacDonald, 2012; Wiener et al., 2012) and even daily function (Savage et al., 2012). Credible associations in these domains could provide considerable prognostic assistance to the clinician, particularly if the genetic associations are compounded by identifiable environmental risk factors.

Personalized medicine has been envisioned through custom arrays to interrogate specific CNVs as well as a host of common genes of small effect. Such arrays could also help identify ‘carriers’ – at-risk individuals and relatives – more reliably and accurately than at present. Thus, genetic counselling for SZ, including prenatal diagnosis may become more feasible. Such work is not without ethical challenges that may vary across cultures. Views of family members and clinicians vary widely on issues related to communication of genetic information, risk and genetic testing (DeLisi & Bertisch, 2006).

It is evident from epidemiological studies that genetic variation cannot explain the aetiology of SZ *in toto* (Gottesman & Shields, 1967). Thus, discovery and validation of environmental risk factors remains a mainstay for gene mapping efforts. For example, infections may be one environmental factor increasing risk in a genetically predisposed individual. Maternal viral or parasitic infection during pregnancy is an important risk factor for the subsequent development of SZ in the adult offspring (Brown & Derkits, 2010; Brown & Patterson, 2011; Ellman et al., 2009; Opler & Susser, 2005). The pathogens implicated in these maternal effects include influenza, herpes simplex virus (HSV), rubella and *Toxoplasma gondii*. Seropositivity to HSV-1, related to cognitive deficits and cerebral grey matter changes has been reported in adult SZ patients (Prasad et al., 2010, 2011, 2012) and antibodies to human herpes virus (HHV-6) or *T. gondii* prior to diagnosis in adults have also been associated with SZ (Carter, 2011; Torrey et al., 2012). Increased seropositivity for CMV has been observed at presentation in first-episode SZ (Torrey et al., 2006). It would thus appear that prenatal, childhood, and adult infections could all act as risk factors, perhaps, in a synergistic or additive fashion. If products of host genes interact with the pathogens in the pathological processes leading to disease, host gene polymorphisms may

well affect virulence, providing another example of how gene – environment factors interact to produce disease (Carter, 2009). These interactions have important medical implications and suggest that targeting the appropriate pathogens may have dramatic effects on the incidence and progression of SZ (Yolken & Torrey, 2008). A large number of cytokine- and chemokine-related genes (*CCR5*, *CSF2RA*, *CSF2RB*, *IL1B*, *IL1RN*, *IL2*, *IL3*, *IL3RA*, *IL4*, *IL10*, *IL10RA*, *IL12B*, *IL18*, *IL18R1*, *IL18RAP*, *LTA*, *TNF*) and major histocompatibility complex antigens (*HLAA10*, *HLA-B*, *HLA-DRB1*) have been implicated in SZ and interact with a range of infective agents (Duan et al., 2010; Jones et al., 2005; Miuller & Schwarz, 2007; Nawa & Takei, 2006; Pert, 1988; Saetre et al., 2007; Shirts et al., 2006, 2007; Wright et al., 2001).

The heritability of SZ is 60–80% (Merikangas & Risch, 2003), with risk increasing the closer the relationship to the proband. While risk charts are available for calculating empirical risk to relatives (Austin & Peay, 2006), these are based on reports of family history or psychiatric diagnoses. Risk based on genetic markers would greatly improve prediction of SZ and help develop accurate preventive strategies. Research into such factors needs to progress rapidly (Ayalew et al., 2012; Carter et al., 2002).

Pharmacogenetics

Several genetic polymorphisms are associated with treatment response or drug-induced adverse events to antipsychotics in SZ. Among these the most investigated have been dopaminergic and serotonergic genes and genes from the cytochrome P450 enzyme family (Zhang & Malhotra, 2011). Most studies have focused on candidate genes which are of modest effect, but GWAS studies, such as those based on collaborative studies, are coming to the fore (Clark et al., 2011). The specificity and sensitivity of such polymorphisms needs to be validated through larger studies. Pharmacogenetics thus remains another important, but unfulfilled promise of SZ genetics research.

Rational drug discovery

In theory, gene mapping studies identify biological targets that can provide the starting point for elucidation of pathogenesis, as well as rational drug discovery. In both these contexts, research into DNA variation necessarily has to be coordinated with other aspects of genomics. Thus, investigation of epigenetic phenomena, changes of expression on a large scale and understanding gene – gene interactions in complex networks using systems biology approaches are emerging as promising lines of enquiry (Archer et al., 2010; Benzel et al., 2007; Edwards et al., 2008; Gasso et al., 2010; Guidotti et al., 2010; Kumarasinghe et al., 2012; Liou et al., 2012; Maric & Svrakic, 2012; Rapoport et al., 2012; Schijndel & Martens, 2010; Smith et al., 2010; Van Winkel et al., 2010; Waddington et al., 2007; Woelk et al., 2011; Zahir & Brown, 2011). These newer genome analysis technologies together with other tools such as imaging and optical manipulation of neural circuits hold promise of developing novel insights into the biology of SZ (Rudan, 2010) that in turn may lead to new therapeutic interventions. For example, many of these genes are differentially expressed in post-mortem brain samples from individuals with SZ. They also have DNA variants that are associated with SZ (Law et al., 2006; Mudge et al., 2008; Vawter et al., 2001). Neurobiological data plausibly link many genes to pathophysiological processes considered

relevant in SZ (Harrison & Weinberger, 2005; Lang et al., 2007; Law et al., 2006; O'Tuathaigh et al., 2007; Talkowski et al., 2008). The relationships between putative SZ related genes (e.g. *DISC1*, neuregulin) and their neuropathological consequences (such as dendritic morphology) are not straightforward, and are likely to be influenced by profound gene – gene and gene – protein interactions, leading to incredibly complex ‘interactomes’ (Banerjee et al., 2010; Camargo et al., 2007, 2008; Guo et al., 2009; Hayashi-Takagi & Sawa, 2010; Jaaro-Peled et al., 2009; Schubert et al., 2011; Sequeira et al., 2012; Sun et al., 2010).

Conclusions

Our survey of gene mapping studies in SZ indicates that currently no laboratory-based DNA analyses can assist the clinician at the bedside. However, we must avoid ‘scientific nihilism’ (Poot et al., 2011).

We disagree with the view that, ‘there are no schizophrenia-predisposing genes with large effect sizes, and due to the diversity of findings, genetics-based novel therapies of schizophrenia are not realistic. The new treatments will have to come from functional studies of intracellular pathways and understanding the confluence of environmental influences and genetic predisposition, and their combined effects on developmental mechanisms and intracellular cascades’ (Vereczkei & Mirnics, 2011). We believe that not only have risk factors of large effect size been detected, but importantly, functional studies must proceed in tandem with gene mapping studies to assist the clinician. Since SZ risk includes environmental components, epigenetics in the broadest sense that incorporates an array of environmental risk factors may be one of the optimal approaches (Toyokawa et al., 2012).

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Table 1

Association reports from India.

Gene	SNP	Sample size (case/control)	MAF (cases/control)	Allelic P	Genotypic P	Reference/publication
<i>COMT</i>	rs362204	215/215	0.34/0.27	0.028		Srivastava et al., 2010
<i>TH</i>	rs6356		0.44/0.47		0.04	Srivastava et al., 2010
<i>DBH</i>	rs1108580		0.34/0.33		0.025	Srivastava et al., 2010
<i>COMT</i>	rs4680	398/241		0.026	0.017 (dominant model)	Gupta et al., 2009a
<i>DRD2</i>	rs11608185	254/225			0.043	Gupta et al., 2009b
<i>DRD2</i>	rs6275				0.011	Gupta et al., 2009b
<i>COMT</i>	rs4680			0.029	0.035	Gupta et al., 2009b
<i>GRIK3</i>	T928G (Ser310Ala)	100/100	0.44/0.31	0.01	<0.000001	Ahmad et al., 2009
<i>SLC6A4</i>	rs2066713	243/243	0.31/0.44	<0.001	<0.001	Vijayan et al., 2009
	5HTTLPR		0.42/0.5	0.008	0.03	Vijayan et al., 2009
	STin2 polymorphisms		0.28/0.39	0.001	0.002	Vijayan et al., 2009
<i>Leptin</i> gene	rs 4731426	154 cases for weight gain	median weight gain extreme weight gain	0.05		Srivastava et al., 2008
				0.019		Srivastava et al., 2008
<i>DRD2(H313HTT)</i>	rs 6275	213/196	0.43/0.49		0.004	Vijayan et al., 2007
<i>DRD2(H313HTT)</i>	rs 6275	101/145			0.0012	Kukreti et al., 2006
<i>DRD3</i>	rs10934254			0.03		Talkowski et al., 2006
<i>SYNGRI</i>	rs909685	193/107	0.53/0.42	0.01	0.03	Verma et al., 2005a
	rs715505		0.45/0.29	0.00007	0.0004	Verma et al., 2005a
	rs6001566		0.17/0.24	0.03	0.10	Verma et al., 2005a
<i>MLC1</i>	rs2235349	193/116				Verma et al., 2005b
<i>MLC1</i>	rs2076137	193/116				Verma et al., 2005b
<i>NOTCH 4</i>	197/198(GAAG) ⁵⁴	182 trios		0.014		Prasad et al., 2004
<i>NOTCH 4</i>	(CTG) ₆	182 trios		0.02		Prasad et al., 2004
<i>HTR2A</i> (promoter)		436/700	0.41/0.47		0.001	Semwal et al., 2002
<i>TPH</i> (gene)		293/440	0.34/0.46		0.001	Semwal et al., 2002
Ch 22 CAG repeat	22CH3	108/129		<0.02		Saleem et al., 2001

SNP: single nucleotide polymorphism; MAF-minor allele frequency.