Molecular genetics of schizophrenia: past, present and future

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Schizophrenia is a severe neuropsychiatric disorder with a polygenic mode of inheritance which is also governed by non-genetic factors. Candidate genes identified on the basis of biochemical and pharmacological evidence are being tested for linkage and association studies. Neurotransmitters, especially dopamine and serotonin have been widely implicated in its etiology. Genome scan of all human chromosomes with closely spaced polymorphic markers is being used for linkage studies. The completion and availability of the first draft of Human Genome Sequence has provided a treasure-trove that can be utilized to gain insight into the so far inaccessible regions of the human genome. Significant technological advances for identification of single nucleotide polymorphisms (SNPs) and use of microarrays have further strengthened research methodologies for genetic analysis of complex traits. In this review, we summarize the evolution of schizophrenia genetics from the past to the present, current trends and future direction of research.

1. Introduction

Schizophrenia is a common disorder with a proven genetic basis but complex mode of inheritance. Onset is generally during adolescence with a lifetime morbid risk being approximately 1% in the general population (American Psychiatric Association 1987). A constellation of features including hallucinations and delusions characterize schizophrenia. Notwithstanding several studies on segregation analyses, a consistent Mendelian inheritance pattern has not been observed. This failure can be attributed to both, the genetic and phenotypic heterogeneity underlying the disease. Twin and adoption studies as well as familial clustering have supported a genetic etiology of this illness. However, absence of full concordance among monozygotic twins suggests a role for non-genetic factors in addition to the genetic component.

Till now, no susceptibility gene for schizophrenia has been detected consistently, though a large number of genes have been speculated to be associated with the disorder. A number of parametric and non-parametric linkage studies done so far have failed to pinpoint a single major gene responsible for the causation of the disease. Multiple genes conferring moderate effects have been proposed to provide susceptibility to schizophrenia (McGuffin *et al* 1995) and this is consistent with the

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Abbreviations used: COMT, Catechol *o*-methyltransferase; DAT, dopamine transporter; DR, dopamine receptor; HLA, human leucocyte antigen; IDDM, insulin dependent diabetes mellitus; MAO, monoamine oxidase; MHC, major histocompatibility complex; RA, rheumatoid arthritis; RFLP, restriction fragment length polymorphism; SNPs, single nucleotide polymorphisms; TDT, transmission disequilibrium test; TH, tyrosine hydroxylase; VCFS, velocardiofacial syndrome.

pattern of risk to the family members and epistatic model of multiple contributing loci given by Risch (1990). However, as yet there is neither a clue to the number of genes involved nor to the degree of interaction between the genes and the contribution of each gene to the overall susceptibility to this multifactorial disorder.

Lack of a consistent phenotypic, cytogenetic, or biochemical marker or a neurophysiological test or any specific features (like neurofibrillary tangles in case of Alzheimer's disease) have been a major drawback in both schizophrenia diagnosis and research. One of the most consistent phenotypic marker that has been observed is the eye movement dysfunction. Though eye movement dysfunction was observed and reported by Diefendorf and Dodge in 1908, further advances did not occur till Holzman *et al* (1973) investigated it further. Since then there have been several reports with elevated rates of eye tracking dysfunction in patients suffering from schizophrenia (reviewed by Levy *et al* 1993), and also non-psychotic first-degree relatives. Recently, Arolt *et al* (1996) defined eye tracking dysfunction as a putative phenotypic marker which mapped to a locus on chromosome 6, a region already implicated for schizophrenia, but it would be premature to draw firm conclusions unless additional replicative studies are undertaken.

2. History

The approach to find the putative biochemical basis in schizophrenia has been a little different from most other disorders. The fortuitous discovery of chlorpromazine, a drug to treat schizophrenia in the 1950's paved the way for such research. Chlorpromazine was found to have beneficial effect on patients with schizophrenia and its extraordinary success led to the hope of understanding biochemistry of the illness. *In vitro* studies on the brain tissues of animals conducted revealed that drugs such as chlorpromazine, haloperiodol and other antipsychotic drugs effective in treatment of schizophrenia, were dopamine receptor antagonists. The clinical efficacy of these drugs was correlated with affinity for dopamine D2 receptors. This led to the development of "dopamine theory" of schizophrenia which postulated brain dopaminergic hyperactivity (Thomson 1996). However, dopamine levels or receptors have not shown to be elevated consistently in affected individuals. This aroused the interest in various other neurotransmitters and their receptors present in the brain. The dopamine theory dominated schizophrenia research for the next two decades and still continues to do so.

A large number of early studies based on segregation analyses supported a genetic etiology underlying this disease. However, it was the development of restriction fragment length polymorphism (RFLP) as a mapping tool by Botstein *et al* (1980) which provided markers that could be used to track the chromosomal region(s) of interest. A cytogenetic marker for the probable location of a schizophrenia gene came much later in 1980's when a balanced translocation was reported in a family with two males affected with schizophrenia, an uncle and a nephew. Both the males were found to be partially trisomic for chromosome 5q11·2-q13·3 and carried an extra copy of this region translocated onto chromosome 1. This initial excitement also occurred because chromosome 5q harbours the gene for glucocorticoid receptor, and disturbances in its metabolism could induce psychotic symptoms (though subsequent studies showed the locus for this receptor to be located outside the 5q11-q13 region). Using RFLP markers, Sherrington *et al* (1988) found linkage in two British and five Icelandic families with 39 cases of schizophrenia and Kennedy *et al* (1988) provided evidence against linkage in this region in Swedish samples. Linkage to this region was also ruled out by McGuffin (1990). Subsequently, all the putative biochemical and cytogenetic markers were evaluated with fervour using linkage and association studies but none have provided consistent results.

The completion of a comprehensive genetic map of human genome using the microsatellite markers in middle of 1990's enabled genome-wide linkage analysis. With a large collection of well-documented families and densely spaced microsatellite markers, all human chromosomes were screened worldwide by independent groups or in collaborations. Many promising candidate regions have since been found and work is in progress to establish linkage or association. The late 1990's has given an additional tool in the form of SNP's, which are present abundantly in the genome and can be used in conjunction with the microsatellite markers.

3. Strategies for finding genes for schizophrenia

The genetic analysis of multifactorial disorders has remained a challenge due to the possible risk conferrred by multiple genes of small effect, incomplete penetrance, complex and uncertain mode of inheritance along with the involvement of non-genetic factors. Currently, both association strategies with robust statistical methods as well as the linkage analyses are being used to unravel the genes for schizophrenia.

The methods to discover the genes for schizophrenia can be broadly dichotomized into parametric and non-parametric methods. (i) Parametric methods need the specification of the Mendelian mode of inheritance, number of genes involved, frequency of each susceptibility gene and their penetrance. These methods are useful

for finding the genes for rare disorders or genes of major effect. Conventional linkage analysis includes the study of segregation of marker along with the disease condition within a family and requires generally a large multi-generational and multi-member affected pedigree. However, the main disadvantage of this approach is that it cannot detect genes of small effect, a hallmark of complex traits. Moreover, the mode of inheritance, which is unclear for schizophrenia, has to be specified. (ii) Non-parametric methods appropriately termed "model free analysis" do not require any model specification. A non-parametric method has also been developed for linkage analysis where affected sib-pairs are used but the major limitation of this method is the large number of sib-pairs required for finding a gene of modest effect.

3.1 *Association studies*

Unlike linkage methods**,** association studies are population based and provide an alternative to linkage studies for detecting the genes of small effect. Both case-control approach and family based designs are commonly used to detect association. In contrast to the conventional case-control approach, often marred by the population stratification bias, family based designs like haplotype relative risk (HRR) and transmission disequilibrium test (TDT) are methods of choice (Ewens and Spielman 1995). TDT however, requires at least one heterozygous parent and uses information only from the informative matings and hence a large number of families are discarded from the analysis resulting in loss of power to detect putative association.

4. Current direction of research in schizophrenia

Current research in schizophrenia includes four directions: (i) Detection of structural abnormalities in brain, (ii) evaluation of the effect of drugs on the target receptors, neurotransmitters and the physiology of the brain, (iii) association and linkage studies with putative genes identified based on the biochemical or pharmacological evidence or candidate regions identified by the genome scan studies and (iv) role of epigenetic factors in disease causation.

Several sophisticated techniques like computed tomography (CT), magnetic resonance imaging (MRI), functional imaging and positron emission tomography (PET) along with the conventional post-mortem studies have been used to study the anatomy of the brain of affected individuals and controls. However, this aspect does not fall in the purview of this review and therefore, will not be discussed.

4.1 *Role of neurotransmitters and drugs in the etiology of schizophrenia*

Most of the therapeutic drugs used for the treatment of schizophrenia interfere with the function of neurotransmitter(s) or its receptor(s). Several key neurotransmitters especially dopamine and serotonin have thus become the focal point of schizophrenia research.

Neurotransmitters have been implicated in the etiology of schizophrenia since the time dopamine hypothesis was conceived. A large number of investigations were carried out to explain the role of dopamine, its various receptors and the genes involved in the dopamine neurotransmission pathway but none of the genes so far have been convincingly implicated in the etiology of schizophrenia. Further, it was observed that the drugs blocking dopamine receptors primarily were not effective in the treatment of all patients. Recently several drugs like clozapine (trade name Clozaril) have been marketed. These drugs appear to be as efficacious as conventional medications, with fewer side effects.

The monoaminergic group of neurotransmitters, their receptors and the genes involved in their uptake, synthesis, transport, reuptake and degradation may all play an important role in the pathogenesis of schizophrenia. Though most studies have focused on the dopaminergic and serotonergic group, role of other neurotransmitters and the genes involved in their metabolism like *g*-aminobutyric acid (GABA) type A has also been evaluated. Briefly, the role of some of the candidate genes would be discussed.

4.1a *Dopaminergic system*: Five dopamine receptors have been identified (Grandy *et al* 1989; Dearry 1990; Giros *et al* 1990; Sunhara *et al* 1991; Van Tol *et al* 1991) so far and these can be broadly classified into 2 families: D1 and D2 (Kebabian and Calne 1979). Each of these receptors comprise of about 400 amino acids and are transmembrane protein with seven hydrophobic domains spanning the neural membrane. The structure of some of these receptors is similar to that of other G-protein coupled receptors.

- *Dopaminergic receptors*

D1 family: This family consists of two receptors: Dopamine receptor D1 (DRD1) and DRD5 (table 1).
D2 family: This family consists of three receptors: DRD2, DRD3 and DRD4 (table 1).

- *Dopamine transporter*

Beside the dopaminergic receptors, dopamine transporter (DAT) gene which is located on chromosome 5p15·3 (Vandenbergh *et al* 1992a) and involved in the reuptake

Table 1.   Genes involved in dopaminergic pathway.

Receptor	Location	Function and significance	Linkage and association studies	Result
D1 family				
DRD1	5q35·1	Involved in memory, emotion and cognition, the functions that are highly disturbed in schizophrenics	Grandy *et al* 1990; Litt *et al* 1991; Nothen *et al* 1993a; Cichon *et al* 1994; Liu *et al* 1995; Kojima *et al* 1999	No significant association with any of the polymorphisms
		Several polymorphisms in 5′ and 3′ UTR of the gene (Grandy *et al* 1990; Litt *et al* 1991; Dollfus *et al* 1996; Kojima *et al* 1999)		
DRD5	4p 15·3	DRD5 is neuron specific and is localized within the limbic regions of the brain	Asherson *et al* 1998	No significant association
		Displays high affinity for dopamine		
D2 family				
DRD2	11q 22-q23	Second most abundant dopamine receptor	Gejman *et al* 1994; Nanko *et al* 1994; Asherson *et al* 1994; Nothen *et al* 1994; Sobell *et al* 1994	No significant association
		Higher density of DRD2 in schizophrenic brains (Sedvall and Farde 1995)		
		Ser311/Cys311 polymorphism reported (Arinami *et al* 1994). Cys311 variant more in schizophrenics	Shaikh *et al* 1994	Positive association
DRD3	3q13·3	Expression of DRD3 is restricted to the limbic areas of the brain, site for emotion and cognition that is highly disturbed in schizophrenics	Crocq *et al* 1992; Nimgaonkar *et al* 1993; Mant *et al* 1994	Significant association
		Selective loss of DRD3 mRNA in parietal and motor regions of postmortem schizophrenic brains (Schmauss *et al* 1993)	Nothen *et al* 1993b; Jonsson *et al* 1993; Nanko *et al* 1993; Chen *et al* 1997a; Prasad *et al* 1999	No association
		A to G substitution polymorphism leading to creation of MscI site in exon 1 of DRD3 gene and increased homozygosity at either allele is associated with schizophrenia (Crocq *et al* 1992)	Please see Jonsson *et al* (1999) for exhaustive reference	
DRD4	11p15·5	Higher affinity than other dopamine receptors for atypical antipsychotic clozapine	Sommer *et al* 1993	No significant association
		Polymorphic 48 base pair repeat in putative third cytoplasmic loop		

of dopamine back in the presynaptic terminal has also been considered as a possible candidate. A 40 bp VNTR polymorphism was identified in the 3′ untranslated region of this DAT gene. Alleles with 9 and 10 repeats have been observed to be predominant in most of the populations (Vandenbergh *et al* 1992b; Perisco *et al* 1993; Nakatome *et al* 1996). But no significant association (Daniels *et al* 1995; Pean *et al* 1995; Perisco and Macciardi 1997) or linkage (Byerley *et al* 1993; Perisco *et al* 1995) has been detected with any of the DAT alleles. Association studies with a RFLP polymorphism due to *Taq*1 restriction site in the DAT gene have also not yielded any significant results (Perisco *et al* 1995; Pean *et al* 1995).

• *Tyrosine hydroxylase*

Tyrosine hydroxylase (TH) is a rate-limiting enzyme in the dopaminergic pathway. A rare allele of a tetranucleotide repeat HUMTHO1, located in the first intron of TH is suggested to be associated with schizophrenia (Meloni *et al* 1995) but there are also several contrary reports (Burgert *et al* 1998; Jonsson *et al* 1998).

4.1b *Serotonergic system*: Serotonin is another important neurotransmitter that governs some of the behavioural aspects like sleep, moods, hallucinations and depression. Apart from the brain, serotonin is present in certain body tissues like smooth muscles and in blood platelets. Till now seven serotonin receptors have been identified: 5HT-1, 5HT-2, 5HT-3, 5HT-4, 5HT-5, 5HT-6, and 5HT-7. There is evidence that there are 5 distinct subtypes of 5HT-2 and 3 distinct subtypes of 5HT-3 (Barnes and Sharp 1999; Matsumoto and Yoshioka 2000).

Structural similarities between LSD, a potent hallucinogen and serotonin have been observed. In addition, drugs like Reserpine have been shown to reduce brain serotonin concentrations and can also be beneficial in treatment (Stahl and Wets 1987). These observations have been some of the major lines of evidence to suggest that serotonin may have an important etiological role. Arora and Meltzer (1991) reported a significant decrease in the number of 5HT2a receptors in patients with schizophrenia as compared to the controls and negated the role of neuroleptics for this difference. Hallmeyer *et al* (1992) did not find any linkage between 5HTR2a gene and schizophrenia. Joyce *et al* (1993) found that serotonin receptors and its uptake sites are altered in the limbic systems of people suffering from schizophrenia.

Polymorphism has been described in several genes in the serotonergic pathway and most of these genes have been studied to detect the association with schizophrenia. These include serotonin transporter (SERT or 5-HTT),

serotonin receptors: 5-HT1A (Erdmann *et al* 1995), 5HT1d beta (Nothen *et al* 1994; Sidenberg *et al* 1993); 5-HT2A (Warren *et al* 1993), 5-HT2C, 5-HT6 (Kohen *et al* 1996; Shinkai *et al* 1999), 5-HT7 (Erdmann *et al* 1996). A meta analysis study by Arranz *et al* (1998) showed association of the 102-T/C polymorphism of 5-HT2A with clozapine response in extreme responders (table 2).

4.1c *Genes involved in the degradation of monoaminergic neurotransmitters*: Monoamine oxidase (MAO) and catechol *o*-methyltransferase (COMT) are two important enzymes that are involved in the catabolism of the neurotransmitters.

MAO is present at both pre-synaptic terminal and postsynaptic cell and breaks down excess dopamine and serotonin. COMT is another inactivating enzyme present in postsynaptic cells of dopamine or NE synapse but not serotonin. Floderus *et al* (1981) reported a higher COMT activity in schizophrenics which has not been replicated in many subsequent studies. COMT gene has been mapped to chromosome 22q11·2 and microdeletions in this region leading to a number of diseases including the velocardiofacial syndrome (VCFS) encompass the COMT locus (Dunham *et al* 1992). Further, Pulver *et al* (1994) have reported VCFS patients to have a high risk for developing schizophrenia.

4.2 *Association and linkage studies with putative genes and candidate regions*

A large number of putative genes chosen on the basis of biochemical and pharmacological evidence and candidate sites identified using genome scans have been tested for association or linkage with schizophrenia. Table 3 lists the location of some important putative genes and chromosome sites based on some of the important linkage/association studies undertaken for schizophrenia. Figure 1 is a graphical presentation of their distribution on different chromosomes.

4.3 *Role of epigenetic factors in disease causation*

Epigenetics is a branch of developmental biology that investigates the mechanism by which heritable changes in gene expression occur without the change in the genetic material. Epigenetic phenomenon has been observed in many organisms and it includes position effect variegation, paramutation, age dependent DNA modification etc. (Bestor *et al* 1994; Petronis *et al* 1999). The epigenetic factors may show only partial stability (metastability) when transmitted from one generation to the next generation (Petronis *et al* 1999). New lines of investigations suggest that epigenetic mechanisms might play

an important role in the etiology of complex traits like schizophrenia. Various epigenetic factors like DNA methylation and interaction(s) among gene products might complement the genetic component (Holliday 1989). However, the role of epigenetics in disease causation has not been investigated intensively at present.

Environmental factors can also cause epigenetic changes in the DNA that can result in altered gene expression leading to disease manifestation. Recent studies are suggestive of the role of viruses in the development of schizophrenia. Neurodevelopmental defects have been seen frequently in children of women encountering viral exposure during pregnancy. This theory is also supported by the fact that viral infections like influenza, measles etc. are more frequent during winter months and several studies indicate that children born during winter months develop schizophrenia more often than others (Battle *et al* 1999). It has been speculated that neurodevelopmental defects occur when a mother contracts a viral infection early during pregnancy. Various viruses like influenza (Crow 1997), borna (Iwahashi *et al* 1998), herpes (DeLisi *et al* 1986) etc. have thus been investigated in schizophrenics.

Retroposons have also been advocated for causation of schizophrenia (O'Reily and Singh 1996; Yolken *et al* 2000). Various endogenous retroposon like sequences are present in the genome which remain latent until some trigger such as an infection from other viruses, hormones or chemical messengers released by immune system trigger them into action resulting in the development of the disease (Yolken *et al* 2000).

Four important theories of schizophrenia have been discussed from an epigenetic point of view in a review by Petronis *et al* (1999) with an intent to answer some very basic aspects of schizophrenia genetics. These hypotheses encompass 'neurodevelopmental hypothesis', 'dopamine dysregulation hypothesis', 'viral hypothesis' and 'genetic anticipation and the unstable DNA hypothesis'. DNA methylation occurring during meiosis, gametogenesis etc. has been suggested to have the potential to cause subtle changes in brain development, resulting in neurodevelopmental defects (Petronis *et al* 1999). Dopamine dysregulation has been correlated to control of DRD2 expression, which is believed to be due to differential methylation patterns. In addition, integration of viruses at

Table 2. Genes invovled in serotonergic pathway.

Receptor	Location	Function and significance	Linkage and association studies	Result
5HT2A gene	13q14	Binds clozapine (antipsychotic) more effectively than dopamine	Williams *et al* 1996, 1997; Spurlock *et al* 1998	Significant association
		Both gene and promoter have been investigated.		
		Gene polymorphism: T to C polymorphism viz. T102C (Warren *et al* 1993; Inayama *et al* 1994)	Nimgaonkar *et al* 1996; Chen *et al* 1997b; Hawi *et al* 1997; Verga *et al* 1997; He *et al* 1999; Lin *et al* 1999	No significant association
5HT2A promoter	Chromosome 13	Regulatory region of 5HT2A gene and thus mutations in this region can influence the 5HT2a gene expression and its density	Spurlock *et al* 1998; Kouzmenko *et al* 1999	No significant association
		A to G polymorphism at position – 1438 (Spurlock *et al* 1998)		
SERT or 5HTT	17q11·2-q12	VNTR in intron 2	Heils *et al* 1996; Hranilovic *et al* 2000	
		44 base pair deletion/insertion in the 5HTT promoter region resulting in long and short variant	Brilhault *et al* 1997	Significant Association
		Short variant leads to reduced 5HTT expression (Heils *et al* 1996)	Naylor *et al* 1998; Oliveira *et al* 1998; Rao *et al* 1998	No significant association
TPH gene	Chromosome 11	Rate limiting enzyme in the synthesis of serotonin	Serretti *et al* 1999	No significant association
		Polymorphic site resulting in U and L allele in the intron		
TPH promoter	Chromosome 11	A to G transition at position 6526	Rotando *et al* 1999	No significant association

Table 3. Notable putative genes and chromosomal regions studied for schizophrenia gene using linkage and association strategies.

Chromo-some No.	Chromosomal region	Significance	Linkage/association studies
1	1p 35-32	*	Garver *et al* (1998)
	1q 42·1	Translocation	St. Clair *et al* (1990)
	(1q44)	*	Blouin *et al* (1998)
	1q 21·3	hSKCa3 gene	Wittekindt *et al* (1998)
2	(2p15-14)	*	Shaw *et al* (1998)
	2q21	Balanced translocation	Maziade *et al* (1993)
3	3p 24	*	Pulver *et al* (1995)
	3q 13·3	Dopamine receptor D3 gene	Crocq *et al* (1992); see Jonsson *et al* (1999) for exhaustive reference
4	4p	*	Asherson *et al* (1998)
	4q 24-32	*	Kaufmann *et al* (1998); Kennedy *et al* (1998); Hovatta *et al* (1999)
5	5p14·1-13·11	*	Silvermann *et al* (1996)
	5q	*	Sherrington *et al* (1988)
	5q21-23	*	Straub *et al* (1997)
6	6p24-22	*	Moises *et al* (1995); Straub *et al* (1995)
		HLA genes	Nimgaonkar *et al* (1992, 1995, 1997); Wright *et al* (1996); summarized in Gibson *et al* (1999)
		Eye tracking dysfunction gene	Arolt *et al* (1996)
	6q 21-22·3	*	Cao *et al* (1997)
7	7q21·1-q21·3	*	Blouin *et al* (1998)
8	8p22-21	*	Pulver *et al* (1995); Kendler *et al* (1996)
9	9q34·3	*	Riley *et al* (1997)
		Dopamine*b* hydroxylase gene	Meszaros *et al* (1996)
		A subunit of NMDA receptor gene	Heresco *et al* (1999)
10	10p15-q21	*	Faraone *et al* (1998); Schwab *et al* (1998); Foroud *et al* (2000)
11	11p15·5	Dopamine D4 receptor gene	Sommer *et al* (1993)
	11q 22-23	Dopamine D2 receptor gene	Gejman *et al* (1994); Shaikh *et al* (1994); reviewed in Gill *et al* (1993)
	11q	Translocation	St. Clair *et al* (1990)
12	–	*	Dawson *et al* (1995)
13	13q14	5HTR2a (serotonin receptor 2a)	Campbell *et al* (1997); Erdmann *et al* (1996)
	13q14·1-q32	*	Riley *et al* (1998)
	13q32	*	Blouin *et al* (1998); summarized in Barden and Morissette (1999)
14	–	*	Craddock and Lendon (1999)
15	15q13-q14	*	Curtis *et al* (1999)
		*a*7 nicotinic cholinergic receptor subunit gene (CHRNA7)	de Leon *et al* (1995); summarized in Riley and McGuffin (2000)
16	–	*	Detera-Wadleigh (1999)

Contd . . .

(**Table 3.** *Contd.*)

Chromosome No.	Chromosomal region	Significance	Linkage/association studies
17	17q11·2-q12	Serotonin transporter gene (5HTT)	Heils *et al* (1996); Rao *et al* (1998)
18	18p	*	Schwab *et al* (1998); Calzolari *et al* (1996)
	18q21·1	*	Williams *et al* (1999); summarized in Riley and McGuffin (2000)
19	–	*	Parfitt *et al* (1996); reviewed in Gejman (1999)
20	20p		Hovatta *et al* (1998)
21	–	*	Byerley *et al* (1995); reviewed in Gurling (1998)
22	22q13	IL2RB gene	Pulver *et al* (1994)
		COMT gene (catechol-o-methyl transferase)	Chen *et al* (1999)
		14-3-3 protein *h*-chain gene (YWHAH)	Toyooka *et al* (1999)
	22q11	Deletion in this region	Basset *et al* (1998); Basset and Chow (1999); Murphy *et al* (1998)
	22q12-q13	*	Pulver *et al* (1994)
	22q (D22S278)	*	Moises *et al* (1995); summarized in Riley and McGuffin (2000)
X	Pseudoautosomal locus	*	Maier *et al* (1995); d'Amato (1994)
	Xp11	*	Dann *et al* (1997)
	Xq27-28	*	DeLisi (1997); summarized in Riley and McGuffin (2000)
Y	Pseudoautosomal region	*	Yamada *et al* (1982); Crow (1992); summarized in DeLisi (1997)

*Indicates candidate regions identified by genome scan studies.

specific positions and their activity is advocated to be under control of epigenetic mechanisms, leading to disruption of neurodevelopmental processes by viral toxic substances, resulting in brain abnormalities associated with schizophrenia. Epigenetic mechanisms have also been suggested to be the molecular equivalents or a cause of anticipation by Petronis *et al* (1999). Subsequently, Petronis (2000) has affirmed the role of genomic imprinting and differential methylation of regulatory regions as epigenetic factors in regulation of Serotonin 2A receptor gene (HTR2A) as well.

Besides neurotransmitter disturbances, immune dysfunction has also been observed in a subset of schizophrenics. Various markers from immune system have thus been studied. A large number of reports indicate that schizophrenia like most other neurological disorders shows phenomenon of anticipation. These two aspects are briefly discussed below.

5. Immune response in schizophrenics

A large number of inherited biochemical markers have been studied for association with schizophrenia including the immunoglobulins, haptoglobin types, blood groups, substance P, enzymes like porphobilinogen deaminase, adenosine deaminase, tyrosine hydroxylase etc. (summarized in Nimgaonkar *et al* 1992). None of the markers have shown a consistent association. However, an increasing number of studies have suggested occurrence of immune dysfunction in a subset of schizophrenics.

Altered levels and numbers of various components of immune system like immunoglobulins, complements, interleukins (IL2), CD3^{+} and CD4^{+} have been reported (Solomon 1981; DeLisi *et al* 1982; Ganguli and Rabin 1989; Muller *et al* 1991; Zamani *et al* 1994). Since the HLA system governs the immune responses, HLA genes were implicated in the etiology of schizophrenia. Past association studies with various HLA class I alleles yielded inconsistent results (summarized in Nimgaonkar *et al* 1992) except HLA-A9. The reason suggested for inconsistencies include population stratification, case-control mismatch, different diagnostic criteria and use of serological techniques which are error prone (Nimgaonkar *et al* 1992). It has been further observed that HLA class II alleles might be more important than HLA class I alleles in view of the autoimmune pathology suggested for schizophrenia.

Autoimmune pathology has been advocated (Knight 1982; Ganguli and Rabin 1987) because of increased levels of antibrain antibodies (Heath and Krupp 1967; Shima *et al* 1991). Also, an inverse relationship between schizophrenia and autoimmune diseases like rheumatoid arthritis (RA) (Eaton *et al* 1992; Wright *et al* 1996) and insulin dependent diabetes mellitus (IDDM) (Finney 1989) has been reported.

Human leucocyte antigen (HLA) class II alleles play an important role in autoimmune responses (Trucco 1992; Lechler 1994) and many autoimmune diseases seem to be HLA DR and DQ associated (Mignot *et al* 1995). Several studies have reported linkage with schizophrenia around the HLA locus (Moises *et al* 1995; Schwab *et al* 1995).

Since RA and IDDM are inversely related to schizophrenia, HLADRB1*04 (DR4) and HLADQB1 region positively associated with RA and IDDM respectively, were studied (Finney 1989; Knight *et al* 1992). A negative association of schizophrenia with DR4 (Wright *et al* 1996) and HLADQB1*0602 (Nimgaonkar *et al* 1992, 1995, 1997) was found. However, Gibson *et al* (1999) in their population did not find any association of schizophrenia with A9, DR4 or DQB1*0602.

Recently Wei and Hemmings (2000) reported that the HSMHC3A5 locus present near the major histocompatibility complex (MHC) class I and class II junction is significantly associated with schizophrenia. This locus harbours the Notch 4 gene, which consists of 30 exons
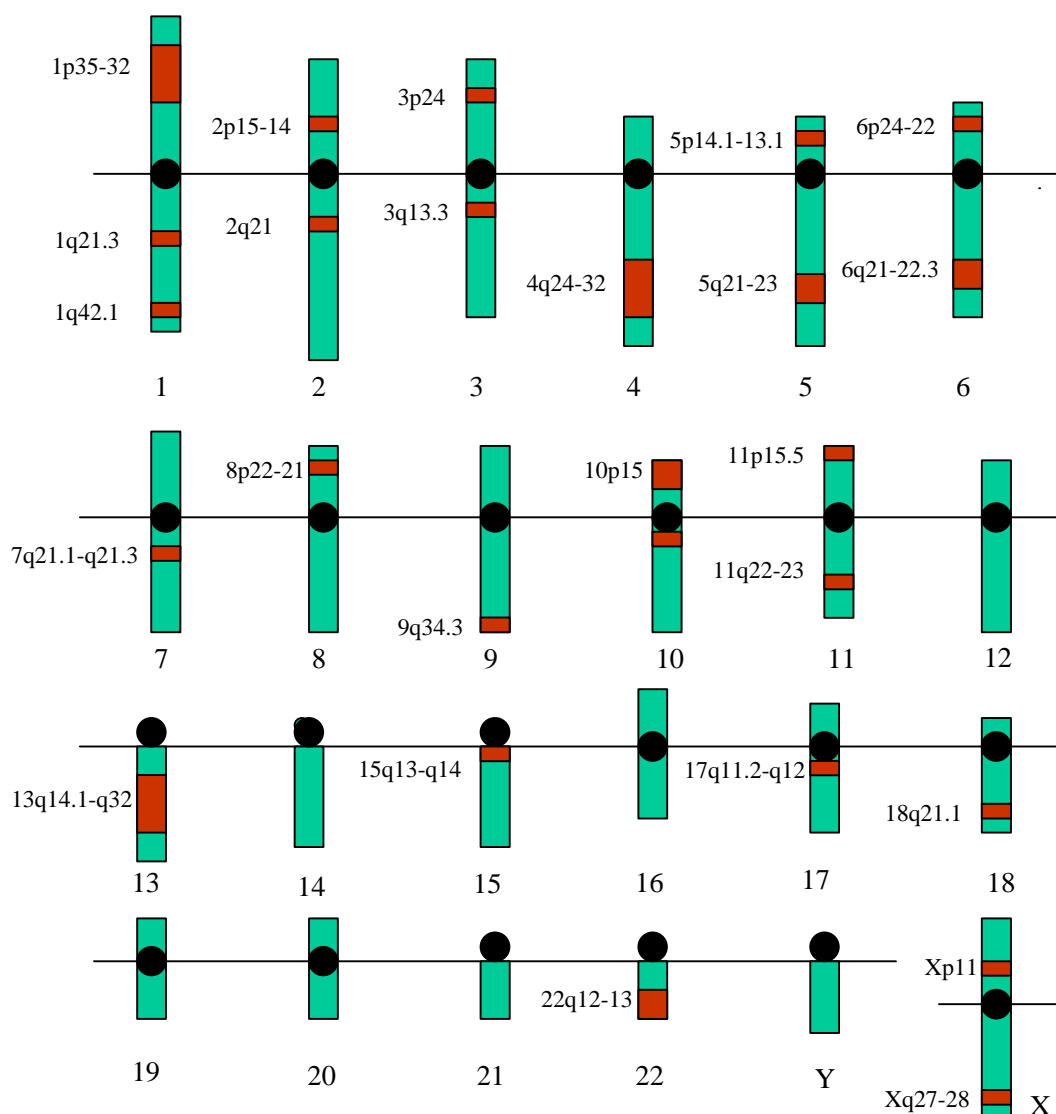

Figure 1. A glimpse of genes/chromosomal sites implicated for schizophrenia based on linkage and association studies. Black circle denotes centromere. Red colour denotes candidate sites/location of candidate genes.

and spans 36·8 kb region inclusive of a putative promo-ter. Haplotype combination of markers especially SNP2-(CTG)n from Notch 4 locus showed strong association with schizophrenia. The function of Notch 4 is not known in humans but animal studies have shown that it is involved in neurodevelopmental process. Thus, non-immune related genes localized to the HLA region may have an etiological role in schizophrenia.

6. Anticipation in schizophrenia

Dynamic mutations characterized by expansion of triplet repeats are known to cause at least 13 different neuro-degenerative disorders. Genetic anticipation, a phenomenon characterized by increase in disease severity combined with an early onset of disease with succeeding genera-tions, has been observed in several neuropsychiatric dis-orders with trinucleotide expansions (Ross 1993; Johnson *et al* 1997) and suggested in schizophrenia as well (Bassett and Honer 1994). Various trinucleotide repeats have been studied using candidate gene as well as the repeat expansion detection (RED) technique (Rubinsztein *et al* 1994; Jain *et al* 1996; McInnis *et al* 1996; Gaitonde *et al* 1997; Saleem *et al* 1998). Large CAG repeats have been reported to be more frequent in patients than in controls (Morris *et al* 1995; O'Donovan *et al* 1995). Therefore, genes with unstable trinucleotide repeats are being considered as suitable candidates for underlying pathology of schizophrenia and are being analysed.

Chandy *et al* (1998) described one such candidate gene which is a human calcium-activated potassium channel gene (hsKCa3), and has been mapped to 1q21·3. This gene at the N-terminal region contains two contiguous CAG repeats with the second repeat being polymorphic (repeat size varying from 12 to 28 repeats). The long allelic variant of the polymorphic repeat is shown to be overrepresented in the schizophrenics in comparison to controls (McInnis *et al* 1998). However, most of the reports have been controversial (Bowen *et al* 1998; Austin *et al* 1999; Guy *et al* 1999. Antonarkis *et al* 1999; Joober *et al* 1999. Saleem *et al* 2000a).

Several other ion-channels like γ-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA) receptor and its ligand (e.g. AMPA) are also being investigated since antagonists to these receptors produce schizophrenic symptoms (Tsai *et al* 1998; Gargus *et al* 1998; Agha-janian and Marek 2000).

7. Schizophrenia research in India

A large number of studies for schizophrenia have been conducted mainly in the Caucasoid population. However, it is desirable to perform similar studies in different ethnic groups to reaffirm the status of the association or linkage identified. Indian population is very well suited for such studies as it satisfies many criteria required for the investigation of complex traits. Besides, Indian population is an attractive large reservoir of samples both due to its population size as well as the high rate of marital stability, the latter essential for family based analysis.

Work on schizophrenia genetics has been initiated since the last 5–6 years by two major groups, one of the authors and the other one based at NIMHANS in Bangalore. The Hindi version of the Diagnostic Interview for Genetic Studies (DIGS) and Family Interview for Genetic studies (FIGS) (Deshpande *et al* 1998) has been validated and is being used by the authors group. A total of 260 families including sib-pairs and trios have been collected and used for genetic analysis. Genes in the dopaminergic and serotonergic pathways in the brain have been studied in predominantly North Indian samples by the authors. Using family based association test, DRD3 locus did not show any association (Prasad *et al* 1999). In another study, four genes (5HT2A, TPH, COMT and DAT) involved in monoaminergic pathway evaluated using TDT, have also failed to show any significant association (Semwal *et al* 2001). An asso-ciation between cytosolic phospholipase A2 (cPLA2) locus and schizophrenia has also been evaluated in the family based samples among Indians but no significant association has been detected (Chowdari *et al* 2001). A large difference in CAG repeat allele sizes in case of patients suffering from schizophrenia compared to the controls has been reported at the Machado-Joseph Disease (MJD) locus. Though longer CAG repeat at MJD locus is not associated with schizophrenia, the role of smaller unstable repeats in disease manifestation cannot be excluded (Saleem *et al* 1998). Saleem *et al* (2000a) observed no association with serotonin transporter (5-HT) in patients suffering from bipolar disorder based on case-control approach. Though no association has been observed with the hSKCa3 polymorphism by the same group (Saleem *et al* 2000b) they have shown that a large difference in allele sizes greater than or equal to five occurs in patients compared to controls. Association studies with candidate genes that may play a role in susceptibility to Tardive Dyskinesia among schizophrenia patients is being investigated by the author's group. This is expected to serve as a model for pharmacogenetic studies especially of complex traits. Presently, the author's group is carrying out high throughput SNP genotyping of several candidate genes in schizophrenia.

8. Future strategies

Considering the complex nature of the common disorders, with no clue to the number and nature of genes involved

or their location, it is difficult to search for the genes using the conventional techniques that help unravel the genes for single gene disorders. Various new experimental and statistical methodologies have been developed and are in current use to hunt for the genes underlying schizophrenia.

Non-parametric method of linkage analysis using large collection of affected sib-pairs along with the genome scan studies using affected sib-pairs would be a more effective and favoured strategy to track genes of minor effect. Considering schizophrenia is a polygenic disorder, gene-gene interaction among putative markers is expected to yield important clues to the underlying pathology. Haplotype analysis could be informative where genotypic combination might be crucial in providing the susceptibility. Along with the exons of candidate genes, intron sequences should also be searched for mutations. SNPs coupled with the powerful technique of DNA microarrays can add a new dimension to the existing research methodologies. Strategies employed in parallel studies on other complex traits such as diabetes and hypertension would also be useful in navigating the search for genes. Type I diabetes exemplifies the role of non-parametric linkage and association mapping in identifying the susceptibility genes and loci. Initially, case-control association studies revealed association of type I diabetes to HLA at 6p21 and the insulin gene on 11p15 chromosomal region (reviewed by Thomson *et al* 1989). Using affected sib–pairs, linkage was subsequently demonstrated to HLA (IDDM1) (Cudworth and Woodrow 1975) and non-HLA genes like IDDM4 (11q13), IDDM5 (6q25), and IDDM12 (2q33) while other non-HLA genes like IDDM2 were identified using association studies (reviewed by Thomson 2001). In hypertension, on the other hand, SNP identification in candidate genes is already underway in search for common variants that might provide susceptibility. Around 874 SNPs in 75 candidate genes for hypertension have been identified by Halushka *et al* 1999 (see review by Gray *et al* 2000).

Association studies, but with more powerful analytical tools such as SNPs, would remain instrumental in searching the genes for common disorders because of their significant power to identify the pathogenic allele(s) in contrast to the linkage strategy. Limitation of small sample size in such studies could be overcome by meta-analysis approach. The meta-analysis method synthesizes information by pooling relatively weak signals from independent genetic association studies into consolidated stronger evidence for genetic effects. Thus, evidence from multiple studies are pooled and variations among studies are accounted for, to arrive at a pooled measure of genetic linkage (Gu *et al* 2001). However, the limitation in performing association studies would still be the requirement of prior knowledge about the candidate genes/candidate chromosomal sites. Therefore, availability of extensive data on polymorphism in the whole genome could provide a large number of markers for effective association studies. SNPs coupled with microsatellite markers seem to be the ideal tools for such studies and use of microarrays could provide a high-throughput genotyping method in the near future.

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