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Review

A systematic review of the effect of genes mediating neurodevelopment and neurotransmission on brain morphology: Focus on schizophrenia

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ABSTRACT

Structural brain abnormalities have been extensively investigated as potential endophenotypes of schizophrenia. Apart from enlarged ventricles and whole brain volume reductions, no other consistently replicated brain morphometric abnormalities have emerged from these studies. The differential effect of genetic variants on brain morphometry could be a major source of variability underlying such inconsistent findings. Schizophrenia is a polygenic disorder, wherein the complex interplay between common risk variants of small effect, rare risk alleles of large effect as well as epigenetic interactions confer vulnerability and mediate the final expression of the clinical phenotype. A comprehensive understanding of the effect of risk genes on brain morphometry is essential for linking the structural endophenotype/s that can be linked with the genetic diathesis for development of schizophrenia. We systematically reviewed published literature to examine the effect of genes mediating neurodevelopment and brain signalling on brain morphometry. A majority of polymorphisms of the above genes was shown to be associated with whole brain and regional volumetric reductions; but importantly, many genes showed mixed effects, i.e., both volume reductions and increases. Modelling such complex interactions of the large number of risk genes on brain volume in vivo poses considerable practical challenges in having adequate sample sizes as well as imaging data for reliable quantification. Therefore,

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Neurotransmission
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it is recommended that the field should move beyond association studies of the morphometric effect of single or limited number of gene polymorphisms in clinical populations to modelling the complex epistatic and epigenetic interactions in silico or using animal and cellular models.

1. Introduction

The nature and extent of structural brain abnormalities in schizophrenia have been explored extensively using advanced neuroimaging tools.[1,2] However, apart from enlarged ventricles[3,4] and whole brain volume reductions,[5] no particular regional volumetric abnormality has emerged so far as a hallmark of schizophrenia.[2,6,7] This implies that any given regional brain morphometric alteration need not be a necessary pre-requisite for development of schizophrenia. Instead, brain volumetric abnormalities in schizophrenia may be epiphenomena resulting from somatic mutations, genetic polymorphisms and/or epigenetic phenomena mediated by the influence of environmental factors acting in a combinatorial manner.[8]

Considerable amount of evidence has pointed towards the link between genetic factors and brain structure.[9] Many of the gene polymorphisms that have an effect on brain structure have also been implicated as candidate genes conferring genetic vulnerability for development of schizophrenia.[10] However, schizophrenia is a polygenic condition wherein the complex interplay between common risk variants of small effect and rare risk alleles of large effect confer vulnerability towards developing the condition.[11] Therefore understanding the individual and interactional effects of different candidate genes on brain volume in healthy subjects and those suffering from schizophrenia is of paramount importance for a comprehensive understanding of how genetic factors mediate brain structural variations that confer risk for developing the disorder.

2. Impact of gene polymorphisms on brain structure in schizophrenia

Genome wide association studies (GWAS) in schizophrenia have identified risk variants with high statistical confidence using large samples from different ethnic backgrounds.[12,13] It was earlier suggested that several genes of small effect interact with environmental factors leading to the expression of the disorder.[14] However, with the advent of GWAS studies and genomic microarray technology, a number of rare variants of high penetrance have also been shown to confer risk towards schizophrenia.[15,16] Thus, the complex interplay between common risk alleles of small effect and rare CNVs (copy number variations) of large effect may be contributing to the overall risk of developing schizophrenia.[17] Many of the candidate genes that confer vulnerability for developing schizophrenia have also been shown to impact brain structure.[18,19] A large body of imaging-genomics studies has examined the extent of genetic influence on structural brain variation in schizophrenia.[20,21] Genes involved in brain maturational processes and signalling have been reported to modulate the emergence and progression of psychosis.[22] A review of the effects of genes on brain morphometry not only in patients with schizophrenia but also in the healthy population would shed further light on the contribution of brain structural abnormalities mediated by genetic risk variants to the pathophysiology and vulnerability for development of schizophrenia.

We therefore, performed a systematic review of peer-reviewed publications that have reported the effect of polymorphisms of various risk genes on brain structure in patients with schizophrenia, those at genetic high risk for development of schizophrenia as well as healthy subjects. We performed the search using the key words ''schizophrenia'', ''single nucleotide polymorphisms (SNPs)'', ''risk genes'', ''candidate genes'' ''risk variants'', ''brain volumetry'', ''brain morphometry'', ''brain structure'' and ''brain structural abnormalities'', in Pubmed, Google Scholar and Science Direct from March 1999 to June 2013.

The above search yielded a wide array of genes that were shown to have an effect on whole or regional brain volumes in patients with schizophrenia, subjects at high risk for developing schizophrenia and/or healthy subjects. We sub-divided these genes having an effect on brain structure into those that predominantly mediate neurogenesis and/or neurodevelopment and those that predominantly mediate signalling in the nervous system (Table 1).

2.1. *Genes that primarily mediate neurogenesis/neurodevelopment*

According to the `two hit' hypothesis of schizophrenia, dysregulation of genes either in the developmental stage (i.e. during morphogenesis) or during neuronal maintenance of the adult brain caused by genetic or environmental factors could lead to destruction of specific neural networks or loss of synaptic plasticity.[23,24] The following section focuses on impact on brain morphology of those genes that predominantly mediate neurogenesis/neurodevelopment, involving functions such as neuronal differentiation, proliferation, migration, regeneration, pruning and survival; synaptogenesis, myelination, neuronal connectivity, etc. The findings of studies that have reported the effect of the genes that regulate neurogenesis/neurodevelopment on brain morphometry are summarized in Table 2 and Figs. 1 and 3.

(i). Disrupted in schizophrenia1 (DISC1)

Disrupted in schizophrenia1 (DISC1) plays a crucial role in neuronal development and synaptic modulation by participating in neuronal migration,[25] dendritic organization[26] and neuronal signalling.[27] It fulfils these developmental processes

Table 1 – List of schizophrenia risk genes reported to have effects on brain morphology, classified according to their predominant role in neurodevelopment or neurotransmission.

A. Genes mediating neurogenesis/neuro-development	B. Genes regulating neurotransmission
1. DISC1 (neuronal progenitor cell proliferation, neuronal migration, cell survival)[c]	1. NRG1 (glutamatergic transmission)[b]
2. NEUROG1 (initiation of neuronal differentiation)[a]	2. DTNBP1 (pre-synaptic glutamatergic transmission)
3. PCDH12 (neuronal differentiation and synaptogenesis)	3. DAOA (activates D-amino acid oxidase involved in the metabolism of D-serine, an agonist at the glycine modulation site of NMDA receptor)[b]
4. RELN (neuronal migration and synapse remodelling)	4. GRIN2A (excitatory neurotransmission, synaptic plasticity-mediating memory function)
5. BDNF (neuronal proliferation, differentiation, neuronal cell survival)[a]	5. GRID1 (excitatory neurotransmission and synaptic plasticity)
6. GSKB (Regulates cell proliferation, synapse rearrangement, cell adhesion)	6. GAD1 (GABA synthesis)
7. PRNP (neuronal development)	7. COMT (catecholamine metabolism)
8. PCM1 (neuronal cell growth)	8. MTHFR (regulates dopamine signalling in prefrontal cortex)[b]
9. TNFRSF1B (neuronal development and neurite outgrowth; nerve cell degeneration)[a]	9. HTR2A (G-protein-coupled 5HT neurotransmission)
10. NTF3 (neuronal survival and differentiation)	10. RGS4 (modulates G-protein signalling in a number of neurotransmitter systems-glutamate, dopamine and serotonin; negatively regulates GPCR signalling)
11. PLXNB3 (axonal guidance, neuritogenesis)	11. ZDHHC8 (regulates activity of the AMPA receptor and GABA receptor B; cell adhesion molecules, ion channels, scaffolding molecules, signalling proteins and neurotransmitter release machinery are modified)[b]
12. MAG (myelination)	12. NRGN (regulates calcium and calmodulin binding)[b]
13. FOXP2 (proper development of speech and language regions during embryogenesis)[a]	13. NRXN1 (GABA-ergic and Glutamatergic transmission)
14. ZNF804A (neural connectivity)	**C. Others**
15. NOTCH4 (initiate neural fates, regulates proliferation and apoptosis)	1. 22q11 locus (contains multiple risk genes conferring susceptibility to schizophrenia)
16. IL6 (regulates apoptosis in granular neurons)[c]	2. IL1 cluster (neurodevelopmental process; acute and chronic degeneration)[c]
17. APOE (nerve injury and regeneration)	
18. VRK2 (prevents apoptosis, axonal development)	

[a] Genes primarily regulating neurogenesis/neurodevelopment and are also involved in neurotransmission.
[b] Genes primarily modulating neurotransmission that are also involved in neurogenesis.
[c] Genes mediating neuronal proliferation, differentiation and other neuroregulatory process via cell-surface receptor linked signal transduction such as Wnt signalling, interleukin signalling, NOTCH signalling or cadherin signalling.

through Wnt (wingless) signalling, a fundamental pathway required for the embryonic development of central nervous system (CNS).[28] DISC1 is a promising candidate gene for major psychiatric disorders.[29] Two common nonsynonymous SNPs, rs6675281 (Leu607Phe) ($P < 0.0000023$) and rs821616 (Ser704Cys) ($P < 0.0052$) within the DISC1 gene have been reported in schizophrenia by previous studies.[30,31]

The Phe carriers ($n = 11$) of Leu607Phe rs6675281 variant showed less gray matter (GM) in the superior frontal gyrus (SFG) and anterior cingulate cortex (ACC) and greater severity of positive symptoms (hallucinations) compared to Leu/Leu homozygotes ($n = 33$) ($t = -2.24$, $df = 1.38$, $P < 0.03$; 95% CI = −261 to −3609) in patients with schizophrenia ($N = 19$) as well as in healthy subjects ($N = 25$).[19] The Phe carriers ($n = 24$) of the SNP Leu607Phe (rs6675281)were reported in another study to have reduced cortical thickness in the left supramarginal gyrus, when compared to Leu homozygotes ($n = 72$).[32] Moreover, the Ser allele at Ser704Cys (rs821616) ($n = 86$) was shown to be associated with genetic risk for schizophrenia ($P < 0.004$) as well as with reduced hippocampal gray matter volume (GMV) bilaterally when compared with Cys homozygotes ($n = 10$) ($P < 0.05$, corrected)[33] and also Ser/Ser subjects ($n = 34$) had greater GMV in bilateral parahippocampus ($P < 0.06$, corrected) compared to Cys allele carriers ($n = 37$) in healthy individuals ($N = 71$).[34] However, there have been conflicting reports of the effect of the SNP rs821616 on hippocampal GMV with one study showing lower[33] and another study reporting greater[34] GMV in hippocampus in healthy subjects.

(ii). Neurogenin 1 (NEUROG 1)

Neurogenin encodes a basic helix–loop–helix transcription factor and regulates transcriptional activity. During neurodevelopment, NEUROG-1 is expressed in the dorsal ventricular zone and in dorsal thalamus.[35] It induces glutamatergic neurons in deeper layers of neocortex and represses subcortical GABA-ergic neurons.[36,37] Fanous et al.[38] reported significant association of NEUROG1 with schizophrenia. In this study, the major allele of rs2344484 and rs8192558 was shown to be over-represented in 25 affected subjects from the Irish Study of High-Density schizophrenia Families ($P < 0.07$).

In a large cohort of patients with schizophrenia ($N = 319$) and healthy control subjects ($N = 173$), Ho et al.[39] demonstrated that the C allele carriers ($n = 425$) of rs2344484 had lower total cerebral GMV and temporal GMV ($F \geq 3.92$, $df = 1491$,

Table 2 – Effects of schizophrenia risk genes and susceptibility loci that regulate *neurodevelopment* on whole or regional brain morphometry in healthy subjects and/or patients with schizophrenia.

Gene and loci (number of articles referred)	SNP	Brain regions	Morphometric findings (H-Healthy; S-Schizophrenia; COS-Childhood onset schizophrenia)
A. Neurogenesis			
DISC1,1q42.1 (11)[b]	rs6675281	Superior frontal gyrus and ACC (bilateral)	↓GMV-S,H (Szeszko et al., 2008)
	rs821616	Bilateral hippocampus	↓GMV-H (Callicott et al., 2005)
	rs6675281	Left supramarginal gyrus	↓Cortical thickness-H (Brauns et al., 2011)
	rs821616	Bilateral hippocampus	↑GMV-H (Di Giorgio et al., 2008)
NEUROG 1, 5q31.1 (5)[c]	rs2344484	Total cerebral and temporal volumes	↓-S,H (Ho et al., 2008)
PCDH12 (2)	rs164515	Coefficient of the gyrification index	Asymmetry-S (Gregorio et al., 2007)
RELN, 7q22 (4)	rs362691	Left and right ventricles	↑-S (Gregorio et al., 2007)
BDNF,11p13 (8)[c]	rs6265	Hippocampal, amygdalar, frontal, temporal, parietal and occipital volumes (bilateral)	↑WMV-H (Toro et al., 2009)
		Left parahippocampal and left supramarginal gyrus	↑GMV-S (Ho et al., 2006)
		Left inferior temporal gyrus, prefrontal cortex and lateral occipital cortex	↑GMV)-H (Ho et al., 2006)
		Frontal, temporal, cingulate and insular cortices	↓GMV-H (Yang et al., 2012)
		Frontal (bilateral)	↓GMV-S (Ho et al., 2007)
		Lateral ventricles	↑-S (Ho et al., 2007)
GSK3B, 3q13.3(7)[b]	rs334558	Posterior regions of right middle and superior temporal gyri	↑-S (Benedetti et al., 2010)
PRNP,20p13 (5)	rs1799990	WMV	↓-S,H (Rujescu et al., 2002)
		CSF compartments	Enlargement-S,H (Rujescu et al., 2002)
PCM1, 8p22 (3)	D8S261, D8S2616, rs445422, rs13276297, and rs370429	Bilateral medial orbitofrontal cortex	↓-S (Gurling et al., 2006)
TNFRSF1B, 1p36.22 (8)[c]	Biallelic marker at 3′UTR	Ventricles	↑-S (Wassink et al., 2000)
		Frontal lobes	↓-S (Wassink et al., 2000)
NTF-3, 12p13.31 (5)	Dinucleotide repeat (CA)n polymorphism	Mean right hippocampal volume	↓-S (Kunugi et al., 1999)
PLXNB3, Xq28 (3)	Haplotype A (I598-D1156)	WMV	↑-S, H (Rujescu et al., 2007)
		CSF	↓-S (Rujescu et al., 2007)
MAG, 19q13.1 (7)	rs720308	Left temporal	↓GMV-S,H (Felsky et al., 2012)
		Left parietal	↓GMV-S (Felsky et al., 2012)
ZNF804A,2q32.1 (6)	rs1344706	Bilateral angular gyrus, right parahippocampal gyrus,right posterior cingulated,right medial orbitofrontal gyrus/gyrus rectus, left inferior frontal gyrus, right inferior temporal gyrus and right cerebellum	↓GMV-H (Lencz et al., 2010)
		Total, frontal and parietal lobe	↑WMV-S (Wassink et al., 2012)
NOTCH4, 6p21.3 (6)[b]	$(CTG)_n$ polymorphism	Frontal volume (bilateral)	↑GMV-S; ↓GMV-H (Wassink et al., 2003)
		CSF	↓-S; ↑-H (Wassink et al., 2003)
FOXP2, 7q31(5)[c]	rs2396753	Bifrontal and temporal cortices with local maxima in left dorsolateral prefrontal cortex extending to amygdala, bilateral insula, anterior cingulate, bilateral premotor area,right somatosensory cortex and bilateral superiolateral temporal cortex	↓GMC-S (Spaniel et al., 2011)
		Bilateral cerebellum, right basal ganglia, bilateral parietal lobe and left occipital lobe. Broca's and wernickes area	↓GMV-S (Spaniel et al., 2011)

Table 2 (*Continued*)

Gene and loci (number of articles referred)	SNP	Brain regions	Morphometric findings (H-Healthy; S-Schizophrenia; COS-Childhood onset schizophrenia)
IL6, 7p21 (5)[b]	rs1800795	Hippocampal volume on right side	↑-H (Baune et al., 2012)
APOE, 19q13.2 (6)	rs429358	Ratio of right hippocampus to hemisphere volumes	↓-S (Hata et al., 2002)
		Right hippocampus volume	↓-S (Hata et al., 2002)
VRK2, 2p16.1 (7)	rs2312147	TBV and WBV	↓-H (Li et al., 2012)
B. Susceptibility loci			
22q11 locus (13)[a]	22q11.2 deletion polymorphism	Brain network comprising anterior, mid and posterior cingulate gyri and insula (bilateral)	↓GMC-S (Liu et al., 2012)
	rs2097603	Left superior temporal gyrus and bilateral temporal lobes	↓GMV -S (Chow et al., 2011)
Haploinsufficiency of COMT and PRODH at 22q11 locus (1)[a]	rs2008720	Right superior temporal gyrus	↑GMV-S (Zinkstok et al., 2008)
	rs450046	Frontal lobes (bilateral)	↓WMV-S (Zinkstok et al., 2008)
	rs4680 and rs20086720	Left frontal lobe (Fasiculus Uncinatus)	↓WMV-S (Zinkstok et al., 2008)
		Left inferior frontal lobe	↑WMV-S (Zinkstok et al., 2008)
IL-1 cluster, 2q13 (9)[a,b]	rs16944 (IL-1β)	Bifrontal-temporal	↓GMV-S (Meisenzahl et al., 2001)
	VNTR polymorphism (IL-1RN)	Right and left ventricles	Enlargement-S (Papiol et al., 2005)

Abbreviations: GMV, gray matter volume; GMC, gray matter concentration; WMV, white matter volume; TBV, total brain volume; CSF, cerebrospinal fluid; ACC, anterior cingulate cortex.

[a] Loci containing genes regulating neurodevelopmental process.

[b] Genes mediate cell–cell signalling, cell–cell adhesion, cell–matrix adhesion via cell-surface receptor linked signal transduction such as Wnt signalling, interleukin signalling, NOTCH signalling or cadherin signalling.

[c] Genes which also regulate activity and function of neurotransmission.

$P \leq 0.05$) in comparison to T-homozygotes ($n = 67$) in both patients and healthy subjects. The frequency of the C allele of rs2344484 was found to be significantly higher in the schizophrenia group ($\chi^2 \geq 9.8$, $P \leq 0.0018$; Odds ratios ≥ 1.51).

(iii). Reelin (RELN) and Protocadherin 12 (PCDH12)

Reelin is an important neurodevelopmental gene involved in neuronal migration and synaptic remodelling[40] while protocadherin plays a major role in neuronal development, neuronal differentiation and synaptogenesis.[41] Wedenoja et al.[42] showed significant association of reelin variants with neuropsychological endophenotypes such as verbal memory, visual working memory and executive functioning in a large family-based schizophrenia sample from Finland. In a haplotype analysis,[43] the four SNPs rs7341475, rs362691, rs736707 and rs362719 of RELN gene showed positive association with schizophrenia ($P < 0.0000256$).

Gregorio et al.[44] examined the association of 32 polymorphisms located in 30 genes with brain structural data in patients with schizophrenia ($N = 25$). Genes involved in neurogenesis and brain development were selected for the analysis. Subjects with CC genotype ($n = 19$) of RELN polymorphism rs362691 demonstrated higher total ventricular brain ratio (VBR) (2.31 ± 0.86, $P < 0.007$) when compared to subjects with CG genotype ($n = 6$). Subjects with GG genotype ($n = 20$) of PCDH12 polymorphism rs164515 showed an association with asymmetry coefficient of the gyrification index (ACGI = 0.0048 ± 0.032). The above morphometric alterations provide preliminary evidence of the role of neurodevelopmental genes RELN and PCDH12 in mediation of brain volumetry in schizophrenia.

(iv). Brain derived neurotrophic factor (BDNF)

Brain derived neurotrophic factor is a neurotrophin pivotal for neurodevelopment[45] that mediates release of dopamine in nucleus accumbens and regulates mesolimbic dopamine pathway via activation of tyrosine kinase receptors.[46] The polymorphism rs6265 (Val166Met) of BDNF gene has been implicated in schizophrenia ($P < 0.005$).[47] Healthy subjects ($N = 331$) with Val/Val genotype ($n = 217$) were shown to have larger whole brain volume ($F = 6.51$; $P < 0.0112$)[48] as well as larger volumes of left inferior temporal gyrus ($P < 0.000$), prefrontal cortex ($P < 0.001$) and lateral occipital cortex ($P < 0.001$) ($N = 144$; $n = 95$), while patients with schizophrenia ($N = 293$) having the Val/Val genotype ($n = 182$) were shown to have increased left parahippocampal ($P < 0.000$) and left supramarginal gyral volumes ($P < 0.001$)[49] and decreased hippocampal volumes [$N = 68$; $n = 44$ (total: $F = 5.102$, $P < 0.025$; left: $F = 4.031$, $P < 0.046$; right: $F = 5.171$, $P < 0.024$)].[50] Yang et al.[51] observed that healthy subjects ($N = 81$) with Met/Met genotype ($n = 17$) were associated with less GM mainly in the frontal, temporal, cingulate and insular cortices (TFCE corrected, $P < 0.05$). Interestingly, the Met allele carriers ($n = 45$) showed greater reductions in frontal GMV with reciprocal volume increases in the lateral ventricles and sulcal (especially frontal and temporal) cerebrospinal fluid (CSF) than Val homozygous patients [($F \geq 6.55$, dfs = 1113, $p \leq 0.01$, ($n = 74$)][52] following treatment with antipsychotics. Thus, the above studies clearly demonstrate that the polymorphism rs6265 is associated with frontal GMV reductions in healthy subjects[51] and patients with schizophrenia.[52] However, in another study (48) healthy

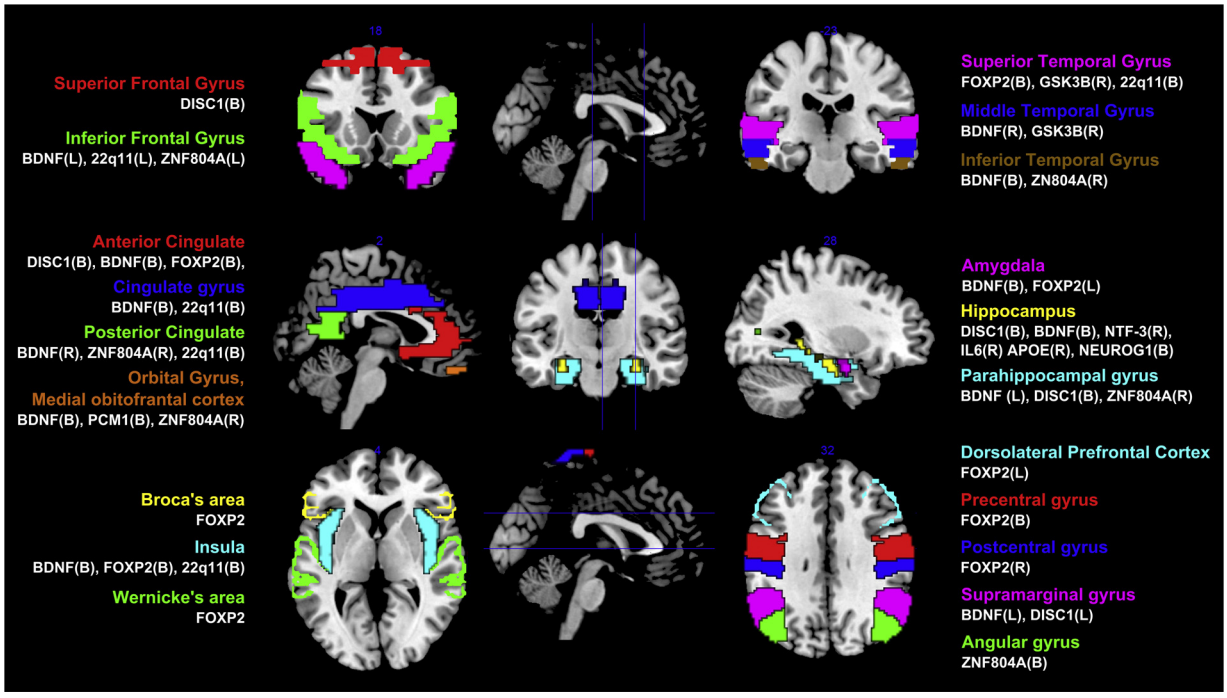

Fig. 1 – Brain regions where association of volumetric alterations with schizophrenia risk genes or susceptibility loci that regulate *neurodevelopment* have been reported in healthy subjects and/or patients with schizophrenia. `L'/`R'/`B' in parenthesis following the gene/locus refers to `left'/`right'/`bilateral' where laterality of effects is explicitly reported in the source reference.

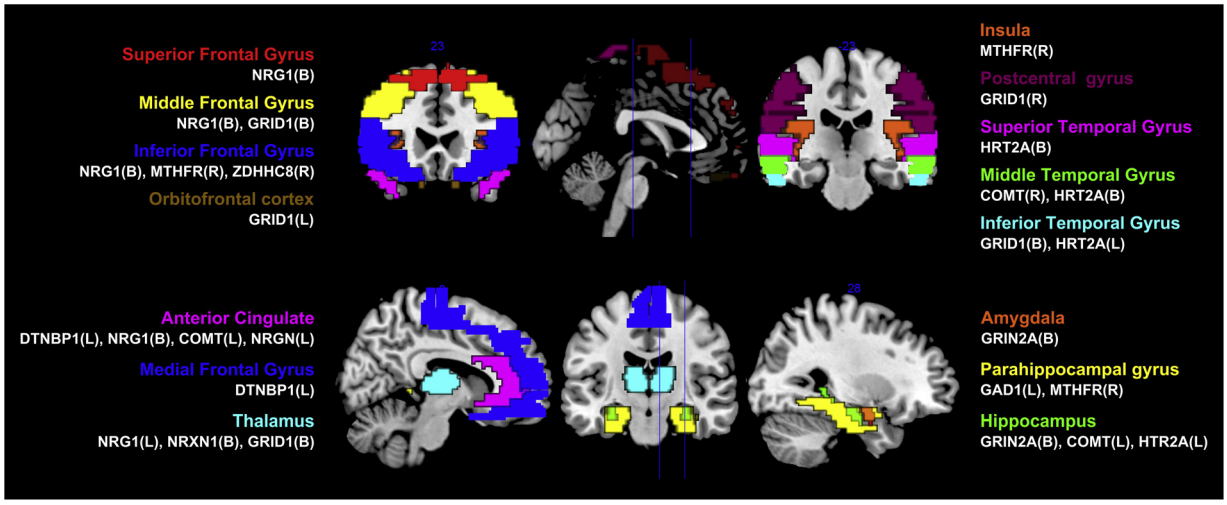

Fig. 2 – Brain regions where association of volumetric alterations with schizophrenia risk genes or susceptibility loci that regulate *neurotransmission* have been reported in healthy subjects and/or patients with schizophrenia. `L'/`R'/`B' in parenthesis following the gene/locus refers to `left'/`right'/`bilateral' where laterality of effects is explicitly reported in the source reference.

subjects with the SNP rs6265 were shown to have an increase in frontal WMV.

(v). Glycogen synthase kinase 3 beta (GSK3B)

The GSK-3 protein is a serine/threonine kinase involved in signal transduction cascades during neurodevelopment. Through Wnt signalling, it regulates cell proliferation, cell adhesion and synapse rearrangement.[53] The two isoforms of GSK-3 are designated as α and β.[54] Kozlovsky et al.[55] reported reduced GSK-3 β levels in frontal cortex of patients with schizophrenia. The polymorphism rs334558 located in the promoter region of GSK3B gene showed association with schizophrenia ($P < 0.01$, corrected), affecting transcription factor binding affinities.[56]

Patients with chronic schizophrenia ($N = 57$) having the less-active C allele of GSK3B ($n = 37$) polymorphism rs334558 revealed higher brain volumes in posterior regions of right

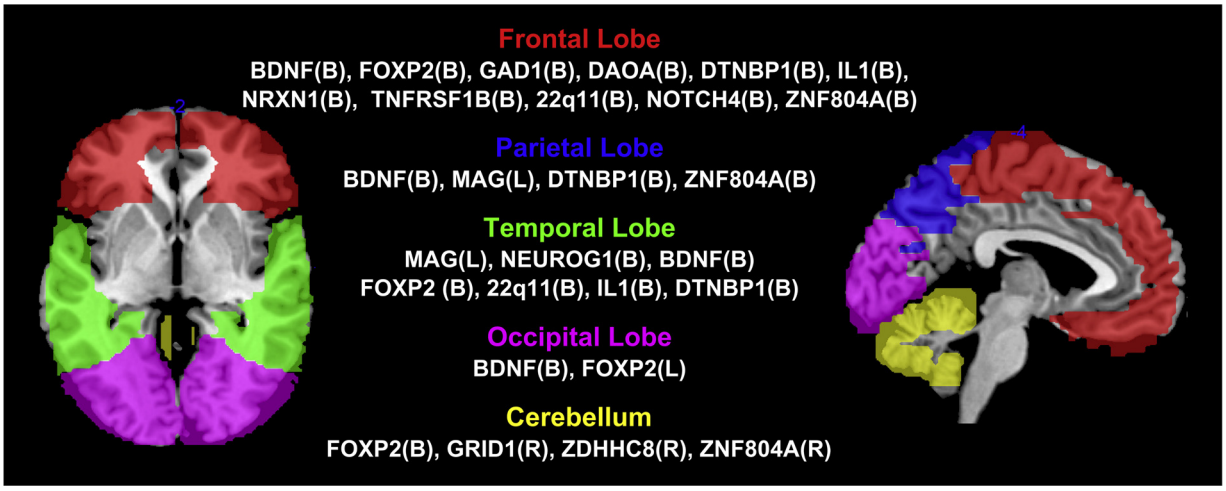

Fig. 3 – Brain lobar regions where association of volumetric alterations with schizophrenia risk genes/susceptibility loci that regulate *neurodevelopment* or *neurotransmission* have been reported in healthy subjects and/or patients with schizophrenia. `L'/`R'/`B' in parenthesis following the gene/locus refers to `left'/`right'/`bilateral' where laterality of effects is explicitly reported in the source reference. *Note*: The following morphological effects of genes on whole brain gray matter and regional white matter morphology are not depicted in the figure: (i) association of NEUROG1, VRK2, DAOA, COMT, HTR2A, RGS4, ZDHHC8, NRGN with total gray matter volume; (ii) association of NRG1 with morphological changes in anterior internal capsule, anterior thalamic radiation, corpus callosum, anterior and superior corona radiata and inferior fronto-occipital fasciculus; (iii) association of PRNP, PLXNB3, ZNF804A and VRK2 with total white matter volume changes; and (iv) association of RELN, BDNF, PRNP, TNFSRF1B and NOTCH4 with ventricular/CSF volume changes.

middle and superior temporal gyri ($Z = 5.47$, $P_{FWE} < 0.002$) as well as a trend towards higher GMV in inferior frontal gyrus, middle frontal gyrus, pre- and postcentral gyri, uncus and inferior occipital gyrus ($P < 0.001$, uncorrected).[57] Since the less active C allele is associated with neuronal resilience, increased neurotrophism and reduced apoptosis,[58,59] the observation of higher temporal lobe GMV in the less-active C allele carriers suggests a neuroprotective mechanism by GSK-3 against the neuronal damage in schizophrenia.

(vi). Prion protein (PRNP)

The prion protein (PRNP) is a copper-binding glycoprotein[60] that regulates neural proliferation.[61] The function of PRNP in schizophrenia pathogenesis is not clearly understood. However, two polymorphisms M129V (methionine/valine at codon 129) and E219K (glutamate/lysine at codon 219) of PRNP gene were identified in 62 Han Chinese patients with schizophrenia having positive family history.[62] Weis et al.[63] demonstrated that the density of prion protein-positive glial cells was significantly reduced in the white matter (WM) of patients with schizophrenia using immunohistochemistry. Patients with schizophrenia ($N = 47$) and healthy subjects ($N = 43$) homozygous for methionine (Met) allele ($n = 33$) of PRNP polymorphism rs1799990 (Met129Val) showed reduced white matter volume (WMV) and ($P < 0.024$) and enlargement of CSF compartments ($P < 0.039$) but no GM volumetric alterations, irrespective of diagnosis.[64]

(vii). Pericentriolar material1 (PCM1)

The PCM1 gene encodes a centrosomal protein and serves a pivotal role in the regulation of microtubular dynamics and neuronal cell growth.[65] The PCM1 gene locus is 8p22, considered as a susceptibility locus for schizophrenia (SCZD6, Online Mendelian Inheritance in Man [OMIM] 603013). Kamiya et al.[66] suggested that PCM1, DISC1 and BBS4 (Bardet-Biedl syndrome 4) proteins interact and form a centrosomal pathway that is relevant for schizophrenia etiopathology. Family ($N = 450$) and trio samples ($N = 100$) affected with schizophrenia showed significant transmission equilibrium with marker D8S261 in the PCM1 gene locus ($P < 0.03$). Patients with PCM1 markers ($n = 14$) (D8S261 (142 bp), D8S26 16 (205 bp), rs445422 (T allele), rs13276297 (T allele), and rs370429 (A allele) showed significant reduction in bilateral medial orbitofrontal cortex volume in comparison to patients without PCM1 markers ($n = 13$) ($P < 0.05$, corrected).[67]

(viii). Tumour necrosis factor receptor-II (TNFRSF1B/TNFR-II)

Tumour necrosis factor is a pro-inflammatory cytokine involved in initiating physiological activities such as neuronal development, neurite outgrowth and nerve cell degeneration.[68] It also regulates the expression and activity of dopamine, serotonin, noradrenaline and neuropeptide Y.[69] Abnormal plasma levels of TNFα have been observed in patients with schizophrenia.[70] One of the soluble receptors for TNFα is TNFR-II. High expression of TNFR-II inhibits the activity of TNFα.[71] Genetic association studies have determined the association of TNFα polymorphism in schizophrenia.[72,73] Absence of TNFR-II receptors was shown to be associated with decreased neuronal survival,[74] and therefore, it has been suggested that variability in TNFRII could be associated with brain morphometry. Wassink et al.[75] reported that patients with schizophrenia ($N = 86$), homozygous for allele1 ($n = 36$) of TNFR II (bi-allelic marker in the 3′UTR) had an earlier age of onset as well as larger ventricles ($F = 4.87$, $df = 1$, $P < 0.03$) and smaller frontal lobes ($F = 3.65$, $df = 1$, $P < 0.06$) compared to subjects with at least one copy of allele2 ($n = 50$).

(ix). Neurotrophin-3 (NTF-3/NT-3)

Neurotrophins belong to a family of growth factors involved in neuronal survival and differentiation.[76] They exhibit high affinity for tropomyosin-related kinase receptors (trk). NTF-3 mRNA is the most abundant neurotrophin mRNA in the developing brain and is highly expressed in the hippocampus.[77] In a haplotype based analysis,[78] the frequency of A3 allele of the dinucleotide repeat polymorphism in NTF3 gene was significantly different in patients with schizophrenia (0.52) in comparison to that among healthy subjects (0.41) ($P < 0.028$). In a similar study, the A3 allele was found to be more common in patients with schizophrenia than in healthy subjects ($P < 0.006$).[79] Kunugi et al.[80] found that A3 allele carriers (23 CA repeats) of the dinucleotide repeat polymorphism $(CA)_n$ ($n = 5$) of NT-3 showed significant reduction of mean right hippocampal volume ($P < 0.022$) only in patients with schizophrenia ($N = 12$) and not in those with bipolar affective disorder ($N = 10$). The authors suggest that interaction of NT-3 with other risk factors may be responsible for the reduced hippocampal volume observed in patients with schizophrenia.

(x). Plexin B3 (PLXNB3)

Plexins are a conserved family of trans-membrane receptors for semaphorin molecules and play a key role in axonal guidance.[81] Plexin B3 induces neurite outgrowth and interacts with neurotrophic GTPase Rin (Ras-like protein expressed in neurons) affecting neuritogenesis.[82] Rujescu et al.[83] examined the effect of PLXNB3 haplotypes on brain morphology in patients with schizophrenia and healthy controls. The PLXNB3 haplotypes A, B (I598-D1156) (V598-D1156) and C (V598-E1156) were characterized by genotyping the SNPs 1906 G>A (V598I) and 3582 G>C (E1156D). These 3 PLXNB3 polymorphisms were chosen in this study as they result in changes of evolutionarily conserved amino acids, covering a genomic interval of 13.271 kb.

Irrespective of diagnosis, patients with schizophrenia ($N = 42$) and healthy subjects ($N = 303$) with haplotype A (I598-D1156) ($n = 58$) of PLXNB3 showed higher WMV (repeated measures MANCOVA $F = 4.275$, df = 1/85, $P < 0.042$) and lower CSF volume (repeated measures MANCOVA $F = 5.302$, df = 1/85, $P < 0.024$). On the other hand, patients with schizophrenia ($N = 42$), irrespective of their genotype, showed higher CSF volume (repeated measures MANCOVA $F = 6.527$, df = 1/85, $P < 0.012$). The authors interpret their findings as supportive evidence for the influence of PLXNB3 haplotype A on WMV.

(xi). Myelin associated glycoprotein (MAG)

Myelin associated glycoprotein is an integral component of myelin formed by oligodendrocytes.[84] Reduced expression of MAG[85] along with decrease in oligodendrocyte density[86] has been reported in post-mortem studies of pre-frontal cortex in patients with schizophrenia. Thus, the alterations in oligodendrocyte–axon interactions caused by MAG dysfunction might underlie the subtle cytoarchitectural changes observed in schizophrenia.[87] In Han Chinese population, the MAG variants rs720308 and rs720309 were significantly associated with schizophrenia ($P < 0.0084$) and the risk haplotype TA (rs720309-rs720308) was shown to be over-transmitted from parents to offspring ($P < 0.0001$).[88,89] The risk variant rs720308 was found to be associated with lower temporal ($F = 7.742$, $P < 0.007$) and parietal GMV ($F = 7.930$, $P < 0.006$) in both patients with schizophrenia ($N = 45$) and healthy subjects ($N = 47$).[90]

(xii). Zinc finger binding protein 804A (ZNF804A)

ZNF804A is expressed throughout the brain particularly in the developing hippocampus, cortex and adult cerebellum.[91] O'Donovan et al.,[92] in a GWA study identified a novel SNP (rs1344706) of ZNF804A gene as a risk factor for schizophrenia ($P < 1.61 \times 10^{-7}$). Moreover in a recent GWAS, loci within ZNF804A gene showed genome-wide significance for schizophrenia ($P < 1.53 \times 10^{-12}$).[93] The function of this SNP in disease pathophysiology is however not clearly understood. Nevertheless, structural and functional imaging studies have revealed the role of this SNP (rs1344706) in brain connectivity.[94]

Healthy volunteers ($N = 39$) homozygous for the risk allele (T/T) ($n = 18$) of the ZNF804A gene rs1344706 polymorphism showed larger total WMV than carriers of the G allele ($n = 21$) ($F(1,27) = 4.61$, $P < 0.041$, partial eta = 0.146).[95] The TT subjects ($n = 18$) also showed reduced GMV in the angular gyrus, parahippocampal gyrus, posterior cingulate, medial orbitofrontal gyrus/gyrus rectus, left inferior frontal gyrus, right inferior temporal gyrus and right cerebellum (FDR-corrected $P < 0.05$). A similar study by Wassink et al.[94] reported greater total ($F = 3.98$, $P < 0.02$), frontal ($F = 4.95$, $P < 0.007$) and parietal lobe ($F = 3.08$, $P < 0.05$) WMV in patients with schizophrenia ($N = 335$) homozygous for the T allele ($n = 126$), when compared to non-risk allele carriers ($n = 209$). The association with altered WMV across the entire brain supports the hypothesis that ZNF804A influences neural connectivity patterns across a distributed network of brain regions. Aberrant structural and functional connectivity has been demonstrated in schizophrenia in the above regions that were linked to the rs1344706 polymorphism.[96]

(xiii). Neurogenic locus notch homolog protein 4 (NOTCH4)

Neurogenic locus notch homolog protein 4 encodes for a receptor with single transmembrane domain.[97,98] In mouse and human embryonic stem cells, NOTCH has been shown to initiate neural fates.[99] NOTCH4 transcripts were detected in the developing nervous system.[100] Wei and Hemmings[101] showed significant association of the NOTCH4 haplotype SNP2-$(CTG)_n$ with schizophrenia ($P < 0.0000078$).

Patients with schizophrenia ($N = 158$) having allele6 ($n = 36$) of the exonic $(CTG)_n$ NOTCH4 polymorphism showed increased frontal GMV ($r = 0.19$, $P < 0.02$), decreased CSF volume ($r = -0.13$, $P < 0.1$) and better performance on Wisconsin Card Sorting Test (WCST) ($r = 0.19$, $P < 0.008$).[102] In contrast, healthy subjects ($N = 48$) with allele6 ($n = 14$) had diminished frontal GMV ($r = -0.27$, $P < 0.07$), increased CSF volume ($r = 0.19$, $P < 0.21$) and poorer performance on the WCST ($r = -0.22$, $P < 0.06$). This finding could perhaps point towards a complex role of NOTCH4 in mediating brain morphology as well as cognitive deficits in schizophrenia.

(xiv). Forkhead Box P2 (FOXP2)

FOXP2 is a transcription factor involved in regulation of synaptic transmission, cell signalling, ion transport, neural development and modulation of plasticity.[103] It plays a pivotal role in language processing; mutations in FOXP2 gene have been shown to result in severe speech and language disorder.[104] FOXP2 was observed to affect specific language circuits, which could play a pivotal role in the pathogenesis of

schizophrenia.[105] Moreover, the FOXP2 variant rs2396753 were shown to be significantly associated with auditory hallucinations in schizophrenia ($P < 0.009$).[106]

The susceptibility C allele ($n = 29$) of FOXP2 polymorphism rs2396753 was linked to reduction in GM concentration of bilateral amygdala, insula, anterior cingulate, premotor cortex and superior-lateral temporal cortex as well as the right somatosensory cortex, with the maxima in left dorsolateral prefrontal cortex (FDR corrected, $P < 0.01$) in patients with schizophrenia ($N = 40$). In addition, GM concentration reductions in bilateral cerebellum, bilateral parietal lobe, right basal ganglia, left occipital lobe, Broca's and Wernicke's language areas and their contralateral homologues (FDR corrected, $P < 0.05$) were also reported.[107] Thus, FOXP2 might mediate the structural aberrations noted in the language processing circuits in schizophrenia.

(xv). Interleukin-6 (IL-6)

IL-6 is a pro-inflammatory cytokine secreted by macrophages and monocytes and activates components of the inflammatory response. It causes excitotoxicity by increasing intracellular calcium levels leading to cell death in granular neurons.[108] IL-6 may function as a neurodegenerative as well as neuroprotective factor. IL-6 promotes synaptic plasticity, long term potentiation (LTP) and memory consolidation.[109] The C allele [$P < 0.002$, odds ratio (OR) = 1.95, 95% confidence interval (CI): 1.18–2.14] of IL6 polymorphism rs1800795 and its carriers (62% vs 42%, $P < 0.003$, OR = 2.28, 95% CI: 1.13–1.94) were more frequent in patients with schizophrenia.[110] Significant alterations have been observed in the levels of IL-6 in CSF and serum of patients with schizophrenia.[111] Baune et al.[112] suggested a neuroprotective role for the G allele ($n = 250$) of the SNP rs1800795 (IL-6), specifically on hippocampal volumes in healthy subjects ($N = 303$) [$x = 24$, $y = -10$, $z = -15$; $F(2,286) = 8.54$, $P_{\text{uncorrected}} < 0.0002$; $P_{\text{AlphaSim-corrected}} < 0.002$; cluster size $k = 577$].

(xvi). Apolipoprotein E (APOE)

Apolipoprotein E is a well-known risk factor for late-onset Alzheimer's disease (AD).[113] ApoE has also been implicated in schizophrenia, given its role in scavenging or neutralization of free radicals.[114] Cerebral neuronal dysfunction mediated by free-radicals has been implicated in the pathology of schizophrenia.[115] Increased ApoE ε4 allele frequency was observed in patients with schizophrenia (26%, $P < 0.01$).[116]

Patients ($N = 21$) with ε4 allele ($n = 7$) of the ApoE polymorphism rs429358 showed a trend towards reduced ratio of right hippocampus to hemisphere volumes ($T = 1.9$, df = 19, $P < 0.10$) compared to ε2 and ε3 allele carriers ($n = 14$).[117] However, no such association between the ε4 allele ($n = 14$) and hippocampal (t = 0.23, df = 33, $P < 0.82$) volumes (t = 0.27, df = 33, $P < 0.79$) was found in patients with childhood-onset schizophrenia (COS) ($N = 40$).[118]

(xvii). Vaccinia related kinase2 (VRK2)

The VRK2 protein is a serine/threonine kinase and a member of casein kinase I group.[119] It is an anti-apoptotic factor present in neuronal cells[120] that prevents apoptosis by binding to JIP1 (Jun NH2-terminal Kinase (JNK) Interacting Protein 1),[121] thus playing a major role in axonal development.[122] In a GWA study, the VRK2 risk variant rs2312147 has been identified as a putative susceptibility variant of schizophrenia (O.R. = 1.09, $P < 3.2 \times 10^{-7}$).[123] Furthermore in a recent GWAS,[93] the loci within VRK2 gene showed significant association with schizophrenia ($P < 1.473 \times 10^{-11}$).

Li et al.[124] confirmed the association between VRK2 and schizophrenia in a meta-analysis involving multiple Asian and European samples ($N = 7498$, $P < 3.17 \times 10^{-4}$). They also reported that the mRNA expression of VRK2 was upregulated in patients when compared to controls ($P < 0.0147$). The VRK2 SNP rs2312147 revealed significant association with reduction in TBV ($P < 0.01$), WMV ($P < 0.008$) and possibly GMV ($P < 0.09$) in healthy subjects ($N = 286$). Individuals with risk allele C of rs2312147 showed a trend towards having smaller brain volumes.

Thus it may be noted from the above description that the genes regulating neurogenesis/neurodevelopment affect gross brain morphology as well as confer risk for development of schizophrenia.

2.2. *Genes that primarily regulate synaptic transmission*

Aberrant synaptic neurotransmission, especially involving glutamate, gamma aminobutyric acid (GABA) and catecholamines has been hypothesized to underlie the various symptom dimensions of schizophrenia.[125] Genes that regulate the function of the above neurotransmitters have been shown to affect brain structure and function.[126–128] Moreover, synaptic transmission plays an integral part during neurodevelopment mediating intercellular communication.[129] Susceptibility genes encoding transcription factors, enzymes, growth factors, receptors and other cell signalling molecules play a key role in neural development and synaptic plasticity. Thus altered neurotransmission and synaptic plasticity in schizophrenia reflect aberrant brain signalling leading on to dysregulation of the neurodevelopmental process resulting in disconnection of various brain regions. The genes that mediate synaptic transmission through their effects on single or multiple neurotransmitters and their effects on brain morphometry in schizophrenia are discussed in this section (Tables 1 and 3, Figs. 2 and 3).

2.2.1. *Glutamatergic neurotransmission*

Glutamatergic dysregulation has been well documented in schizophrenia using animal models, post-mortem studies and in vivo brain imaging studies.[130,131] Intracellular proteins of the glutamatergic pathway are involved in various regulatory functions such as receptor organization, modulation of receptor activity and coordination of signal transduction.[132] Disruption of any of these cellular/molecular functions would lead to alterations in glutamatergic transmission thereby predisposing to development of schizophrenia. The influence of genes affecting glutamatergic transmission on brain structure is detailed below.

(i). Neuregulin1 (NRG1)

Neuregulin is implicated in numerous functions associated with neural development and synaptic plasticity.[133] NRG1 has a major role in the expression and activation of glutamate receptors.[134] It is a human homolog of the neuron specific rat gene RC3/neurogranin. NRG1 encodes a protein kinase that binds to calmodulin and plays a pivotal role in calcium–calmodulin pathway.[135] Different NRG1 isoforms have been shown to be expressed throughout the brain.[136] Importantly,

Table 3 – Effects of schizophrenia risk genes and susceptibility loci that regulate *neurotransmission* on whole or regional brain morphometry in healthy subjects and/or patients with schizophrenia.

Genes and loci (Number of articles referred)	SNP	Brain regions	Morphometric findings (H – Healthy; S – Schizophrenia; COS – Childhood onset schizophrenia)
A. Glutamatergic transmission			
NRG1, 8p12 (9)[a]	rs6994992	Superior, middle and inferior frontal gyri; ACC (bilateral)	↓GMV-H (Barnes et al., 2012)
		CC – genu, body; anterior and superior corona radiata; anterior limb of IC and EC traversed by anterior thalamic radiation and inferior fronto-occipital fasciculus	↓WMV-H (Barnes et al., 2012)
		IC-tip of the right anterior limb	↓White matter intensity-H (McIntosh et al., 2008)
		Left anterior thalamic radiation	↓White matter integrity-H (Sprooten et al., 2009)
DTNBP1,6p22.3 (6)	rs1018381	Whole brain volume	↓-S (Narr et al., 2009)
		CSF	↑-S(Narr et al., 2009)
		Areas of sensorimotor and frontal, temporal and parietal association cortices (bilateral)	↓Cortical thickness-S (Narr et al., 2009)
		Left anterior cingulate gyrus	↓GMV-H (Tognin et al., 2011)
	rs2619538	Left medial frontal area	↓WMV-H (Tognin et al., 2011)
DAOA, 13q34 (8)[a]	rs3916965; rs3916967; rs2391191; rs778294	Whole brain	↑WMV-S (Hartz et al., 2010)
		Frontal lobe (bilateral)	↓Overall volume-S (Hartz et al., 2010)
GRIN2A, 16p13.2 (7)	$(GT)_n$ repeat polymorphism	Medial temporal volumes-Hippocampus and amygdale	↓GMV-H (Inoue et al., 2010)
GRID1, 10q23.1 (4)	rs3814614	Anterior thalamus (bilateral), bilateral middle frontal gyrus, right postcentral gyrus and left orbitofrontal cortex	↑ Gray matter density-H (Nenadic et al., 2012)
		Right inferior temporal lobe, left inferior/lateral temporal lobe	↓White matter density-S (Nenadic et al., 2012)
		Right medial cerebellum	↑Gray matter density-S (Nenadic et al., 2012)
B. GABA-ergic transmission			
GAD1, 2q31 (7)	hCV2177464, rs872123, rs2270335, rs2241165 hCV8823522 and rs769395	Frontal lobe (bilateral)	↑GMV-COS (Addington et al., 2005)
	rs3749034	Left parahippocampal gyrus	↓Cortical thickness-H (Brauns et al., 2013)
C. Dopaminergic transmission			
COMT, 22q11.1 (5)	rs4680	Left ACC; right middle temporal gyrus	↓GMV-S (Ohnishi et al., 2006)
	rs4680 and rs2097603	Left hippocampus; DLPFC	↑GMV-H (Honea et al., 2009)
MTHFR, 1q36.3 (8)[a]	rs1801133	Right insula, right inferior frontal gyrus,right rolandic opercula,right parahippocampal gyrus and right medial temporal lobe	↑Gray matter density -S,H (Zhang et al., 2013)
		Gray matter density	↑ -H; ↓ -S (Zhang et al., 2013)
D. Serotoninergic transmission			
HTR2A, 13q14 (10)	rs6314	Left hippocampus; left inferior temporal gyrus; bilateral middle and superior temporal gyri	↓GMV-H (Filippini et al., 2006)
E. Regulators of multiple neurotransmission			
RGS4, 1q21 (8)	rs159729374 and rs159735809	Bilateral DLPFC	↓GMV-S (Prasad et al., 2005)
ZDHHC8, 22q11.21(5)[a]	rs175174	Right inferior frontal gyrus and right cerebellum	↓GMV-S (Ota et al., 2013)
NRGN, 11q24(7)[a]	rs12807809	Left ACC	↓GMV-S (Ohi et al., 2012)
NRXN1,2p16.3 (7)	rs858932	Frontal lobe (bilateral) and (bilateral)thalamus	↓ WMV-S,H (Voineskos., 2011)

Abbreviations: IC, internal capsule; EC, external capsule; CC, corpus callosum; GMV, gray matter volume; WMV, white matter volume; CSF, cerebrospinal fluid; TBV, total brain volume; DLPFC, dorsolateral prefrontal cortex; ACC, anterior cingulate cortex.

[a] Genes which also mediate neurogenesis such as neuronal maturation, neuronal plasticity and memory, neuronal migration and neuronal progenitor proliferation.

NRG1 is considered as a leading candidate gene for schizophrenia.[137] Significant association of the NRG1 polymorphism rs6994992 has been observed in individuals at high risk of developing schizophrenia ($P < 0.001$).[138]

The carriers of the risk T allele ($n = 46$) of neuregulin variant SNP8NRG243177 (rs6994992) were shown to have decreased WM density in the right anterior internal capsule (peak 1: MNI coordinates = (29, 30, 7), $t = 4.41$, $P_{corrected} < 0.028$; peak 2: MNI coordinates = (29, 26, 8), $t = 4.38$, $P_{corrected} < 0.016$; peak 3: MNI coordinates = (29, 23, 12), $t = 4.26$, $P_{corrected} < 0.023$)[139]; reduced WM integrity ($n = 30$) in the left anterior thalamic radiation ($P < 0.001$);[140] decreased GMV ($n = 41$) in several frontal gyri ($P < 0.003$) and decreased WMV in the regions of the genu and body of the corpus callosum, anterior and superior corona radiata, anterior limb of the internal capsule and the external capsule regions, traversed by major WM tracts of the anterior thalamic radiation and the inferior fronto-occipital fasciculus ($P < 0.004$).[127] The findings from the above two independent studies by Barnes et al.[127] and Sprooten et al.[140] also clearly demonstrate the significant impact of NRG1 polymorphism rs6994992 on anterior thalamic radiation, where the polymorphism rs6994992 was shown to be associated with reduced WMV/white matter integrity in anterior thalamic radiation in healthy subjects.

(ii). Dystrobrevin binding protein1 or dysbindin (DTNBP1)

Protein and gene expression studies provide evidence for DTNBP1 involvement in glutamate neurotransmission through phosphatidylinositol 3 (PI3)-kinase-Akt signalling.[141] In brain, DTNBP1 binds to beta-dystrobrevin and is expressed in axon fibres of corpus callosum and mossy fibre terminal fields in the hippocampus.[142] DTNBP1 is a common susceptibility gene implicated in schizophrenia. Several SNPs within the 140-kb DTNBP1 gene have been strongly associated with schizophrenia.[143] The DTNBP1 polymorphism rs1018381 demonstrated significant association with schizophrenia ($P < 0.0006$).[144]

In patients with schizophrenia ($N = 62$), the risk allele carriers ($n = 24$) of the DTNBP1 risk variant rs1018381 (P1578) showed reduction in whole brain volume, cortical thinning in temporal and parietal association cortices within the left ($P_{corrected} < 0.002$ and 0.001 respectively) and right hemisphere ($P_{corrected} < 0.006$ and 0.015); in contrast, thickening in frontal, sensorimotor and occipital cortices ($P_{corrected} < 0.017$ and 0.02 for the left and right hemisphere respectively) was observed in healthy subjects ($N = 42$; $n = 11$).[145] In another study, carriers of the risk A allele ($n = 11$) of the risk variant rs2619538 showed reduced GMV in the left anterior cingulate gyrus ($P < 0.002$ after FWE correction; voxel size = 57) and reduced WMV in the left medial frontal area ($P < 0.015$ after FWE correction; voxel size = 7).[146]

(iii). D-Amino acid oxidase activator (DAOA/G72)

DAOA is an activator of the enzyme D-amino acid oxidase (DAAO) which metabolizes the amino acid D-serine.[147] It modulates glutamatergic transmission by affecting the binding of agonist D-serine at the glycine modulation site of the NMDA receptor. SNP-based fine mapping studies and linkage studies have shown significant association of DAOA with schizophrenia.[148,149]

Hartz et al.[150] observed that variation in DAOA modulates progressive brain structural changes seen in schizophrenia. As a part of the Iowa Longitudinal Study of Recent Onset Psychoses, four SNPs (rs3916965, rs3916967, rs2391191, rs778294) were genotyped in patients ($N = 110$) in whom two brain MRI scans were acquired an average of three years apart. In prior studies these variants were shown to have positive association with schizophrenia.[151–153] A meta-analysis by Detera-Wadleigh and McMahon[152] revealed that markers spanning more than 82 kb of DAOA gene were highly significant ($P < 0.001$) in patients with schizophrenia. Schumacher et al.[149] demonstrated significant association of rs2391191 with schizophrenia ($P < 0.037$, O.R. = 1.28) Multivariate analysis of co-variance (MANCOVA) analysis revealed significant association of haplotypes 1 (AGAG) and 3(GAGA) with brain volumes. Individuals homozygous for haplotype1 ($n = 16$) demonstrated an accelerated rate of frontal lobe tissue loss ($P < 0.008$), while individuals homozygous for haplotype 3 ($n = 9$) showed a tendency towards increase in cerebral WMV ($P < 0.0008$) over time compared to subjects with other G72 haplotypes. Thus, DAOA might have a role to play in the progressive reduction of frontal lobe WMV reported in patients with schizophrenia.[154]

(iv). N-methyl-D-aspartate receptor 2A subunit (GRIN2A)

The NMDA receptor is an ionotropic glutamate receptor with a pivotal role in brain development, excitatory neurotransmission, synaptic plasticity and memory function.[155] Since NMDA antagonists have been shown to trigger psychotic symptoms in normal individuals,[156] genes for NMDA receptor have always been of special interest for schizophrenia neurobiologists.[157] In one of the newly implicated genome wide significant loci, GRIN2A gene has been identified ($P < 1.28 \times 10^{-8}$).[93]

A functional $(GT)_n$ repeat polymorphism in the promoter region of GRIN2A was identified,[158] the repeat length of which determines the transcriptional activity of GR1N2A ($P < 0.05$). When the repeat length becomes long, the transcriptional activity is attenuated. A case-control study by Iwayama-Shigeno et al.[159] reported a significant association of the $(GT)_n$ polymorphism in schizophrenia, wherein individuals with longer alleles ($n = 55$) were overrepresented. Subjects homozygous for the long allele ($n = 55$) showed significant reductions of the volume of medial temporal structures such as hippocampus and amygdala ($F(1,142) = 4.61$, $P < 0.034$) in comparison to short allele carriers ($n = 89$),[160] thus supporting the role of the NMDA receptor in human brain development.

(v). Glutamate receptor delta 1 (GRID1)

Glutamate receptor delta 1 belongs to the ionotropic receptor family which mediates fast glutamate transmission.[161] Delta receptors D1 and D2 were shown to induce presynaptic differentiation.[162] Treutlein et al.[163] reported association of the GRID1polymorphism rs3814614 with schizophrenia ($P < 0.0193$).

GM density in the anterior thalamus (bilaterally), superior prefrontal cortex and orbitofrontal cortex was found to be higher in healthy subjects ($N = 54$) with TT genotype ($n = 8$) of GRID1 polymorphism rs3814614 ($P < 0.001$, uncorrected). In patients ($N = 62$) with TT genotype ($n = 19$), the GM density was higher in the medial parietal cortex and lower in the right medial cerebellum while the WM density was lower in the right inferior temporal lobe and left inferior/lateral temporal lobe ($P < 0.001$, uncorrected).[164]

2.2.2. *GABAergic neurotransmission*

Reduced GABA levels have been demonstrated in brains of patients with schizophrenia using magnetic resonance spectroscopy.[165] Post mortem studies have provided substantial evidence for GABA-ergic hypofunction in schizophrenia.[166,167] The genes regulating GABA-ergic transmission and their association with regional brain abnormalities are detailed in this section.

(vi). Glutamic acid decarboxylase 1 (GAD1) gene

Glutamic acid decarboxylase 1 gene encodes an enzyme glutamic acid decarboxylase 67 (GAD67) involved in GABA synthesis.[168] Post-mortem studies in patients with schizophrenia have shown reduction in the parvalbumin (PV) (+) GABA-ergic inter-neuronal density.[169] There have been consistent reports of reduced expression levels of GAD67 in patients with schizophrenia.[170,171] Moreover, positive association has been reported between the three GAD1 polymorphisms hCV2177452, rs2270335 and rs2241165 and schizophrenia ($P < 0.022$–0.057).[126]

The SNPs hCV2177464, rs872123, rs2270335, rs2241165 hCV8823522 and rs769395 were significantly associated with increase in frontal lobe GMV ($P < 0.04$–0.02) in patients with childhood onset schizophrenia ($N = 72$).[126] Furthermore, left parahippocampal cortical thickness was found to be reduced (cluster-wise probabilities, CWP = 0.0083) in homozygotes of the G allele ($n = 53$) of GAD1 polymorphism rs3749034 in healthy individuals ($N = 94$).[172] Upon stratification of the above subjects based on their COMT Val158Met (rs4680) genotype, it was seen that reduction of cortical thickness was present only in those G allele homozygotes who belonged to the COMT Val/Met and Val/Val subgroups. Straub et al.[173] also reported an epistatic interaction between COMT and GAD1 SNPs suggesting the role of interaction between GABA-ergic and dopaminergic systems in structural aspects of brain development.

2.2.3. *Dopaminergic neurotransmission*

The dopamine hypothesis has occupied a central position in pathophysiological conceptualizations of schizophrenia ever since the discovery of antipsychotic properties of the D2 antagonist chlorpromazine in the 1950s. Functional imaging studies in patients with schizophrenia following administration of the dopamine agonist amphetamine showed increase of synaptic dopamine in the striatum.[174–176] Besides positive symptoms, dopamine dysfunction was shown to affect cognitive and affective functions as well in schizophrenia. Alteration of D1 receptor transmission was observed in patients with working memory deficits.[177] Backman et al.[178] demonstrated working memory to be associated with striato-frontal brain regions and phasic dopaminergic neurotransmission.

(vii). Catechol-O-methyl transferase (COMT)

Catechol-O-methyl transferase is an enzyme involved in the degradation of catecholamines.[179] The nonsynonymous SNPs of COMT have a well-known effect on neural function related to cognitive and affective processing. However, very few studies have analyzed the influence of COMT gene polymorphisms on brain morphology. One of the well-studied SNPs of COMT is rs4680 which results in the substitution of valine for methionine at amino acid position 158. This substitution leads to low levels of dopamine due to increased enzyme activity in Val carriers.[180] In a GWA study, the rs4680 polymorphism of COMT gene has been shown to be significantly associated with schizophrenia ($P < 0.02$).[181]

Patients with schizophrenia ($N = 47$) homozygous for the Val-COMT allele ($n = 19$) showed significant reduction of volumes in the left anterior cingulate cortex (ACC) ($P_{FDR\text{-}corrected} < 0.007$) and the right middle temporal gyrus (MTG) ($P_{FDR\text{-}corrected} < 0.016$) compared to Met-COMT carriers ($n = 28$). Genotype–diagnosis interaction effects were significant in the left ACC ($P_{FDR\text{-}corrected} < 0.044$), the left parahippocampal gyrus and the left amygdala-uncus ($P_{FDR\text{-}corrected} < 0.048$).[182] Interaction between rs4680 and a promoter variant P2 (rs2097603) of COMT was observed in a large group of healthy volunteers ($N = 151$).[128] This interaction affected the GM regional volume in hippocampus and dorsolateral prefrontal cortex (DLPFC). A U-shaped relationship between hippocampal volume and presumed COMT activity was noted, whereby, the low activity haplotype [COMT-met combined with the low activity G-allele of the P2 promoter ($n = 58$)] and high activity haplotype [val158 on the ancestral P2-A allele ($n = 80$)] had larger volumes than the intermediate COMT activity haplotype [P2-G allele and val158, and P2-A allele and 158met ($n = 159$)] [$P < 0.01$, corrected, for hippocampal ROI (−34, −14, −13)]. This observation implies that the risk variant in the promoter region (rs2097603) and coding region of COMT play a major role in modulating hippocampal GMV.

(viii). Methylene tetrahydrofolate reductase (MTHFR)

Methylene tetrahydrofolate reductase is an enzyme involved in folate metabolism. It affects the intracellular availability of folate metabolites required for methylation.[183] Roffman et al.[184] suggested that MTHFR dysfunction could affect dopaminergic transmission since methyl groups are required by COMT to inactivate prefrontal dopamine. A functional polymorphism at codon 677 C→T (rs1801133) of MTHFR gene resulted in diminished enzyme activity leading to low folate and high homocysteine levels.[185] Lee et al.[186] demonstrated that homocysteine levels affect dopamine turnover in the striatum. A study by Kinoshita et al.[187] showed positive correlation between homocysteine and DNA methylation in peripheral leukocytes of patients with schizophrenia. In addition, studies in different ethnicities have identified the MTHFR rs1801133 polymorphism as a risk factor in schizophrenia (O.R. = 1.796, $P < 0.0020$).[188,189]

The risk allele T of MTHFR polymorphism rs1801133 (O.R. = 1.27, 95% CI = 1.12–1.43) was shown to have opposite effects on GM density in healthy subjects ($N = 29$) and in patients with schizophrenia ($N = 33$), with CT carriers in healthy subjects ($n = 25$) having significantly higher GM density in brain regions involved in episodic memory function while patients with the CT carriers ($n = 27$) tended to have lower GM density.[190] The greater GM density observed in specific regions such as insula, inferior frontal gyrus, rolandic operculum, parahippocampal gyrus and medial temporal lobe in the right hemisphere mediated by the risk variant T allele of MTHFR [i.e. patients and healthy subjects with carriers of CT genotype ($n = 52$)] may underlie the allele-load-dependent deficit in episodic memory noted in patients with schizophrenia.

2.2.4. *Serotonergic neurotransmission*

The potential role of serotonergic dysfunction in schizophrenia is exemplified by the utility of second-generation

antipsychotics that were designed as serotonin dopamine antagonists (SDAs).[191] The core positive symptoms of schizophrenia such as delusions and hallucinations were observed to occur after activation of the 5-HT receptors.[192,193] A recent study by Rasmussen et al.[194] using positron emission tomography (PET) reported lower serotonin binding in the frontal cortex of patients compared to healthy control subjects.

(ix). Serotonin receptor 2A (5HTR2A)

Reynolds et al.[195] demonstrated the role of the 5HT2A receptor in episodic memory. A recent study[196] in Han Chinese population demonstrated significant association of the T (Tyrosine) allele of HTR2A polymorphism, rs6314, with schizophrenia (O.R. = 1.60, 95% CI = 1.11–2.30, $P < 0.01$). The tyrosine allele, which attenuates the function of the 5HT2A receptor,[197] has also been shown to be associated with poorer memory performance in healthy, young Swiss subjects.[198] A decrease in 5-HT2A receptor density has been observed in a post-mortem study of the frontal cortex in patients with schizophrenia.[199]

Individuals with 452Tyr allele ($n = 15$) of the His452Tyr polymorphism of HTR2A showed significant reduction of the fractional volume of the temporal WM, reduced GM in left hippocampus, left inferior temporal gyrus and bilateral middle and superior temporal gyri ($P < 0.05$ with small volume correction). These morphometric abnormalities were suggested to underlie the poor memory performance observed in 452Tyr subjects ($n = 15$) compared to His452His subjects ($n = 61$).[200]

2.2.5. *Genes regulating action of multiple neurotransmitters*

In this section, genes that regulate the activity of multiple neurotransmitter systems and their effects on brain morphology are discussed.

(x). Regulator of G-protein signalling subtype 4 (RGS4)

Regulators of G-protein signalling (RGS) are GTP-ases involved in the negative regulation of G-protein signalling neurotransmitter systems such as metabotropic glutamate,[201] dopamine[202] and serotonin[203] receptors. RGS proteins also act as integrators by integrating G proteins with signalling pathways linked to cell growth and differentiation, cell motility and intracellular trafficking.[204] G-protein-coupled receptors (GPCRs) maintain homeostasis in neuronal cells, and therefore, dysfunction of these receptors directly or through their downstream molecules could play an important role in schizophrenia pathogenesis.[205] Down-regulation of RGS4 mRNA was observed in the prefrontal, motor and visual cortices of patients with schizophrenia. Therefore, low level of RGS4 has been suggested to be a risk factor for developing schizophrenia.[206] Williams et al.[207] showed significant association of RGS4 SNPs rs 951436 and rs2661319 with schizophrenia ($P < 0.017$ and $P < 0.038$, respectively).

Patients with schizophrenia ($N = 30$) homozygous for the T allele ($n = 15$) and A allele ($n = 16$) of the RGS4 polymorphisms rs951436 (SNP4) and rs2661319 (SNP18) respectively had smaller bilateral DLPFC volumes [SNP4 ($F(5,57) = 0.95$, $P < 0.004$) and SNP 18 ($F(5,57) = 3.56$, $P < 0.008$) for the left DLPFC and SNP4 ($F(5,57) = 3.42$, $P < 0.01$) and SNP18 ($F(5,57) = 3.12$, $P < 0.016$) for the right DLPFC volumes].[18]This reduction in DLPFC volumes associated with the particular risk alleles was not observed in healthy control subjects ($N = 27$). Thus, RGS4 might regulate DLPFC volumes by its interaction with other risk variants or environmental factors implicated in schizophrenia.

(xi). Zinc finger DHHC domain containing protein 8 (ZDHHC8)

The ZDHHC8 gene encodes for a putative trans-membrane palmitoyl transferase enzyme.[208] The enzyme plays a pivotal role in palmitoylation, a post-translational lipid modification process. Palmitoylation enhances the hydrophobicity of neuronal proteins.[209] It affects membrane localization and regulates activity of the AMPA receptor and GABA receptor B.[210] Many neuronal proteins including cell adhesion molecules, ion channels, scaffolding molecules, signalling proteins and proteins associated with neurotransmitter release machinery are palmitoylated. Faul et al.[211] observed that in samples of schizophrenia proband-parent triads ($N = 204$), the heterozygous parents transmitted allele G and allele A of the ZDHHC8 polymorphism, rs175174, preferentially to females and males respectively (heterogeneity $\chi^2 = 4.43$; $P < 0.035$).

Patients with schizophrenia ($N = 138$) with GG genotype ($n = 26$) of ZDHHC8 polymorphism rs175174 were shown to have lower GMV in right inferior frontal gyrus and higher GMV in posterior brain regions in comparison to A allele carriers (AA + 1/2AG, $n = 82$). Subjects who were G allele carriers (GG + 1/2AG, $n = 56$) had lower GMV in right cerebellum in comparison to AA genotype group ($n = 52$).[212] These preliminary results suggest a plausible role of the ZDHHC8 polymorphism rs175174 on cortical structure, which requires further examination.

(xii). Neurogranin (NRGN)

Neurogranin is a postsynaptic brain-specific protein involved in signal transduction.[213] It regulates calmodulin interaction with calcium by binding to calmodulin.[214] During embryonic development, the role of NRGN gene in cortical synapse formation and dendritic growth is regulated by thyroid hormones and retinoids.[215] Given its role in neurodevelopment and cognition, NRGN may be particularly relevant for schizophrenia pathogenesis.[216] The NRGN variant rs12807809 demonstrated genome wide significant association with schizophrenia ($P < 2.4 \times 10^{-9}$) with an average risk allele control frequency of 83% and a combined odds ratio of 1.15.[217] In another study,[93] the loci within NRGN gene showed genome wide significance for schizophrenia ($P < 2.804 \times 10^{-12}$).

A trend towards genotype–diagnosis interaction in Japanese patients with schizophrenia was observed on GMV in the left anterior cingulate cortex (ACC) ($P_{\text{uncorrected}} < 0.001$). Patients with schizophrenia ($N = 99$) who were carriers of allele T ($n = 95$) of NRGN risk variant rs12807809 showed smaller GMV in left ACC ($P_{\text{FEW-corrected}} < 0.0042$), in comparison to carriers of non-risk C allele ($n = 4$).[218]

(xiii). Neurexin-1 (NRXN1)

Neurexin is a cell-surface receptor molecule that binds to neuroligins (NLGNs).[219] This calcium-dependent NRXN-NLGN complex mediates GABA-ergic and glutamatergic neurotransmission.[220] Several groups have identified microdeletions disrupting promoter and exons of NRXN1 in patients with schizophrenia. Neurexin-1 has been considered as a major susceptibility gene in schizophrenia.[221,222]

The impact on brain morphometry of 11 NRXN1 SNPs lying within regions overlapped by deletions implicated in autism spectrum disorders (ASD) and schizophrenia was examined in healthy subjects ($N = 53$).[223] The G allele of rs858932 ($n = 6$) demonstrated reduced frontal WMV ($F_{2,51} = 5.472$, $P < 0.007$) as well as lower thalamic volumes compared to T allele carriers ($n = 47$). A significant volume by region interaction for the rs858932 was observed for thalamic structures [left thalamus ($F_{2,48} = 8.9$, $P < 0.001$); right thalamus: ($F_{2,48} = 7.3$, $P < 0.002$)], thereby impacting the thalamocortical circuitry that is reported to be dysfunctional in schizophrenia. Reduced frontal WMV was associated with the C allele of rs1045881 ($n = 33$) ($F_{1,49} = 8.231$, $P < 0.006$). This neurexin SNP rs1045881 influences response to clozapine in patients with schizophrenia ($P < 0.033$).[224] An in silico analysis further revealed that the C allele of rs1045881 is a micro RNA binding site for hsa-miR-339 and hsa-miR-1274. Moreau et al.[225] showed that the expression of miR-399 was dysregulated in the cortex of patients with psychosis. This could provide a plausible mechanism for the effect of this SNP on brain structure and cognition.

2.3. *Susceptibility loci*

Multiple significant susceptibility loci have been identified in schizophrenia.[67] Quantitative trait loci (QTL) studies in schizophrenia have identified several susceptibility loci associated with neurocognitive endophenotypes.[226,227] However, only few studies have analyzed the influence of susceptibility loci or genes located in those loci on brain morphology.

(i). 22q11 Locus

The 22q11 locus has been shown to increase the risk for schizophrenia, with 1:4000 live births reporting hemizygosity in the locus.[228] This locus has gained interest as an important susceptibility locus for schizophrenia ever since high frequency of 22q11 microdeletions were reported in patients with schizophrenia.[229] Furthermore, individuals with 22q11 microdeletion were noted to subsequently develop schizophrenia or schizoaffective disorder in adolescence or adulthood. The 22q11 deletion syndrome (22qDS), also called velo-cardiofacial syndrome is characterized by palatal abnormalities, congenital heart and other birth defects, as well as learning disabilities.[230] Murphy et al.[231] reported that more than 25% of the patients with 22qDS developed psychotic symptoms. Moreover, in the International Schizophrenia Consortium,[232] patients with deletions at 22q11 locus ($n = 11$) showed the strongest association with schizophrenia (empirical $P < 0.0017$; genome-wide corrected $P < 0.0046$; O.R. = 21.6), supporting the evidence that hemizygosity in 22q11 locus is a rare but powerful genetic risk factor for schizophrenia. The 22qDS has also been proposed to represent a genetic subtype of schizophrenia.[233] Thus, any significant morphometric abnormality related to this locus could reveal the functional relevance of genes located in the 1.5 Mbp deletion of this so called `schizophrenia critical region'.

Significant bilateral GMV reductions in the temporal lobes and superior temporal gyri ($P_{FDR} < 0.029$) were observed in patients with schizophrenia ($N = 29$) having 22q11.2 deletion in comparison to subjects having 22q11.2 deletion with no history of psychosis ($N = 34$).[234] Temporal lobe sub-divisions, particularly the superior temporal gyri, are amongst the regions that have been most consistently implicated in schizophrenia pathogenesis.[6,235] Other studies have reported widespread changes throughout the brain in individuals with 22q11.2 deletion syndrome.[236–238] Thus, 22q11.2 deletion syndrome could be considered as a promising neurodevelopmental model for studying the etiopathogenesis of schizophrenia.

Liu et al.[239] showed that patients with schizophrenia ($N = 140$) having deletions in the cytoband 22q13.31 ($n = 12$) had reduction in GM concentration in cingulate gyrus and insula ($P < 1.44 \times 10^{-4}$) in comparison to patients without the deletions ($n = 128$). Thus, copy number variations (CNVs) at 22q13.31 may cause susceptibility towards schizophrenia through reduction in GM concentration of the peri-limbic cortex.

The haploinsufficiency of genes such as COMT and proline dehydrogenase (PRODH) located at chromosome 22q11 provides another good model to study brain alterations that lead to vulnerability for schizophrenia. Zinkstok et al.[240] investigated the effect of COMT (rs4680 and rs2097603) and PRODH (rs2008720, rs450046 and rs372055) polymorphisms on brain morphometry in patients with schizophrenia and schizoaffective disorder ($N = 51$). Patients with AA genotype ($n = 23$) of COMT SNP rs2097603 had increased right superior temporal gyrus GMV ($P_{corrected} < 0.039$). Subjects with GG genotype of PRODH rs2008720 ($n = 12$) revealed WM reduction in frontal lobes (bilaterally) ($P_{corrected} < 0.05$) while those with AA genotype of PRODH rs450046 ($n = 46$) had reduction in WM of left frontal lobe (fasciculus uncinatus) ($P_{corrected} < 0.009$). Finally, an epistatic interaction between COMT Val allele (rs4680) and one or two mutated PRODH rs20086720 alleles (GT or TT genotypes) ($n = 31$) was found to be associated with an increased WM in left inferior frontal lobe.

(ii). Interleukin-1 cluster (IL-1 cluster)

The IL-1β and IL-1RN genes encoding for interleukin-1h (IL-1h) and interleukin-1 receptor antagonist (IL-1RN) respectively have been mapped to the IL-1 cluster. Nawa et al.[241] suggested that the interleukins IL-1h and IL-1RN play an important role in neurodevelopmental processes. Genetic association studies have demonstrated genetic variation in IL-1 cluster in patients with schizophrenia.[242,243] The high levels of IL-1RN were associated with a promoter polymorphism in IL-1h and the high levels of IL-1h have been linked to VNTR polymorphism in IL-1RN.[244,245] The IL-1β polymorphism rs16944 is located in the promoter region and the VNTR polymorphism is located in the intron2 of IL-1RN gene.[246] The allele*2 of IL-1RN gene is linked to an increased risk for developing schizophrenia (O.R. = 2.24).[247] In a recent meta-analysis,[248] the combined allele-wise odds ratio (O.R.) for schizophrenia of the rs16944 (IL-1β gene; T-511C) polymorphism was 0.86 (95% CI: 0.77–0.96).

Patients ($N = 44$) with T allele (allele2) ($n = 23$) of IL-1β polymorphism showed bifrontal-temporal GMV deficits (frontal: $F = 6.06$, df = 1, 42, $P < 0.02$; temporal: $F = 11.62$, df = 1, 42, $P < 0.001$) and generalized WM tissue deficits ($F = 5.54$, df = 1, 42, $P < 0.03$).[249] The rs16944 polymorphism, however, did not have any effect on the brain morphology of healthy subjects ($N = 48$). Papiol et al.,[246] on the other hand, could not find any significant influence of the IL-1β polymorphism rs16944 on fronto-temporal brain regions, but found an association

between significant enlargement of both lateral ventricles [left ($P < 0.002$); right ($P < 0.01$)] with IL-1RN VNTR allele*2 (2 repeats) in patients with schizophrenia ($N = 23$). A high level of interleukin1-β (IL1-β) has been reported in patients with schizophrenia.[242] The observed bifrontal-temporal GMV and WM tissue deficits could potentially be the result of an interaction between schizophrenia risk factors and elevated levels of IL1-β.

3. Methodological issues in imaging-genomic studies

Several GWAS have identified multiple risk variants as well as single loci that affect brain volumes in healthy subjects as well as in patients with schizophrenia.[9] However approaches that reliably model the cumulative gene–gene interactional effects on brain volume in a polygenic disorder such as schizophrenia are unavailable. Examining the effect on brain volumes of hundreds of variations of the candidate genes may generate false-positives if stringent correction for multiple comparisons is not employed.[250] In addition, many confounding factors such as genetic heterogeneity, incomplete penetrance, pleiotropic effects, diverging ethnic populations with different gene pools and small sample sizes could lead on to conflicting results.[251]

A major issue in brain morphometric research in schizophrenia is the poor replicability of findings across studies.[7,252,253] Confounding factors such as age, age of onset,[254] illness chronicity,[255] medication,[256] substance use,[257,258] symptom heterogeneity[259] and unequal gender distribution[260,261] or handedness of study samples[261,262] could contribute to the inconsistent findings, especially when they are not controlled for in the analyses. Other issues related to MRI acquisition (strength of the magnet, acquisition protocols, etc.)[263] and analyses (hypothesis-free whole brain voxel-based analyses vs ROI-based analyses, with or without a priori hypotheses) also deserve attention while examining the problem of poor replicability of brain morphometric findings. Perhaps the most serious methodological consideration in whole-brain voxel-wise MRI analysis is the statistical correction for multiple comparisons. Definitive conclusions regarding relationship between brain structural alterations and gene polymorphisms should only be made when the results survive the appropriate correction for multiple comparisons.[7,253] Uncorrected results should only be considered as trends, which should guide future studies in estimating an appropriate sample size that could generate reliable results that survive statistical correction.

4. Promising leads from imaging-genomic studies

It is evident from this review that a majority of polymorphisms of genes linked to neurogenesis/neurodevelopment was associated with whole brain and regional volumetric reductions; however mixed results (both volume reductions and increases) were reported with DISC1, ZNF804A and BDNF. Interestingly, with GSK3β, RELN, PLXNB3 and IL-6, the limited available literature shows whole brain and/or regional volumetric increases. Similarly, polymorphisms of most of the genes involved in neuronal signalling were associated with lower whole brain and regional gray and white matter volumes. However, mixed results were reported with DTNBP1, DAOA, GRID1, GAD1, COMT and MTHFR. The evidence therefore points to a differential effect of various schizophrenia risk genes on brain volumes, rather than a unidirectional effect. Perhaps, the most compelling evidence for relationship between brain volumes and gene polymorphisms are for NRG1 rs6994992, DTNBP1 rs1018381 and DISC1 rs6675281 and rs821616 polymorphisms. Another gene polymorphism that has been consistently shown to reduce brain volumes, especially in the language areas is the FOXP2 polymorphism rs2396753.

The 22q11 locus, otherwise referred to as the schizophrenia critical region,[264] is considered to be noteworthy for future research as it harbours the susceptibility genes such as COMT and PRODH. A microdeletion at the 22q11.2 locus results in an autosomal dominant condition variously referred to as DiGeorge syndrome, Velocardiofacial syndrome, etc., wherein co-occurrence of schizophrenia has been frequently reported.[231,265] Moreover, an increased prevalence of the microdeletion at 22q11 locus was reported in schizophrenia when compared to the general population.[229] The deletion polymorphism, as well as polymorphisms of COMT and PRODH genes at 22q11 locus was associated with reduced frontal and temporal lobe volumes.[234,240]

5. Future directions

A promising approach to identify genes linked to brain structural phenotypes is hypothesis-free scanning of the entire genome as in GWAS. Genome-wide association studies and haplotype-tagging studies permit us to identify multiple rare risk variants associated with structural brain variations.[9] A large multinational imaging genetics consortium, ENIGMA (Enhanced Neuro Imaging Genetics through Meta-Analysis), has used structural imaging measures and genome-wide scan data of 20,800 individuals from 21 sites to identify genetic variants associated with measurable brain differences. The samples were collected from patients with depression, anxiety, Alzheimer's disease and schizophrenia as well as healthy subjects. Common risk variants associated with mean bilateral hippocampal, total brain and intracranial volumes were identified.[266] It was shown that an intergenic variant rs7294919 was associated with hippocampal volume (12q24.22; $N = 21{,}151$; $P < 6.70 \times 10^{-16}$) and with the expression levels of the candidate gene TESC (tescalin) in brain tissue. Another variant rs10784502 within HMGA2 gene (high-mobility group AT-hook 2) was associated with intracranial volume (12q14.3; $N = 15{,}782$; $P < 1.12 \times 10^{-12}$). A suggestive association of rs10494373 within DDR2 gene (discoidin domain receptor tyrosine kinase 2) was associated with total brain volume (1q23.3; $N = 6500$; $P < 5.81 \times 10^{-7}$). The GWA signals of this ENIGMA study have been made available online by the investigators to enable others to check plausible association of various SNPs with brain volumes (http://enigma.ini.usc.edu/enigma-vis/#).[267] A follow up effort of ENIGMA's initial project,

the ENIGMA2, is currently underway. In this project, the genome is screened for analyzing the effects of genetic variants on major subcortical volumes.[268] The volumes of subcortical structures such as thalamus, and caudate that have been implicated in a wide range of psychiatric conditions have shown high heritability estimates.[269] The ENIGMA-schizophrenia working group has reported that the hippocampal volume showed the highest effect size for any subcortical brain structural difference in schizophrenia based on a meta-analysis of data from 1136 patients with schizophrenia and 1401 healthy control subjects.[270,271] Other ongoing projects by the ENIGMA consortium include ENIGMA-DTI (Diffusion Tensor Imaging) that explores genetic associations with WM microstructure[272] and ENIGMA and CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) consortia working together on genome-wide meta-analysis of hippocampal and intracranial volumes.[273]

Additional support for the effect of risk genetic variants on hippocampal volumes using GWAS comes from Hass et al.[274] who demonstrated significant genome-wide association of SNPs on chromosomes 1, 2, 10 and 19 with reduced hippocampal volume in patients with schizophrenia ($N = 328$). Single nucleotide polymorphisms in the novel 19p loci revealed significant association with hippocampal volumes when further tested by in silico analysis and expression in biopsy brain samples. It is expected that the huge volume of imaging-genetics data that would be made available upon the completion of the ENIGMA1 & 2 projects would allow researchers to examine more closely and reliably the relationship between genetic variants and brain volumes in schizophrenia, Alzheimer's disease, major depression and anxiety disorders.

In most of the studies reviewed in this paper, specific variants of a single gene have been shown to be significantly associated with structural abnormalities in schizophrenia. However, only few studies have correlated the interactive effects of multiple gene polymorphisms with brain morphometry in schizophrenia [e.g., Ref. 240]. In a recent study[253] from our laboratory, we examined the individual and additive effects of candidate genes that affect glutamatergic signalling (neuregulin and dysbindin) on brain morphometry. We found a trend towards individual and additive differential effects of risk alleles of these candidate genes on brain morphometry, irrespective of phenotype. This observed variation/differential effect due to genes acting either singly or in a combinatorial manner (additive model) could account for the inconsistent regional brain morphometric abnormalities reported across different samples of patients with schizophrenia. Therefore we suggest that volumetric alterations may be an independent function of the individual and additive effects of the multiple schizophrenia risk genes on brain volume, rather than a function of the disorder per se. Thus, epistatic interactions need to be considered in future brain morphometric studies in schizophrenia.

Algorithm-based approaches such as polymorphism interaction analysis (PIA) and multifactor dimensionality reduction enable the identification of putative gene–gene interactions. Polymorphism interaction analysis is based on ranking and scoring of SNP combinations, which identifies plausible interactions that could be further confirmed by statistical methods.[275] Multifactor dimensionality reduction (MDR) is used to characterize combinations of attributes or independent variables that interact to influence dependent or class variables. It enables computational analysis of high order epistatic interactions and multi-locus gene effects in the presence of genotyping error, phenocopy and locus or genetic heterogeneity.[276,277] Online databases such as SNPExpress (http://compute1.lsrc.duke.edu/softwares/SNPExpress/index.php), which includes data on gene expression in post-mortem frontal cortex of 93 subjects with no defined psychiatric condition, enable checking of associations between SNPs lying in a 100 kb surrounding region of the transcripts or exon.

Animal models engineered to represent regional brain abnormalities/behavioural phenotypes allow quantification of the interactive effects of multiple risk genes by characterizing their temporal expression patterns during CNS development.[278] Multiple mutations leading to neuroanatomical changes have been studied using double and multiple mutant mice models.[279,280] Furthermore, expression quantitative trait loci (eQTL) mapping studies in mice permit examination of the effect of regulatory factors in gene expression in different brain regions, which could in turn enable the detection of epistatic interactions mediating brain structure.[281,282]

The advent of in vitro cellular models using human induced pluripotent cells (hiPSC) offers the possibility of isolating hiPSCs from skin fibroblasts/lymphoblasts of patients with schizophrenia and reprogramming and differentiating them into neurons. The expression and interaction of different candidate genes mediating neurogenesis/neurodevelopment and brain signalling, as well as those identified through GWAS could be studied in these neurons.[283] The findings from these studies could form the basis for future in vivo studies in patients with schizophrenia and healthy subjects.

Epistatic interactions amongst multiple risk genes and the epigenetic alterations stemming from interactions with the environment could mediate the various morphometric deviations that ultimately lead on the brain structural endophenotype/s of schizophrenia. Modelling such complex interactions in vivo poses considerable practical challenges in having adequate sample sizes as well as imaging data for reliable quantification of interaction effects of the large number of possible risk genes on brain volume. Therefore, it is recommended that the field should move beyond association studies of the effect of single gene polymorphisms in clinical populations to modelling such complex interactions in silico and using cellular or genetically modified complex animal models. Fig. 4 highlights the complexity of the gene–gene, gene–protein and protein–protein interactions between the 34 schizophrenia risk genes that affect brain morphometry that were reviewed in this paper. In this interaction model generated using the GeneMania algorithm,[284] the genes mediating neurodevelopment and signalling are seen to be interacting in multiple domains (co-expression, co-localization, gene–gene interactions, physical interactions, predicted interactions and shared protein domain interactions) directly or through mediating genes.

Such gene and protein interactions might be responsible for regional morphometric changes in specific brain regions depending upon their co-expression and co-localization to those regions. For example, genes harbouring damaging de

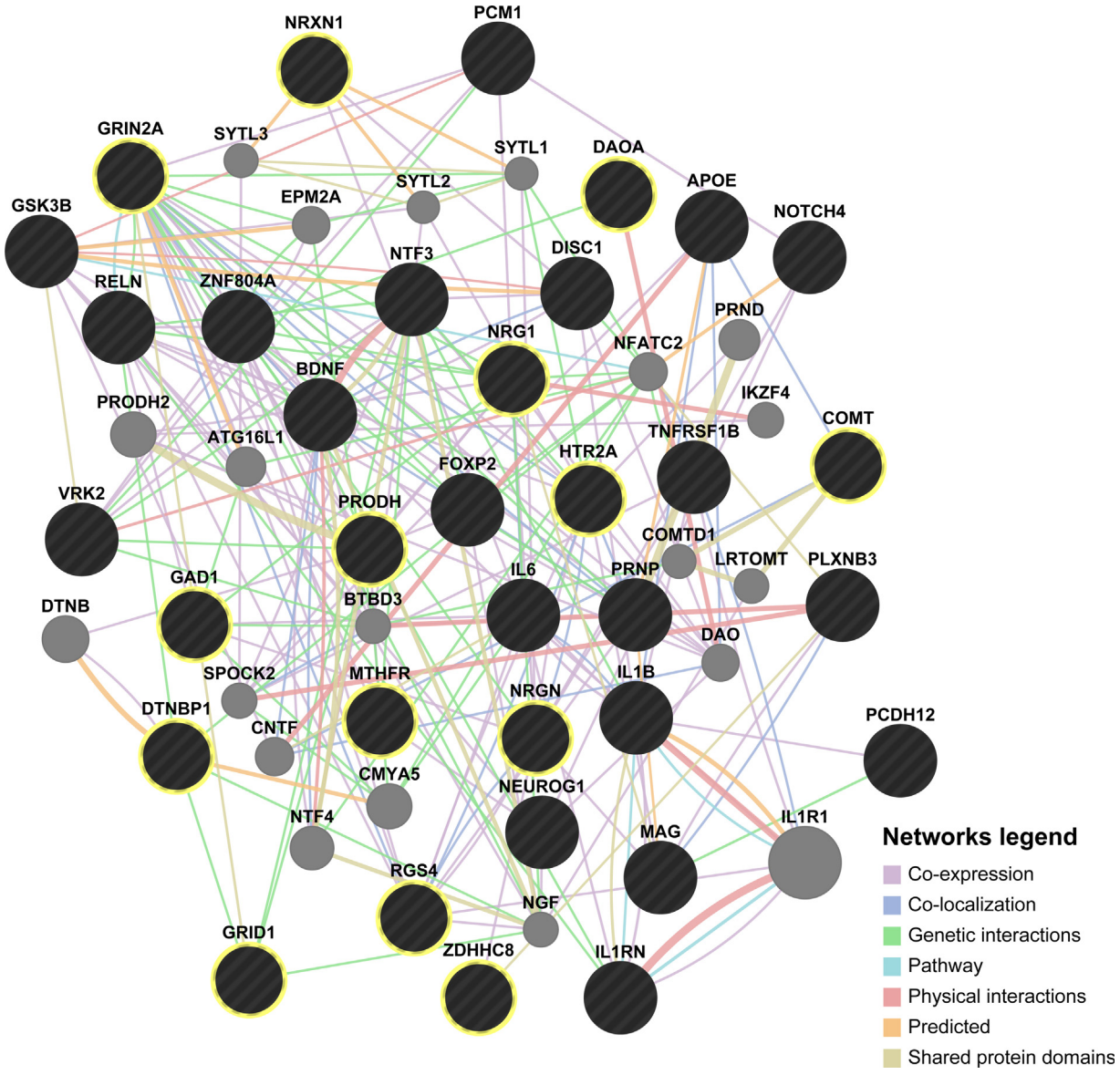

Fig. 4 – Model depicting interactions between genes regulating neurodevelopment and neurotransmission [N = 34; neurodevelopmental: 20 genes (18 + IL-1β and IL1-RN genes on the IL-1 susceptibility locus; signalling: 14 genes (13 + PRODH on the 22q11 susceptibility locus)] using GeneMania algorithm (http://www.genemania.org). Network weighting was according to the default "automatically selected weighting method" option. Dark circles with yellow outline represent genes that regulate synaptic transmission; dark circles without yellow outline represent genes that regulate neurodevelopment; and gray circles represent genes that mediate the various interactions between the queried genes.

novo mutations in schizophrenia, and involved in neuronal migration, neurotransmission, signalling, transcriptional regulation and transport were found to form a transcriptional co-expression- and protein interaction-enriched network in the dorsolateral and ventrolateral prefrontal cortex during foetal development.[285] Examining the differential expression of the risk genes in brain regions using expression datasets from Gene Expression Omnibus (accession GSE30272); and dbGaP (accession phs000417.v1.p1) via a standalone application (http://www.libd.org/braincloud) could help us decipher the observed interaction pattern and identify the expression quantitative trait loci (eQTL); i.e. the interactive effect of regulatory factors in gene expression in different brain regions. Therefore a comprehensive evaluation of interactions and expression patterns of genes that mediate neurodevelopmental processes and/or signalling in relation to brain morphology could potentially throw light on the mechanisms by which different schizophrenia risk genes act in a combinatorial manner to influence brain morphology.

6. Summary and conclusions

In summary, we reviewed the effect on brain morphometry of all the genes that have been shown to confer susceptibility towards development of schizophrenia. We noted that such

schizophrenia risk genes having an effect on brain morphometry ($N = 34$) could be broadly divided into those that primarily mediate neurodevelopmental ($n = 20$) and those that primarily mediate signalling processes ($n = 14$). Several risk variants of the above genes were shown to affect brain morphology in schizophrenia and/or healthy subjects. Polymorphisms of a majority of these risk genes were shown to be associated with whole brain and regional volumetric reductions; but importantly, many genetic variants showed mixed effects, i.e., both volume reductions and increases. However, many confounding factors such as genetic heterogeneity, incomplete penetrance, pleiotropic effects and ethnic diversity, apart from methodological issues of brain morphometric analysis such as inadequate statistical corrections to rule out false positive findings as well as sample heterogeneity have to be kept in mind while interpreting the findings of the above studies. Most importantly, since schizophrenia is a polygenic condition, the individual and interactional effects of multiple risk genes that have an impact on brain morphology could play a major role in determining brain morphometric variations associated with the condition. Modelling such complex interaction effects of the large number of possible risk genes on brain volume in vivo poses considerable practical challenges with respect to having adequate sample sizes as well as imaging data for reliable quantification. Therefore, it is recommended that the field should move beyond association studies of the effect of single or limited number of gene polymorphisms on brain morphometry in clinical populations to modelling the complex epistatic and epigenetic interactions in silico and/or using genetically modified complex animal models and cellular models. Such models could provide a framework for future biological validation of the interactions that mediate brain morphometry in health and disease.

Conflict of interest

This review work was completed in the absence of any commercial or financial relationships for any of the authors that could be interpreted as a potential conflict of interest.

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