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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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ARTICLE INFO

Article history:
Received 26 March 2014
Received in revised form
20 August 2014
Accepted 18 November 2014
Available online 9 January 2015

Keywords:
Schizophrenia
SNP
Risk genes
Brain volume
Morphometry
In silico analysis
GWAS

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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http://dx.doi.org/10.1016/j.npbr.2014.11.003

Neurotransmission
Neurodevelopment
Gene interactions

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