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FEATURE REVIEW

Chromosome 8p as a potential hub for developmental neuropsychiatric disorders: implications for schizophrenia, autism and cancer

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Defects in genetic and developmental processes are thought to contribute susceptibility to autism and schizophrenia. Presumably, owing to etiological complexity identifying susceptibility genes and abnormalities in the development has been difficult. However, the importance of genes within chromosomal 8p region for neuropsychiatric disorders and cancer is well established. There are 484 annotated genes located on 8p; many are most likely oncogenes and tumor-suppressor genes. Molecular genetics and developmental studies have identified 21 genes in this region (*ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, DPYSL2, EGR3, FGF17, FGF20*, *FGFR1, FZD3, LDL, NAT2, NEF3, NRG1, PCM1, PLAT, PPP3CC, SFRP1* and *VMAT1/SLC18A1*) that are most likely to contribute to neuropsychiatric disorders (schizophrenia, autism, bipolar disorder and depression), neurodegenerative disorders (Parkinson's and Alzheimer's disease) and cancer. Furthermore, at least seven nonprotein-coding RNAs (microRNAs) are located at 8p. Structural variants on 8p, such as copy number variants, microdeletions or microduplications, might also contribute to autism, schizophrenia and other human diseases including cancer. In this review, we consider the current state of evidence from cytogenetic, linkage, association, gene expression and endophenotyping studies for the role of these 8p genes in neuropsychiatric disease. We also describe how a mutation in an 8p gene (*Fgf17*) results in a mouse with deficits in specific components of social behavior and a reduction in its dorsomedial prefrontal cortex. We finish by discussing the biological connections of 8p with respect to neuropsychiatric disorders and cancer, despite the shortcomings of this evidence.
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Introduction

Autism and schizophrenia are complex neuropsychiatric syndromes affecting between 0.3 and 0.6% of children and approximately 1% of the adult world population.[1,2] These disorders are chronic, debilitating conditions with profound human and economic consequences.[3,4] Therefore, each discovery that further elucidates disease mechanisms, and each new molecular diagnostic test or therapeutic advance has the potential to improve the quality of life for many people.[5,6]

The assumption that neuropsychiatric disorders are phenotypically heterogeneous with overlapping findings suggests the participation of more than one etiological factor and pathophysiological process, some of them being partly shared across the traditional classification categories.[7,8] Probably, as in human cancers, the heterogeneity in clinical results and treatment outcomes stems directly from the underlying variation in disorder biology.[9] It is no wonder then that this remarkable biologic heterogeneity of autism (*autism spectrum disorders*), schizophrenia (*schizophrenias*) or bipolar disorder (bipolar spectrum) is intimately related to the complexity of the genetic control of brain development and function. For instance, several of the susceptibility loci and genes in these disorders play a principal role in the development, plasticity and maintenance of the central nervous system (CNS).[10–13] However, the molecular mechanics, the neural

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systems and the concepts used are, with few exceptions, excessively vague.[14,15]

Recognizing these limitations and approaches, we focus our attention on the 8p chromosome region for several reasons. First, human chromosome 8 spans approximately 145 million base pairs (bp), which represents between 4.5 and 5.0% of the genome. The short arm spans approximately 45.2 million base pairs and only represents 1.5% of the genome, and includes 484 genes (110 pseudogenes). Many of these genes encode proteins that control cell proliferation, apoptosis or both, and may play important roles in several normal and pathological processes such as development or signaling in the CNS and immune response, and cancer and developmental neuropsychiatric disorders, respectively. Currently, it is estimated that there are approximately 41 (8.47%) genes on chromosome 8p involved in the genetic control of cerebral development and function, and approximately 80 (15.53%) genes involved in cancer biology (see Table 1 and Supplementary Table S1 at Supplementary Information). It is important to bear in mind that 8p has lower rates of base pairs and genes than other chromosomal regions with significant linkage to schizophrenia (1q, 6p and 22q), autism (7q and 15q) and bipolar disorder (13q). Only 18p, associated with bipolar disorder risk, has lower rates than 8p (Supplementary Table S2). Although chromosome 8 is typical in several characteristics, such as length, gene or repeat content, a unique feature of this chromosome is a big region of approximately 15 megabases on distal 8p that appears to have a high mutation rate. Likewise, this distal subregion on 8p shows an immense divergence between human and chimpanzee, suggesting that the high mutation rates at distal 8p have contributed to the evolution of the primate brain.[16] Interestingly, a high mutation rate has been associated with high homologous recombination in the human genome.[17] Consequently, an extraordinary recombination rate could increase the duplication genetic process, and allow us a better understanding of the biological connections between 8p, cancer and mental illness at a molecular level.

Second, various studies have recently evaluated the contribution of structural variation of DNA (that is, insertions and deletions of DNA, collectively termed copy number variants (CNVs), as well as balanced rearrangements such as inversions) in the human genetic variability and in the susceptibility to common and complex diseases such as cancer, obesity or neuropsychiatric disorders.[18–21] Now, it seems most likely that this structural variation contributes more to genetic diversity in healthy individuals and to phenotypic variation in unhealthy individuals than single-nucleotide polymorphisms.[22] Subsequently, chromosomal 8p region is one of the 'hotspot' regions of CNVs in the human genome, because it contains clusters of three to four copy number polymorphisms (Supplementary Table S3). Other regions were 6cen and 15q13-14, which are also related with schizophrenia and autism.[18] Moreover, many of the genes affected by the identified structural variants encode proteins that have been shown to mediate response to environmental challenge ('environmental sensor genes'), such as immune response, perception of smell and perception of chemical stimuli.[22,23] It is interesting to take note of the presence of olfactory dysfunction in autism[24] and schizophrenia subjects.[25,26] Furthermore, these neuropsychiatric disorders may be associated with various immune system anomalies.[27,28] The new generation sequencing technologies have detected 343 copy number variations of 146 genes on chromosome 8p. Several of these genes CNVs have been associated with schizophrenia,[10] autism spectrum disorders,[29] cancer[21,30] and Crohn's disease[31] (for updated summary, see Supplementary Table S4). It is noted that, 8p is also enriched in single-nucleotide variants across the entire genome.[32,33] The short arm of chromosome 8p is one of the most enriched regions in structural and single-nucleotide variation across the human genome, but, in any case, little is known about the role of such genetic diversity in disease association.

Third, given that there are genetic factors to schizophrenia and other major neuropsychiatric disorders, the remaining questions are which are the related chromosomal regions and how will the genes be identified?[34] In relation to this, 8p is among the best-supported genomic regions implicated in schizophrenia and bipolar risk,[35–40] as well as in other important human diseases such as cancer.[41,42] For example, the 'Top Results' list of Schizophrenia Gene Database,[43,44] displaying the 27 genes most strongly associated with schizophrenia, includes three 8p genes (1st VMAT1/SLC18A1; 15th NRG1; 26th PPP3CC). It is noted that, it is the chromosome region (arm) with a greater number of schizophrenia susceptibility genes in this ranking. In addition, Bray *et al.*[45] observed that variant(s) within 8p may modulate schizophrenia risk though a transacting effect on dystrobrevin-binding protein 1 (*DTNBP1*) expression. *DTNBP1* is one of the best-supported susceptibility genes for schizophrenia, bipolar disorder and major depressive disorder.[40,46–48] These data provide complementary evidence for chromosome 8p as a neuropsychiatry susceptibility locus.

Fourth, the animal models of human behavioral disorders represent an obvious step forward in the arena of the study of the genetics of behavioral domains.[49] We recently described a mouse mutant that lacks the *Fgf17* gene (*Fgf17* is a member of the fibroblast growth factor (Fgf) family of genes), which is located in 8p21.3. It has abnormalities in the patterning of frontal cortex (that is, a reduction in dorsal and dorsomedial frontal cortex (FC) and FC projections to subcortical targets, and a rostromedial shift of caudal cortical areas) and social behavior deficits.[50–52] Thus, this type of developmental lesion may be a relevant mechanism for some forms of autism, schizophrenia and related syndromes.

From these observations, it is reasonable to expect that 8p chromosome, as a whole, could be a

Table 1 8p Genes involved in cerebral development, cancer, neuropsychiatric and brain disorders

LOCUS	GENE SYMBOL	CEREBRAL DEVELOPMENT AND FUNCTION	CANCER	NEUROPSYCHIATRIC DISORDERS	*CEREBRAL DISORDERS
8p23.3 (4 GENES)	*DLGAP2*				
	CLN8				
	mir-596				
	ARHGEF10				
8p23.2 (1 GENE)	*CSMD1*				
8p23.1 (18 GENES)	*DEFB103A*				
	MCPH1				
	ANGPT2				
	DEFB1				
	DEFA6				
	DEFA1				
	DEFA3				
	DEFB4				
	CLDN23				
	MFHAS1				
	mir-597				
	mir-124-1				
	MSRA				
	SOX7				
	PINX1				
	mir-598				
	GATA4				
	CTSB				
8p22 (10 GENES)	*DLC1*				
	mir-383				
	TUSC3				
	MSR1				
	FGF20				
	PDGFRL				
	MTUS1				
	PCM1				
	NAT1				
	NAT2				
8p21.3 (21 GENES)	*PSD3*				
	ChGn				
	LPL				
	VMAT1/SLC18A1				
	LZTS				
	GFRA2				
	DOK2				
	NPM2				
	FGF17				
	mir-320				
	PIWIL2				
	PHYHIP				
	PPP3CC				
	KIAAA967				
	BIN3				
	EGR3				
	PEBP4				
	RHOBTB				
	TNFRSF10C				
	TNFRSF10D				
	LOXL2				
8p21.2 (13 GENES)	*NKX3-1*				
	STC1				
	ADAM28				
	ADAM7				
	NEF3				
	NEFL				
	GNRH1				
	BNIPEL				
	PNMA2				
	DPYSL2				
	ADRA1A				
	PTK2B			CNVs	
	CHRNA2				
8p21.1 (9 GENES)	*CLU*				
	SCARA3				
	PBK				
	PNOC				
	ZNF395				
	FZD3				
	EXTL3				
	HMBOX1				
	KIF13B				

Table 1 Continued

8p12 (11 GENES)	*GSR*				
	WRN				
	NRG1				
	FUT10				
	DUSP26				
	GPR124				
	EIF4EBP1				
	LSM1				
	BAG4				
	PPAPDC1				
	FGFR1				
8p11.23 (17 GENES)	*TACC1*				
	ADAM9				
	ADAM32				
	ADAM5P				
	ADAM18				
	ADAM2				
	C8ofr4				
	SFRP1				
	mir-486				
	ANK1				
	MYST3				
	AP3M2				
	PLAT				
	POLB				
	DKK4				
	CHRNB3				
	CHRNA6				
	THAP1				
8p11.2-p11.1 (1 GEN)	*CEBPD*				
	105	**41**	**80**	**21**	**25**

*Cerebral Disorders such as Epilepsy, Alzheimer Disease, Parkinson Disease, Down Syndrome and others.
Abbreviation: CNVs, copy number variants (see Ref.[10]).
Total number of genes on chromosome 8p = **484**; genes involved in cancer = **80 (15.5%)**; genes involved in neuropsychiatric disorders = **21 (4.3%);** genes involved in cerebral development and function = **41 (8.5%)**; genes involved in brain disorders = **25 (5.2%)**.

significant opportunity to explore the relationship among candidate genes, several neuropsychiatric disorders and other human diseases, including cancer, Parkinson's disease and Alzheimer's disease, and to define new pathophysiology pathways.

Therefore, the main goal of this review is to carefully provide a brief overview of previous findings that support the role of 8p not only in genetic susceptibility to neuropsychiatric disorders but also to human cancer. Moreover, we aimed to analyze 21 candidate genes (*ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, DPYSL2, EGR3, FGF17, FGF20, FGFR1, FZD3, LPL, NAT2, NEF3, NRG1, PCM1, PLAT, PPP3CC, SFRP1* and *VMAT1/SLC18A1*) from a total of 484 genes located in this region, that may lead to expression of different neuropsychiatric phenotypes, ranging from autism to schizophrenia to affective disorders. They were identified by a systematic review in PubMed and in the SchizophreniaGene (SZGene),[43] AlzheimerGene (AlzGene)[53] and Parkinson's Disease (PDGene)[54] Databases, supplemented with a manual search of reference lists. These genes are likewise involved in the relevant metabolic pathways and some aspects of the neural development. In addition, there are seven microRNAs (miRNAs) located on the short arm of chromosome 8. Two of these nonprotein-coding RNAs (*hsa-mir-124-1* and *hsa-mir-320*) are most likely to be critical in the CNS development and in various human disease states.[55] We also present a new developmental animal model that establishes a relationship between a gene of this region (*Fgf17*) that mediates the patterning of frontal cortex, and specific components of social behavior. Finally, we discuss the pertinence of 8p to understand the biological connections between neuropsychiatric disorders and cancer.

Chromosome 8p, neuropsychiatric disorders and cancer

In recent years, as mentioned above, many studies have identified a number of liability genes for major neuropsychiatric disorders and other serious human diseases, such as cancer, that are located on chromosome 8p. Then, an electronic search covering the period 1963–July 2008 was conducted using Medline database, supplemented with a manual search of reference lists. The diagnostic terms autism (and related disorders such as Asperger syndrome, Fragile X mental retardation, Rett syndrome, Tuberous Sclerosis Complex), schizophrenia, bipolar disorder or manic depression, depression and cancer were combined with keywords indicating chromosomal relationship and genetic analysis (chromosome 8, 8p chromosome, 8p genes, linkage and association

genetic studies). Our electronic and manual search identified 639 references for neuropsychiatric disorders and 867 for cancer. Further, we used the information of three databases of genes: SZGene, AlzGene and PDGene Databases.[43,53,54]

Cytogenetic studies

Kallmann's syndrome. The study of rare chromosomal or karyotypic abnormalities can provide critical information about the localization of disease genes.[34] The region discussed—8p—is involved in microdeletions that are present in individuals with the Maestre de San Juan–Kallmann–de Morsier syndrome.[56] This is a congenital disorder of hypothalamic function and reduced pituitary gonadotropic activity with resulting association of hypogonadism, eunuchoidism and anosmia (or hyposmia). Anosmia is caused by a migration disturbance that affects the axon projections of olfactory neurons to brain. Franz Josef Kallmann[57,58] was one of the first psychiatrists to study the genetic basis of mental disorders, and he reported some cases of schizophrenia and mental retardation in individuals with this syndrome. More recently, Cowen and Green[59] have drawn attention to some parallels between schizophrenia and Kallmann's syndrome, including the fact that olfactory dysfunctions (that is, smell identification deficits) are present in a subgroup of patients with schizophrenia.[60] Versiani *et al.*[61] also confirm the association of Kallmann's syndrome and schizophrenia, and abnormalities of cognition and behavior such as learning disabilities. However, other authors consider that this association is rare and confined to olfactory dysfunction.[62]

Autism and other related syndromes. There are several clinical reports associating chromosomal interstitial 8p (p21-23, p12-23, p12-21.2) rearrangements (that is, translocations, inversions, deletions, duplications) with autism (reviewed by Papanikolaou *et al.*[63]). It is noted that the autistic patients of these cytogenetic studies have milder phenotypes than other reported cases with abnormalities in other chromosomes. These bands might represent a critical region for social and communication deficits indicating an autism spectrum disorder, unrecognized until 3 or more years and with a negative family history of autism.[64]

In a Finnish population sample,[65] there is also evidence that 8p anomalies are associated with mental retardation epilepsy. The patients with mental retardation epilepsy are distinguished from the majority of epilepsy cases in that they suffer mental deterioration following the onset of seizures. Moreover, the degree of mental deterioration correlates with the severity of cerebral atrophy.[66] Autism includes a high prevalence of mental retardation, with rate estimates of 40–55% or higher,[67] and comorbid epilepsy, observed in approximately 30% of autistic subjects.[68] Furthermore, the occurrence of schizophrenia-like symptoms and secondary affective symptoms has been shown in patients with epilepsy.[69] Even more interestingly, a family history of epilepsy is a significant risk factor for schizophrenia.[70]

Aberrations in the short arm of chromosome 8 may also be a relatively common cause of corpus callosum malformations.[71] Moreover, 8p21-p23 is a suitable candidate locus for agenesis of the corpus callosum.[72] The association of corpus callosum anomalies with cognitive deficits, epilepsy, autistic-like behavior or schizophrenia-like symptoms is relevant and well known.[73] Finally, several recent studies have detected novel submicroscopic 8p abnormalities using a new generation of microarray analysis. For example, Butler *et al.*[74] using an array comparative genomic hybridization analysis in Prader-Willi syndrome, detected that most Prader-Willi syndrome subjects had CNVs on 8p and 3q. The autistic-like symptomatology in Prader-Willi syndrome[75] and the association with schizophrenia and affective psychosis[76] are also well known.

Cancer. Despite 8p being a relatively small chromosome arm, it is one of the most frequently altered genomic regions in human cancer,[41] and is also rich in candidate oncogenes and tumor-suppressor genes associated with the development of certain types of cancers (see Table 1 and TS1 at Supplementary Information). The high frequency of cytogenetic aberrations and genomic rearrangements (principally deletions and translocations) affecting 8p in lung and prostate cancers suggests that this region may harbor potential candidate genes involved in the pathogenesis of these types of cancer.[77,78] However, the loss of heterozygosity involving 8p is also a common feature of the malignant progression of others, including breast cancer,[79] gastric cancer,[80] colorectal cancer,[81] bladder carcinoma[82] and hepatocellular carcinoma, especially during metastasis.[83]

In spite of several methodological issues and heterogeneous results, the epidemiological studies of the relationships between schizophrenia and cancer detected a reduced incidence of cancer observed in patients with schizophrenia compared with the general population (reviewed by Catts and Catts,[84] Jablensky and Lawrence,[85] Grinshpoon *et al.*[86]). It is intriguing that two rigorous population-based studies found a significantly lower risk of respiratory and prostate cancer in people with schizophrenia and their relatives compared with people without schizophrenia after adjustment for confounder variables.[87,88] More recently, the first meta-analysis of cancer incidence rates in patients with schizophrenia, their parents and siblings has been published.[89] Catts *et al.*[89] report a discrepancy between cancer risk exposure and cancer incidence in schizophrenia, consistent with a possible genetic protective effect. Although other possible

explanations may be involved (that is, epidemiological bias, cancer-protective effect of classical antipsychotic medications, obstetric complications and lifestyle differences),[90–92] the authors propose that the genetic predisposition toward schizophrenia confers genetically reduced susceptibility to cancer.

In contrast with schizophrenia, few studies have explored in detail the cancer rates in patients with autism, bipolar disorders or other neuropsychiatric disorders. However, the co-occurrence of autism spectrum phenotype and tuberous sclerosis complex has been recognized for decades.[93] Tuberous sclerosis complex is an autosomal dominant inherited disorder characterized by benign tumors that form during the development (hamartomas) in various organs such as brain (known as tubers). These brain lesions are associated with epilepsy, cognitive disability and autism.[94] Despite the presence of several factors among patients with bipolar disorder that might affect the risk for cancer (that is, diet, smoking and medications), several studies found a nonsignificant statistical risk for cancer.[87,95] Likewise, Carney and Jones[96] in a population-based controlled study found that hyperlipidemia, lymphoma and metastatic cancer were the only medical conditions less likely to occur in persons with bipolar disorder. More recently, BarChana *et al.*[97] found an enhanced risk for cancer among patients with bipolar disorders. However, the risk for breast cancer was higher, but not significantly, than in the general female population. Then, no firm conclusions could be drawn.

On the basis of these clinical and cytogenetic findings, there is some evidence supporting 8p as a schizophrenia/autism overlap risk region. Curiously, the autistic patients with 8p rearrangements might have a benign clinical presentation compared with other autistic cases with abnormalities in other chromosomes. In addition, the same genetic factors located in this chromosomal region might induce cancer in the general population, but have also a possible protective effect for lung and prostate cancer in individuals with schizophrenia and their relatives. In this respect, 8p may represent a landmark for the identification and cloning of genes involved in cancer, schizophrenia and others.

Linkage studies

Linkage studies have provided evidence for one or more loci in the 8p region that influence susceptibility to several neuropsychiatric phenotypes.

Schizophrenia. The seminal study of Pulver *et al.*[35] and three independent investigations have reported logarithm of odds (LOD) scores above 3.0[38,98,99] and another four have confirmed a LOD score above 1.5.[36,38,100,101] Moreover, this region is supported by the results of published meta-analyses of schizophrenia linkage studies.[102,103] However, a published study has not been able to find significant evidence for linkage on 8p region.[104] It is important to take into consideration that Kendler *et al.*[105] found an association between 8p22-21 locus and some clinical features in 265 multiplex schizophrenia pedigrees. More specifically, affected individuals from families with evidence of linkage to 8p had significantly more affective deterioration and thought disorders, a worse outcome, and fewer depressive symptoms than affected individuals from the other families in the study. Furthermore, Chiu *et al.*[106] have also shown that schizophrenia susceptibility appears to be associated with 8p21 region in some families, where the affected siblings are more likely to have experienced bizarre delusions, attendance to a special school, affective symptoms early in the course of illness and seizures.

Affective disorders. Although chromosome 8p showed no evidence of linkage in a genome-wide linkage scan study of schizophrenia and bipolar people,[102,107] five genome scan studies and one of the two published meta-analyses supports this region in bipolar disorder.[108–113] Indeed, the psychotic bipolar disorder subtype was further studied in a genome-wide linkage analysis of 40 extended bipolar pedigrees (only subjects with psychotic features were considered affected), and the two strongest regions in the genome were 9q31 and 8p21.[112] These findings are additionally supported by a new genome-wide linkage scan in a large bipolar disorder sample from the National Institute of Mental Health (Genetics Initiative) that found a suggestion of linkage (8p22) for bipolar patients with psychotic symptoms.[114]

In major depression, the 8p region is supported by two genome-wide linkage studies with partially shared samples of families with two or more probands of early-onset recurrent major depression.[115–117] Zubenko *et al.*[116] reported a positive association between a history of suicide attempts and several chromosomal regions. It is noted that the highest ΔLOD score (ΔLOD = 5.08) was located at 8p22-p21 (D8S1145; 37.0 cM, 18.2 Mbps, $P < 0.0001$). It is relevant to take into account that suicide is a prevalent outcome of neuropsychiatric disorders, and that repetitive, self-injurious behavior may appear in individuals with autism or related disorders.[118,119] The other positive linkage was observed in a secondary analysis after Holmans and colleagues[117] controlled for the sex of affected pair. Their results suggest that the contribution of 8p loci may be sex dependent, and that 8p contains genes that contribute to susceptibility to severe and persistent episodes of depression.

Other neuropsychiatric disorders. Other linkage analyses have also shown linkage of other neuropsychiatric disorders and developmental cognitive deficits to chromosome 8p. Subsequently, the region has been implicated in reading disability or developmental dyslexia in individuals with attention-deficit/hyperactivity disorder,[120] anxiety-related personality traits such as harm avoidance and neuroticism,[121–123] late-onset Alzheimer's disease,[124]

late-onset Alzheimer's disease with positive symptoms of psychosis[125] and idiopathic late-onset Parkinson's disease.[126] In contrast with these disorders, there has been no strong evidence for linkage on chromosome 8p in any of the genome-wide linkage studies of autism.[127,128] Only one linkage analysis on multiplex autism families stratified according to delayed expressive speech found higher linkage signals in the delayed groups for some loci on chromosome 8p.[129]

Given this linkage scenario, chromosome 8p should be considered as a robust candidate for a susceptibility region for schizophrenia especially with clinical features that bring to mind the classical dementia-praecox syndrome described by Emil Kraepelin.[130] In addition, there is suggestive evidence for bipolar disorder with psychotic symptoms, major depression with recurrent episodes and suicide attempts, and specific anxiety-related personality traits such as neuroticism and harm avoidance, but insufficient evidence for other neuropsychiatric phenotypes, including autism, Parkinson's disease and Alzheimer's disease. It is noteworthy, therefore, that the 8p arm appears to increase the probability that several major neuropsychiatric disorders will show higher levels of affective severity, suicidal behavior, psychotic symptoms and poor outcome. Some aspects of this clinical variability concur in part with deficits in social cognition.[119] Nevertheless, on the basis of 8p linkage findings, at least some risk genes affect, in part, the expression of specific phenotypes across the nosological boundaries.

Studies of individual genes: association, gene expression and endophenotype investigations

To our knowledge, there are 484 genes located on 8p (for exhaustive and update information about their localization and description—locus, bases, names, ID, MIM, type and ontology: functions, processes and components—see Supplementary Table S1 at Supplementary Information section). In recent years, as mentioned above, many studies have identified several susceptibility genes for schizophrenia and other neuropsychiatric disorders that are located on chromosome 8p. Specifically, our electronic and manual search identified 19 potential candidate genes from association studies. Following the first recommendation (broad view) proposed by Lohmueller *et al.*[131] to reduce false positive associations, we consider those associations that have been replicated at least once with an independent sample. Nine genes located on 8p satisfy the criteria of Lohmueller *et al.*[131]: *DPYSL2, EGR3, FGF20, FZD3, LPL, NAT2, NRG1, PPP3CC* and *VMAT1/SLC18A1*. We also consider the current state of evidence for 11 additional candidate genes that do not satisfy the Lohmueller *et al.* criteria, but have a significant association in only one study: *ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, FGFR1, NEF3, PCM1, PLAT* and *SFRP1*. Finally, we consider three additional genes as other potential candidate genes on 8p chromosome from molecular genetics and cerebral developmental studies: *FGF17, hsa-mir-124-1* and *hsa-mir-320*.

Table 2 summarizes the published findings about 8p genes in neuropsychiatric disorders, highlighting results that show the relationship among this candidate genes and a number of normal and pathological conditions, such as neurodevelopmental processes, gene expression in the CNS and in the peripheral sources of patients, endophenotype investigations, experimental disease models and cancer research.[132–345] Other 14 genes located on 8p (*ADRB3, BIN3, CLU, CTSB, EPHX2, GNRH1, NAT1, NEFL, PDLIM2, PEBP4, PIWIL2, PNOC*, *SLC39A14, SORBS3* and *WRN*) were investigated in at least one study that did not show association with neuropsychiatric disorders (see Ref.[43,53,54]).

A developmental animal model from 8p: potential implications for autism, schizophrenia, affective disorders and cancer

Numerous studies have reported that social cognition impairments, especially deficits in theory of mind, emotion perception and social perception, are a core of autism and schizophrenia.[346–348] Although the molecular and cellular mechanisms underling social cognitive deficits have not been clarified, recent studies have linked social dysfunction changes in rodents to neurodevelopmental abnormalities associated with autism,[349] depression and schizophrenia,[350] and Rett syndrome.[351] More specifically, genes involved in neurodevelopment are essential for normal social behaviors. Fgf are particularly interesting in this regard. Fgf genes encode a family of 22 signaling molecules, which signal through at least four FGF receptors, play a central role in development and in tissue homeostasis.[158,159] Blocking Fgf receptor signaling by expressing a dominant-negative Fgf1R receptor during embryonic development resulted in decreased cortical thickness.[160] Expressing the dominant-negative Fgf1R in dopamine neurons reduced the number of dopamine neurons, increased dopamine levels in the striatum and impaired prepulse inhibition,[352] changes which may have relevance to the neuropathology and sensorimotor gating deficits in schizophrenia.[353,354] Moreover, *FGF20* at 8p21.3-22 was identified as a risk factor for Parkinson's disease.[161–164] Likewise, Murase & McKay[168] showed, *in vitro* experiments, that FGF signals (specifically, FGF20 and FGFR1) to elevate dopamine levels and protect the specific midbrain neuron type. Because Parkinson's disease is characterized by loss of midbrain dopaminergic neurons, it is possible that altered FGF-signaling might have permanent effects on CNS function by the dopaminergic nigrostriatal system.[355,356]

FGF-signaling defects are also linked to major depression. Two recent postmortem analyses, showed a reduction, on the one hand, of FGF members (*FGF1, FGF2, FGFR2* and *FGFR3*) in the frontal cortex of

Table 2 List of candidate 8p genes associated with neuropsychiatric disorders and investigated in several domains

Gene symbol position	*Neurodevelopmental (or biological) process*	*Expression in the CNS and in peripheral sources of patients*	*Positive studies*	*Negative studies*	*Other studies (endophenotype investigations, disease models, case reports)*	*Cancer*	*Commentaries*
DPYSL2 8p21.2[a]	*DPYSL2* is an important molecule in neurite outgrowth and in neurite degeneration, and is expressed in the developing and adult nervous systems[132,133]	SZ: Increase of *DPYSL2* in the hippocampus[134] SZ + BD + MD: the expression of *DPYSL2* is decreased in the FC,[135] and in the ACC[136] SZ: no differences in *DPYSL2* expression at lymphocytes[137] AD: Decrease of *DPYSL2* in the hippocampus[138] DS: Dysregulation of *DPYSL2* protein and decrease of mRNA in brain[139,140]	SZ: 2 CCS[141,142] SZ: 1 FBS[143] BD: 1 FBS[143]	SZ: 2 CCS[142,137] BD: 1 CCS[144] METH psychosis: 1 CCS[145]	SZ: *DPYSL2* is associated with paranoid type but not with hebephrenic schizophrenia[141] DM: Deregulation of *DPYSL2* expression in the brain upon aging of transgenic mouse models of AD[146] DM: *DPYSL2* is a marker for escitalopram resistance in stress model of depression[147] CR: Several clinical studies have described a variety of neurodevelopmental abnormalities in subjects with defects of *DPYSL2*[148,149]	Cancer: Goulet *et al.*[150] found an increase of *DPYSL2* expression in HCT116 colon cancer cells treated with selenomethionine, which is an anticancer drug. This finding suggests that *DPYSL2* could play a functional role in the growth inhibitory effects of selenomethionine	The pm [a]2236T > C in the 3′ untranslated region of the *DRP-2* gene has been shown to be a negative genetic risk factor for paranoid-type schizophrenia.[141] However, Hong *et al.*[142] found that the *DRP-2* [a]2236 C allele may influence susceptibility to Schizophrenia [b]Meta-analysis of all published SZ-association studies (4 CCS) for rs17666 ([a]2236T > C) pm (OR (95% CI) = 1.06 (0.68, 1.65))
EGR3[a] 8p21.3	*EGR3* is a zinc-finger transcription factor and plays important roles in cellular growth and in neuronal development. For example, *EGR3* may be a critical regulator of endogenous **GABRA4** during development[151]	SZ + BD: *EGR3* mRNA levels were decreased in the DLPFC of schizophrenic, but not bipolar subjects[152] SZ: Expression of *EGR3* was significantly lower in the hippocampus of schizophrenic smokers compared with control smokers[153]	SZ: 1 CCS[152] SZ: 1 FBS[152]		DM: Evidence for support a role for BDNF as the mediator of *EGR3*-induced GABRA4 regulation in developing neurons and epilepsy[154] DM: *EGR3*$^{-/-}$ mice display abnormalities in social and aggressive behavior, and defects in synaptic plasticity.[155] The aggression of *EGR3*$^{-/-}$ mice was reversible by treatment with clozapine, an antipsychotic drug[156]	Cancer: Suzuki *et al.*[157] showed an estrogen-mediated induction of *EGR3* in breast carcinoma cells. *EGR3* also plays an important role in estrogen-meditated invasion and is an independent prognostic factor in breast carcinoma	There are only two published studies that have reported involvement of *EGR3* in neuropsychiatric disorders. The findings to date need to be confirmed by replication in other populations and methods
FGF20[a] 8p22	*Fgf* genes play a central role neuronal development[158–160]		PD: 1 CCS[161] PD: 3 FBS[162–164]	PD: 2 CCS[165,166] SZ: 1 CCS[167]	DM: Murase and McKay[168]showed, *in vitro* experiments, that *FGF* signals (specifically, *FGF20* and *FGFR1*) to elevate dopamine levels and protect the specific midbrain neuron type	Cancer: members of the Fgf family are associated with a variety of human cancers[169–171] *FGF20*, *JAG1* and *DKK1* are target genes of the Wnt–catenin signaling cascade[172]	[b]Meta-analysis of all published PD-association studies (4 CCS) for rs1989754 pm (OR (95% CI) = 1.04 (0.86, 1.27))
FZD3[a] 8p21.1	Wnt-Fz is a ligand-receptor pair with a conserved role in neuronal process development. For example, *FZD3* activity mediates Wnt-dependent neurogenesis and neurite outgrowth[173–175]	BD: *FZD3* mRNA levels were decreased in the orbitofrontal cortex of bipolar subjects[176] BD: *FZD3* has been identified as a biomarker for high mood in whole-blood (predominantly lymphocytes) samples[177]	SZ: 2 CCS[178,179] SZ: 1 FBS[180]	SZ: 4 CCS[181–184] SZ: 3 FBS[181,185,186] BD: 1 CCS[183] MD: 1 CCS[183]	DM: Inactivation of *Fz3* in mice causes the absence of, or a great reduction in, several axon tracts, including the anterior commissure, corticospinal tract, corpus callosum, fornix, thalamocortical and corticothalamic tracts, stria medullaris, stria terminalis and hippocampal commissure. Thus, *Frizzled3* plays an important	Cancer: Wnt path way-related genes are associated with cancer.[189] For instance, *Frizzled* could play a role in the invasive migration of melanoma cancer cells through noncanonical Wnt5a signaling pathway.[190] *FZD3* exhibited significantly increased	[b]Three meta-analyses of the published SZ-association studies: 5 CCS for rs960914 pm (OR (95% CI) = 0.91 (0.77, 1.08)) 6 CCS for rs2241802 pm (OR (95% CI) = 0.98 (0.89, 1.07)) 4 CCS for rs352203 pm (OR (95% CI) = 0.94 (0.83, 1.07)) Using a mathematical

Table 2 Continued

Gene symbol position	*Neurodevelopmental (or biological) process*	*Expression in the CNS and in peripheral sources of patients*	*Positive studies*	*Negative studies*	*Other studies (endophenotype investigations, disease models, case reports)*	*Cancer*	*Commentaries*
					role in outgrowth and/or guidance axonal[187,188]	expression in patients with ulcerative colitis[191]	approach for testing genetic epistasis underlying complex diseases, *Kang et al.*[192]found an interactive effects for SZ among variants of the genes *NRG1*, *G72* (13q34), the regulator of G-protein signaling-4 (*RGS4*, 1q21–q22) and *FZD3*
LPL 8p21.3	*LPL* is one gene involved in lipid metabolism[193] *LPL* plays an important role in the modifiability of neuronal response plasticity ''Metaplastic control''[194]	AD: a common polymorphism in the lipoprotein lipase gene modulates the risk level for sporadic AD in the eastern Canadian population but more importantly, indirectly modulates the pathophysiology of the brain in autopsy-confirmed cases[195] SZ: changes in *LPL* expression in the DLPFC of schizophrenic subjects[196]	AD: 6 CCS[195,197–200]	AD: 6 CCS[198,201–205]	Lipoprotein lipase gene might influence in the differential lipid response to treatment with antipsychotic drugs[206] Decreased lipoprotein lipase as a risk factor for atypical neuroleptic-induced hypertriglyceridemia[207] Relation between gene of lipoprotein-lipase and life duration in patients with chronic cerebral ischemia[208]	Cancer: Thomassen *et al.*[209] suggest that *LPL* and *EPHX2* at 8p21-22 are candidate metastasis suppressor genes in breast cancer. *LPL* was found to be promising biomarker candidates for the detection of hepatocellular carcinoma[210] *LPL* deletion is associated with prostate cancer[211]	[b]Two meta-analyses of the published AD-association studies: 3 CCS for rs320 (*Hin*dIII) pm (OR (95% CI) = 0.73 (0.59, 0.9)) 5 CCS for rs328 (S447Ter) pm (OR (95% CI) = 0.83 (0.88, 1.04))
NAT2 8p22	*NAT2* is one of two *N*-acetyl transferase isoforms expressed in humans, which are involved in the detoxification of heterocyclic or aromatic amines and their metabolites[212]		SZ: 1 CCS[212] AD: 2 CCS[213,214] PD: 8 CCS[215–222]	AD: 3 CCS[223–225] AD + PD with Dementia[226] PD: 6 CCS[227–232] PD: 1 FBS[233]	Variants in *NAT2* are associated with the risk to develop systemic lupus erythematosus[234]	Cancer: The *NAT2* slow acetylator phenotype is associated with an increased risk of bladder cancer (owing to decreased detoxification of carcinogens from tobacco smoke), but has been associated with decreased risk of colorectal cancer (owing to reduced activation of carcinogens).[235] *NAT2* with other cancers such as brain tumors, prostate cancer, bladder cancer and breast cancer[236]	
NRG1[a] 8p12	*NRG1* is the member of a family of proteins that exert a key role in neurodevelopmental processes and synaptic plasticity, including neuronal migration and specification, oligodendrocyte development, and regulation of acetylcholine, GABA and glutamate[237–239] Specific genetic variation in *NRG1* is associated with reduced white	SZ: Type I *NRG1* mRNA was found to be upregulated in the DLPFC and in the hippocampus of patients.[241,242] Further, Hashimoto *et al.*[241] showed that Type I *NRG1* expression positively correlates with antipsychotic medication dosage. SZ: *NRG1*-ICD protein levels were increased in prefrontal	SZ: 19 published CCS (see Ref. 43) SZ: 11 FBS (see Ref. 43) BD: 3 CCS[249–251] BD: 1 FBS[251] ADP: 1 FBS[125]	SZ: 10 published CCS (see Ref. 43) SZ: 9 FBS (see Ref. 43) BD: 3 FBS[143,252,253] AUT: 1 FBS[254]	SZ + SZ-Rel: Gruber *et al.*[255] found a link between *NRG1* genetic variation and hippocampal volume reductions in schizophrenic patients and nonaffected relatives (SMRI) SZ: Specific *NRG1* risk allele was associated with poorer premorbid social functioning and with the	Cancer: Overexpression of *NRG1* is found in many different cancer types and correlates with cancer progression and an aggressive phenotype.[260] Overexpressed NRG1 in cancers may function as oncogenes and promote cancer development by	SZ: Three published meta-analyses showed a strong positive association for six pm and the at-risk haplotypes in *NRG1* with schizophrenia[261–264] [b]Eight meta-analyses of the published SZ-association studies:

Table 2 Continued

Gene symbol position	*Neurodevelopmental (or biological) process*	*Expression in the CNS and in peripheral sources of patients*	*Positive studies*	*Negative studies*	*Other studies (endophenotype investigations, disease models, case reports)*	*Cancer*	*Commentaries*
	matter density and connectivity in the anterior limb of the internal capsule of human brains using *DTI*[240]	cortex of patients[243] SZ: Evidence of increased *NRG1* signaling and/or function was found in the prefrontal cortex of patients[244] SZ: Petryshen *et al.*[245] reported an increased expression of SMDF, a type III isoform, in the PBLs of patients compared with their unaffected siblings SZ: *NRG1* mRNA expression in PBLs was also lower than that in siblings and healthy controls. This expression was gradually increased in antipsychotic treated patients[246] SZ: *NRG1* GGF2 isoform showed a lower expression in immortalized lymphocytes of SZ patients before and after olanzapine stimulation. In contrast, *NRG1* GGF isoform showed no significant difference between patients and unrelated-family controls[247] SZ + BD + MD: Bertram *et al.*[248] found a reduced number of *NRG1* inmunoreactive neurons in the brain of schizophrenic and depressive patients			different trajectories of change in lobar volumes of COS subjects, using *SMRI*[256] SZ: Specific *NRG1* risk allele predicts conversion to psychosis, abnormal activation of frontal and temporal lobes, and cognitive impairment in individuals at high genetic risk of schizophrenia.[249] BD + SZ: Green *et al.*[249] found that variations in *NRG1* may exert a specific effect in bipolar subjects with mood-incongruent psychotic features, as well as in schizophrenia cases that had experienced mania. Similar findings have been found by WalssBass *et al.*[258] BD + SZ: A new *NRG1* marker risk was associated with a ''typical'' bipolar I phenotype characterized by excellent recovery between episodes and no mood incongruent psychotic features.[251] DM: NRG1 knockout mice exhibited hyperactivity and defects in social interaction domain (aggressive behavior and behavior response to social novelty) rather than in emotional/anxiety domain[259]	regulating tumor suppressor genes and/or genes that control cell differentiation or apoptosis[261] Cancer: also see Discussion section	4 CCS for rs10503929 pm (OR (95% CI) = 0.87 (0.79, 0.97)) 19 CCS for rs35753505 (SNP8NRG221533) pm (OR (95% CI) = 1.04 (0.96, 1.12)) 6 CCS for rs3924999 (Gln38Arg) pm (OR (95% CI) = 0.96 (0.88, 1.04)) 4 CCS for rs4733376 pm (OR (95% CI) = 1.08 (0.94, 1.24)) 12 CCS for rs6994992 (SNP8NRG243177) pm (OR (95% CI) = 1.01 (0.94, 1.10)) 4 CCS for SNP8NRG221132 pm (OR (95% CI) = 0.92 (0.83, 1.03)) 12 CCS for SNP8NRG241930 pm (OR (95% CI) = 0.95 (0.87, 1.04)) 5 CCS for SNP8NRG433E1006 pm (OR (95% CI) = 1.04 (0.83, 1.30))
PPP3CC 8p21.3	PPP3CC is expressed in the rodent brain (hippocampus and cerebellum). The data suggest a potential importance of calcineurin in neurodevelopment.[265] Calcineurin may play important roles in neuroplasticity and neuronal adaptation.[266] Calcineurin has been implicated in neurodegenerative disorders.[267] For instance, in PD[268]	SZ: PPP3CC mRNA levels were decreased in the hippocampus of schizophrenic patients.[269] SZ + BD: PPP3CC mRNA levels in the DLPFC did not differ among schizophrenics, bipolar and controls.[270] SZ: No significant differences were found in PPP3CC protein levels either in the prefrontal or in the hippocampus of schizophrenia patients compared with matched control subjects.[271] SZ: Expression of PPP3CC gene in the whole-blood sample was not altered in patients with schizophrenia relative to control subjects[272]	SZ: 2 CCS[273,274] SZ: 2 FBS[270,75] BD: 1 CCS[276]	SZ: 3 CCS[277–279] SZ: 2 FBS[143,278] BD: 1 FBS[143]	DM: CNB knockout mice exhibited increased locomotion, defects in social interaction, impaired prepulse and latent inhibition, and severe working/episodic-like memory deficits. These behavioral abnormalities reminiscent of both schizophrenia and bipolar phenotype.[280,281] SZ: variations on *PPP3CC* gene, including rs2461491, showed significant associations with the subgroup of schizophrenia with deficits of sustained attention and the executive functioning (CPT, WCST)[275]	Cancer: Expression of PPP3CC was significantly downregulated in prostate cancer and in recurrent prostate cancer[283,284]	[b]Meta-analysis of all published SZ-association studies (5 CCS) for rs2461491 pm (OR (95% CI) = 1.06 (1.01, 1.12))

Table 2 Continued

Gene symbol position	*Neurodevelopmental (or biological) process*	*Expression in the CNS and in peripheral sources of patients*	*Positive studies*	*Negative studies*	*Other studies (endophenotype investigations, disease models, case reports)*	*Cancer*	*Commentaries*
					SZ: The *PPP3CC* gene expression level was positively correlated with the BPRS score[272]		
VMAT1/ SLC18A1[a] 8p21.3	*VMAT1* might be important neuronal migration, development of neurosecretory pathways, and the neuronal survival[284–286]		SZ: 5 CCS published with positive results[287–291] BP: 1 CCS[292] AX: 1 CCS[293]	SZ: 1FBS[291]	Studies *in vitro* have shown that lithium and valproate increased the *VMAT1* expression in nerve growth factor-differentiated PC12 cells, suggesting that this gene might be a rational target for mood drugs[294] CR: The JARID1C-regulated genes *SCN2A*, *CACNA1H*, *BDNF* and *SLC18A1* have been associated with autism and cognitive dysfunction[295]	Cancer: VMAT1 might be related with human neuroendocrine tumors, such as endocrine tumors of the gastrointestinal tract and pancreas[296]	[b]Meta-analysis of all published SZ-association studies (4 CCS) for rs2270641 (A277C) pm (OR (95% CI) = 1.63 (1.03, 2.57)) AX: 5 positive linkage studies[121–123,297] Two SZ-association studies found a gender-by-genotype effect for SZ[288] and for AX[293] significant differences were observed in females, but not in males
ADRA1A[a] 8p21.2	The adrenergic system regulates key biological processes that are often dysregulated in these severe mental disorders such as sleep, learning, memory, attention, arousal and adaptation to stress[298]		SZ: 1 CCS[311] SZ: 1 FBS (trend[155]) AD: 1 CCS (trend[312])	SZ: 3 CCS[313,314] BD: 1 FBS[155]	The α_1-adrenergic subtypes have effects on the cognitive functions of prefrontal cortex relevant to schizophrenia in animals[316,317]	Cancer: The selective α_1 adrenergic receptor antagonist doxazosin (Dox) has been reported to inhibit prostate cancer proliferation[318] Dox treatment inhibits proliferation and induces apoptosis in breast cancer cells *in vitro*[319]	
ARHGEF10 8p23.3	*ARHGEF10* is a myelin-related gene, involved in myelin structure, composition, development or maintenance[308] The Rho GTPases are the molecular regulators of the cell motility processes and are involved in cell-cycle progression and gene transcription[309]		SZ: 1 CCS[167]			Cancer: Alteration in the expression pattern of *ARHGEF10* in retinoblastoma tumors[309]	
CHRNA2[a] 8p21.2	Nicotinic acetylcholine receptors (nAChRs) constitute a heterogeneous family of ion channels that mediate fast synaptic transmission in neurons. They have also been found on non-neuronal cells such as bronchial epithelium and keratinocytes The cellular roles of non-neuronal nAChRs, including regulation of cell proliferation, angiogenesis, apoptosis, migration, invasion and secretion[310]		SZ: 1 FBS[311] BD: 1 FBS[312]	SZ: 1 CCS[313] SZ: 1 FBS[143] BD: 1 CCS[314] BD: 1 FBS[143] AD: 3 CCS[315–317]	Nocturnal frontal lobe epilepsy is associated with variations in *CHRNA2* gene[318]	Cancer: Mesothelioma cells growth is modulated by the cholinergic system in which agonists (i.e. nicotine) have a proliferative effect and antagonists (i.e. curare or α-cobratoxin) have an inhibitory effect. Furthermore, apoptosis mechanisms are under the control of the cholinergic system[319,320]	The significant association did not reach gene-wide significance after correction by permutation.[312] New evidence reinforces interest in nicotinic acetylcholine receptors as potential disease candidates and chemopreventative targets[321]

Table 2 Continued

Gene symbol position	*Neurodevelopmental (or biological) process*	*Expression in the CNS and in peripheral sources of patients*	*Positive studies*	*Negative studies*	*Other studies (endophenotype investigations, disease models, case reports)*	*Cancer*	*Commentaries*
CHRNA6[a] 8p11.23	See *CHRNA2* annotation		SZ+BD: 1 FBS[322]	BD: 1 FBS[312] AD: 3 CCS[315–317]		Cancer: Lam *et al.*[323] found that nonsmall-cell lung cancers from nonsmokers showed higher expression of nAChR 6 ($P<0.001$) and 3 ($P=0.007$) subunit genes than those from smokers, adjusted for gender	
CHRNB3[a] 8p11.23	See *CHRNA2* annotation		SZ+BD: 1 FBS[322]	SZ: 1 FBS[143] BD: 2 FBS[143,312]		Cancer: Analysis of 28 aqueous cell lung carcinomas showed increased levels of 5 and 3 nAChR mRNA[324]	
DKK4 8p11.23	DKK4 is involved in embryonic development through its interactions with the Wnt signaling pathway[325]		SZ: 1 CCS[186] SZ: 1 FBS[186]			Cancer: the loss of DKKs may facilitate tumorigenesis. *DKK4* was frequently silenced in endometrial cancer[326] and colorectal cancer[327]	
FGFR1[a] 8p12	See *FGF20* annotation	MD: *FGFR1* was upregulated in prefrontal cortex.[328] *FGFR1* was also observed to be upregulated in hippocampus.[329] BD: *FGFR1* has been identified as a biomarker for low mood in whole-blood (predominantly lymphocytes) samples[177]	SZ: 1 CCS[167]			See *FGF20* annotation. The fibroblast growth factors are potent angiogenic inducers in the embryonic brain and might play a principal role in the formation of the vascular cancers[330]	
PCM1 8p22	The gene *PCM1* is involved in the maintenance of centrosome integrity and the regulation of the microtubule cytoskeleton. Its protein structure bears similarities to the structural myosin proteins, which are microtubule-associated proteins involved in axon guidance, synaptogenesis, functioning of the synapse, and intracellular transport along axons and dendrites[331]		SZ: 1 CCS[332] SZ: 1 FBS[332]		SZ: variations on *PCM1* gene are associated with orbitofrontal gray matter volumetric deficits (SMRI)[332]	Cancer: Alterations in *PCM1* structure are associated with diverse myeloid malignancies[334]	
PLAT 8p11.23	The plasmin genes are involved in the degradation of Aβ peptides, the accumulation of which in brain is a hallmark of AD[334]		AD: 1 CCS[334]	AD: 2 CCS[334,335] AD: 1 FBS[334]		Cancer: PLAT is associated with oligodendrogliomas[336]	[b]Meta-analysis of all published AD-association studies (3 CCS) for rs4646972 (Alu ins/del) pm (OR (95% CI) = 1.34 (0.78, 2.31))

Table 2 Continued

Gene symbol position	*Neurodevelopmental (or biological) process*	*Expression in the CNS and in peripheral sources of patients*	*Positive studies*	*Negative studies*	*Other studies (endophenotype investigations, disease models, case reports)*	*Cancer*	*Commentaries*
SFRP1 8p11.23	Secreted frizzled related protein 1 (SFRP1) and Wnt signaling in innervated and denervated skeletal muscle[337]		SZ: 1 FBS[186]	SZ: 1 CCS[186]		Cancer: The frequent methylation and silencing of Wnt antagonist genes (i.e., SFRP family genes) in HCC, and suggest that their loss of function contributes to activation of Wnt signaling during hepatocarcinogenesis[338] SFRP1 was shown to be hypermethylated in renal cell carcinoma and other cancer types[339]	
FGF17[a] 8p21.3	See *FGF20* annotation FGF-signaling, through *FGF8*, *FGF15*, *FGF17*, has a fundamental role in controlling the size of the frontal cortex[340–342]				DM: Fgf17-null mice showed specific social behavior deficits[52]	Cancer: see *FGF20* and *FGFR1* annotations and Discussion section	
NEF3[a] 8p21.2	*NEF3* belongs to the dopamine receptor interacting protein (DRIP) gene family. DRIP family affects many aspects of dopamine receptor activity[343,344]			SZ: 1 FBS[143] BD: 1 FBS[143]	Association of *NEF3* with early response to antipsychotic medication[344]	Cancer: *NEF3* has been suggested to be potentially involved in pancreatic cancer development and progression[345]	
mir-124-1 8p23.1	*hsa-mir-124-1* are most likely to be critical in the CNS development[55]					Cancer: see Discussion section	
mir-320 8p21.3	*hsa-mir-320* are most likely to be critical in the CNS development[55]					Cancer: see Discussion section	

Abbreviations: ACC, anterior cingulate cortex; AD, Alzheimer's disease; ADP, Alzheimer's disease families with psychoses; AUT, autism; AX, anxiety-related personality traits; BD, bipolar disorders; BPRS, the Brief Psychotic Rating Scale; CR, case reports; DLPFC, dorsolateral prefrontal cortex; DM, disease model; DS, down syndrome; DTI, diffusion tensor imaging; CCS, case–control Studies; COS, childhood-onset schizophrenia subjects; CPT, continuous performance test; CNS, central nervous system; FBS, family-based studies; FC, frontal cortex; *GABRA4*, GABA(A) receptor, α4 subunit gene; MD, major depression; METH, Methamphetamine-induced psychosis; OR, odds ratio; PBL, peripheral blood leucocytes; PD, Parkinson's disease; pm, polymorphism; SMDF, sensory and motor neuron derived factor NRG1 isoform; SMRI, structural magnetic resonance imaging; SZ, schizophrenia; SZ-Rel, relatives of subjects with schizophrenia; WCST, Wisconsin Card Sorting Test.
Official gene symbols are reported, according to the Entrez gene database (http://www.ncbi.nlm.nih.gov/sites/entrez (last accessed 29 June 2008)).
[a]Indicates genes that are expressed in the CNS (see Supplementary Table S5 for more information).
[b]Indicates odds ratio estimates by SZGene, AlzGene and PDGene databases.[43,53,54] (last accessed 26 July 2008)].

major depressed subjects compared with control and bipolar subjects[357] and, on the other, of *FGFR2* in the temporal cortex of major depressed subjects compared with control,[358] although this finding has been challenged by the findings of a separate study using prefrontal postmortem cortices.[328] In this last study, however, *FGFR1* was upregulated in subjects with major depression or suicide. *FGFR1* was also observed to be upregulated in hippocampus of subjects with major depression when compared with controls.[329] The FGF system is also modulated by psychotropic drugs, including fluoxetine, diazepam and the atypical antipsychotic clozapine.[359]

FGF-signaling, through FGF8, FGF15, FGF17, has a fundamental role in controlling the size of the frontal cortex.[340,341] Recently, we described a Fgf17$^{-/-}$ mutant mice that showed a reduction in the size of dorsomedial prefrontal areas and a circumscribed set of higher order social deficits, without affecting olfaction, pheromone responses, aggression or an array of nonsocial behaviors.[50–52,360]

In the analysis of the *Fgf17*$^{/}$ mice, the authors used a panel of gene expression markers to examine the role of *Fgf17* in the regionalization of the rodent FC. They reported that the dorsal FC of *Fgf17*$^{/}$ mice was reduced in size, whereas ventral and orbital FC regions appeared normal. Thus, in addition to an overall effect on neocortical patterning, *Fgf17* has an unexpectedly selective role in regulating dorsal FC development.[50,51,360] The reduction in the dorsal FC area was complemented by a rostromedial shift of caudal cortical areas. These changes in regionalization persisted into adulthood and were accompanied by a reduction in FC projections to subcortical targets. This reduction of prefrontal cortex output to striatal or midbrain dopaminergic neurons may have important physiologic ramifications for the regulation of neural pathways involved in reward, cognition and social behavior.[361]

It has long been known that dorsal and ventral FC subdivisions have distinct roles in regulating cognition and behavior in rodents and primates, including humans.[361,362] For example, subdivisions of the dorsal prefrontal cortex are implicated in working memory, attention, response selection, temporal processing of information, effort-related decision making and social valuation, whereas ventromedial and orbital subdivisions are implicated in behavioral flexibility, emotional regulation, delay-related decision making, evaluation of rewards and autonomic control.[363] Therefore, the *Fgf17*$^{/}$ mutant mice provide an opportunity to examine the behavioral and neurophysiologic consequences of an early developmental genetic lesion that selectively affects the dorsal FC. We propose that elucidating the signaling pathways downstream of *Fgf17* will provide important insights into the genetic pathways that regulate FC development and that may be disrupted in disorders that affect cognition, emotion and social interactions, such as autism and schizophrenia.

In addition, members of the fibroblast growth factor family are significantly associated with a variety of human cancers.[169–171] For example, *FGF17*and *FGFR1* are commonly overexpressed in advanced human prostate cancer.[364,365] It is noted that there is evidence of a selective overexpression of *FGFR1* and *FGFR4* in clinical prostate cancer, which specifically supports the notion of targeted inhibition of these receptors to disrupt FGF signaling.[366] Moreover, fusions between *FGFR1* and several genes have been identified in the hematologic malignancy 8p11 myeloproliferative syndrome.[367] Consequently, the above mentioned relationship between certain types of cancer involving 8p and schizophrenia could be in part explained, thanks to the potential function of FGF17/FGFR1 in tumorigenesis and in cerebral development.

Discussion

Chromosome 8p is rich in genes that are implicated in neuropsychiatric disorders. *VMAT1/SLC18A1, NRG1, PPP3CC* and *DPYSL2* are clearly associated with schizophrenia and probably with bipolar disorder. In addition, findings reveal that *EGR3* (schizophrenia or SZ), *FGF20* (Parkinson's Disease or PD), *FGFR1* (SZ), *LPL* (Alzheimer's Disease or AZ), *NAT2* (PD) and *PCM1* (SZ) seem to be promising candidate genes as well, while *FZD3* (SZ, bipolar disorder or BD and major depression or MD) and *NAT1* (SZ, BD, PD and AZ) mainly gave negative results (see Ref.[55,65,66] and Table 2). As discussed above, we suggest that alterations in *FGF17, hsa-mir-124-1* and *hsa-mir-320* should be considered to endow susceptibility to mental illness.

It is clearly premature to conclude that many of the 8p genes are connected to mental illness. Associations with mental illness and variants on *ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, LDL, PLAT and SFRP1* are weak (based only in one molecular genetics study) or contradictory (studies with positive and negative results). In addition, meta-analysis has only been performed on polymorphisms of *DPYSL2, FZD3, NRG1, PPP3CC, VMAT1/SLC18A1, FGF20* and *LPL*, and many of these meta-analysis results may represent false-positive findings, in particular those based on small (<10) sample size.[44]

Despite the shortcomings of much of the evidence, it is worth continuing positional and association studies to scrutinize 8p, but using larger samples of different ethnic populations and more stringent criteria for replication or low *P*-values, focusing on those findings that have been previously replicated.[131,368] Toward this goal, various genome-wide association studies are being applied to identify and characterize single-nucleotide polymorphisms in the DNA of hundreds or thousands of people worldwide with and without a particular disease or families with schizophrenia[279] or bipolar disorder.[369] Likewise, several genome-wide association studies have found that other forms of genetic variation on 8p, beyond the single-nucleotide scale, such as structural variations

are associated with autism[29] and schizophrenia[10] among other disorders.[370] Surely, these technologies are revolutionizing the genetics of behavioral traits, complex disorders or our individuality.[368]

Cancer and Schizophrenia: tumor-suppressor genes, oncogenes and microRNAs

Tumor-suppressor genes and oncogenes on 8p. There is considerable evidence that suggests mechanistic connections of genes on 8p among certain types of cancer and schizophrenia. It is biologically plausible that specific tumor-suppressor genes on 8p, that are downregulated in lung and prostate cancer, could be upregulated in schizophrenia. This phenomenon has been considered for various tumor-suppressor genes, such as *TP53* on 17p13,[371] *APC* or adenomatous polyposis coli on 5q21-22.[372] and *TGFBR2* or transforming growth factor-β receptor on 3p22, however in this last case with negative association for 10 single-nucleotide polymorphisms in the Japanese population.[373]

The tumor-suppressor *TP53* gene has been identified as the most commonly mutated gene in human neoplasms.[374] The p53 tumor-suppressor protein regulates the cell cycle, checkpoint control, repair of DNA damage and apoptosis,[375,376] and several developmental processes, including cerebral vascularization,[377] neurogenesis and neural crest migration.[378] Independent genetic evidence for *TP53* as a schizophrenia susceptibility gene is strong, with five of six studies reporting significant association.[379–383] Genotype and allele frequencies at *Msp*I polymorphisms of *TP53* are likewise significantly different between Korean schizophrenia and lung cancer subjects.[371]

TP53 activates the transcription of PTEN (tumor-suppressor phosphatase with tensin homology), and therefore functions as a negative regulator of the entire phosphatidylinositol-3-kinase (PI3K)-AKT signaling pathway that drives tumorigenesis[384] and many critical signaling systems involved in neural development, survival and plasticity.[385] The inappropriate inhibition of PI3K-AKT pathway has been associated with diseases as diverse as diabetes and schizophrenia.[386,387] Deregulation of PTEN function is also implicated in autism and brain tumors.[388,389] It is noted that the NQO1 enzyme protects against oxidative stress and carcinogenesis, including stabilization of TP53.[390] *NQO1*2* is a missense variant (NP_000894:p.187P>S) that predicts poor survival among women with breast cancer mediated, in part, by TP53-linked roles of NQO1.[391] Even more interestingly, one study suggests an increased risk for tardive dyskinesia in schizophrenic *NQO1*2* carriers.[392] Nevertheless, other studies failed in finding this association.[393,394]

Defects in tumor-suppressor *APC* gene, which is associated with colon and other cancers,[395,396] are also associated with susceptibility to schizophrenia; furthermore, *APC* is upregulated in patients with schizophrenia.[372] *APC* is a key component of the Wnt/Winless signaling transduction pathway, which plays important roles in a number of developmental processes and in tumorigenesis.[171,397] Thus, there may be a relationship between the functions of these tumor suppressors and the molecular mechanisms and cellular biology underlying schizophrenia.

Unfortunately, almost nothing is known about the role of 8p tumor suppressors in schizophrenia or other neuropsychiatric disorders. On the other hand, there are many putative mental illness susceptibility genes on 8p (*ADRA1A, ARHGEF10, CHRNA2, CHRNA6, CHRNB3, DKK4, DPYSL2, EGR3, FGF17, FGF20*, *FGFR1, FZD3, LDL mir-124-1*, *mir-320, NAT2, NEF3, NRG1, PCM1, PLAT, PPP3CC, SFRP1* and *VMAT1/SLC18A1*) involved in both cancer and neuropsychiatric disorders' biology (see Table 1 and TS1 at Supplementary Information). *NRG1*, without a doubt, is one of the most frequently studied genes in schizophrenia (see Table 2).[237,398] Over the course of last two decades, numerous investigators have tried to unravel the biological function of the *NRG1* and of other related molecules (that is, of its receptors, the Epidermal Growth Factor Receptor/ErbB family of proto-oncogenes which signal in part through PI3K-AKT-PTEN) in the human brain and cancer.[399] These genes have critical functions in many aspects of neural development and function.[247] Furthermore, overexpression of NRG1 is found in many different cancer types and correlates with cancer progression and an aggressive phenotype,[260] where it may regulate tumor-suppressor genes and/or genes that control cell differentiation or apoptosis.[261] Another attractive hypothesis is that the *NRG1* locus is broken in several types of epithelial cancers, such as breast, pancreatic or colon cancer.[400] It is possible that most of these breaks represent chromosome translocations, but accompanied by variable amplifications, deletions and inversions proximal to these breakpoints.[401]

The breakage of *NRG1* might have many complex effects, because there are multiple splice forms of NRG1 with different activities. In this regard, Tan *et al.*[402] suggest that genetic regulation of NRG1 type IV isoform may have the dual effect of both protecting against cancer while increasing the risk for schizophrenia. Therefore, the schizophrenia risk-associated single-nucleotide polymorphism, rs6994992, which is a functional promoter variant associated with schizophrenia genetic predisposition and NRG1 type IV expression,[403] might be as a negative regulator of tumorigenesis. Subsequently, Kanakry *et al.*[404] using a B lymphoblast cell model, showed that NRG1 regulates cell adhesion by ErbB2/PI3K-AKT pathways. The cell lines derived from patients with schizophrenia showed a deficiency in NR1α-induced adhesion, suggesting a cellular phenotype that could contribute to disease risk. Nevertheless, evidence for a cosegregation of cancer with susceptibility or protective *NRG1* variants for specific neuropsychiatric disorders has not been reported; this would be more persuasive evidence for the link between these disorders.

miRNAs on 8p. miRNAs play critical roles in the regulation of gene expression by translational or post translational mechanisms, and influence human genetic variation and normal development.[55] miRNA expression can be dysregulated in tumor cells.[171,405,406] Lujambio *et al.*[407] have observed that DNA hypomethylation induces a loss of miRNA expression in cancer cells, such as the 8p brain-specific miRNA miR-124a. The authors functionally linked the epigenetic loss of miRNA-124a expression with the activation of oncogenes (*CDK6* (cyclin D kinase 6)) and tumor-suppressor genes (*Rb* (retinoblastoma)). Moreover, miRNA-124a may be also deregulated in subjects with acute myeloid leukemia.[408] Most recently, Silber *et al.*[409] have shown that miRNA-124 and miRNA-137 can induce neuronal differentiation of oligodendroglioma tumor stem cells and glioblastoma multiforme (GBM) stem cells, and inhibit proliferation of GBM cell lines suggesting an anticancer effect of these miRNAs. miR-320 is also located at 8p; its altered expression in human cholangiocarcinoma cell lines may contribute to cholangiocyte-specific responses to chemotherapy.[410] In patients with cytogenetically normal acute myeloid leukemia, Marcucci *et al.*[411] found an altered expression of 12 miRNAs (including miR-124a and miR-320) that was associated with clinical outcome in a subgroup of patients with high-risk acute myeloid leukemia. Interestingly, the methyl-CpG-binding domain (MBD) proteins (MBD1, MBD2, MBD3, MBD4 and MeCP2) are critical mediators of DNA methylation-regulated epigenetic processes. The MBD family proteins are associated with tumorigenesis and drug resistance. Mutations in *MBD2* and *MeCP2* genes are likewise implicated in a number of related but distinct postnatal neurodevelopmental disorders, including X-linked mental retardation disorders, autism and Rett syndrome,[412–415] and are putative targets for miR-124a and miR-320 predicted by computational analysis.[416] Thus, miRNAs may provide a homeostatic mechanism for maintaining MBD2 and MeCP2 levels. It is noted that using this database of predicted miRNA target genes, we have identified new putative targets for miR-124a (*FMR1* or fragile X-linked mental retardation) and miR-320 (*NLGN3* or neuroligin3; *AUTS2* or autism susceptibility candidate 2; *A2BP1* or ataxin 2-binding protein 1, also called FOX1), which are associated with autism, schizophrenia and related syndromes.[417] The function of some of these genes is presently unknown (*AUTS2).* Others are important in glutamatergic synapse function and/or in neuronal cell adhesion (*FMR1* and *NLGN3*), neuronal activity regulation (*FMR1* and *A2BP1*) and in endosomal trafficking (*A2BP1*).

miRNAs expression is the subject of considerable interest in schizophrenia.[418–423] Very little is known about the role of miRNAs in autism; however, current findings suggest that alterations in the interactions between miRNAs and their mRNA targets may contribute to autism phenotypic variation.[424–426] For instance, Abu-Elneel *et al.*[426] found that miRNA-320 (at 8p21.3) and miRNA-598 (at 8p23.1) are dysregulated in postmortem cerebellar cortex from 13 individuals with autism spectrum disorders compared with nonautism controls.

Conclusions and future directions

Although many questions remain unanswered,[427] the research should focus on common or related pathways, or processes that potentially represent a point of convergence for molecular signaling not only among schizophrenia, autism or other neuropsychiatric disorders, but also with cancer. Compared with classical approaches, focusing on a group of genes belonging to the same functional pathway or that operates together as a network could yield the best results. The cross-sectional dimension raises the possibility that shared components of the schizophrenia/cancer phenotype, or other common human diseases, might be used to distinguish genetic and molecular pathways in these severe disorders. Consistent with this idea, analysis of the genes within chromosome 8p represents a rich resource to understand the biological connections among disorders that are considered to be distinct.

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