Update

Research Focus

Contact in the genetics of autism and schizophrenia

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Although autism and schizophrenia are considered to be distinct neuropsychiatric developmental disorders, recent studies indicate that they share genetic factors. The same chromosomal rearrangements and several single genes have emerged as genetic risks in both disorders. One such gene is contactin-associated protein-2 (*CNTNAP2*). These findings raise the possibility that these neuropsychiatric disorders share pathogenic mechanisms and that similar defects in biological pathways of brain development might underlie the phenotypic spectrum of these disorders.

Introduction

Developmental and congenital disorders of the brain can be caused by environmental or genetic interference with normal brain development and result in neuropsychiatric disease. Autism and schizophrenia are estimated to have the highest genetic load and penetrance among the neuropsychiatric disorders. Identification of disease genes in these and other disorders is realized through recent genetic technology. Whereas cytogenetic, linkage and association studies have indicated loci of interest [1], assessment of submicroscopic copy number variations (CNVs) has revealed a treasure trove of potential disease genes. CNVs are deletions or duplications in the genome and can result in dosage-dependent gain or loss of expression of the genes that they contain. Recently, several large CNV studies in autism have identified a staggering number (hundreds) of important candidate loci [2–5]. Many of these CNVs affect a single gene. For schizophrenia, four large CNV studies are now available [6–9], and more about both disorders is to be expected soon. The data challenge current concepts in this area of psychiatry.

Genetics of autism and schizophrenia

The spurt of genetic studies on autism has markedly revised the view on the genetics of this disorder. Although the involvement of common gene variants with small effects in manifold has been the conceptual trend for a decade, the current view acknowledges the involvement of single or few rare variants with a relatively high effect size and a considerable heterogeneity among these [10]. Several hundreds of different autism-specific CNVs have been encountered in patient cohorts; the recurrence of the most frequent CNVs is ~1% or less. There is a high proportion of *de novo* CNVs [2], but inherited CNVs roam in families affecting males more than females. The seeming heterogeneity of autism genes, however, converges onto limited biological processes; many of the candidate genes code for potential players in pathways of neurodevelopment and synapse functions.

A similar situation is emerging from CNV studies of schizophrenia. There is a high frequency of *de novo* CNVs [6], a large heterogeneity in rare variants [7,8] and a low recurrence and many 'private' mutations. The 22q11.2 region is probably the best-known region of which CNVs predispose for autism and schizophrenia. Patients with deletions in this region have variable clinical phenotypes, including velocardiofacial syndrome and DiGeorge syndrome. A substantial proportion of patients is diagnosed with autism spectrum disorder during childhood and up to 30% develops schizophrenia during adulthood. Statistical evidence in a very large sample of schizophrenic patients has been obtained for three recurrent deletions: 1q21.1 (occurrence 0.02% in patients versus 0.00% in controls; odds ratio = 14.8), 15q11.2 (0.55% versus 0.19%; odds ratio = 2.7) and 15q13.3 (0.17% versus 0.02%; odds ratio = 11.5) [8], and for 1q21.1 and 15q13.3 in an independent study [9]. Surprisingly, these three loci are each familiar to the genetics of autism (Figure 1). Duplications of 1q21.1 have recently been found in patients with autism [11,12]. The 15q13.3 region has also been found to harbor a deletion or duplication in patients with autism and a variety of neuropsychiatric traits [13]. Chromosome 15q11.2 is the most proximal region of the well-known Prader-Willi/Angelman loci. Both disorders are 15q11–q13 deletion syndromes. More pronounced autistic features were observed in cases of Angelman syndrome in which the small 15q11.2 region was included at the proximal end of the deletion. The cytoplasmic fragile X mental retardation protein (FMRP)-interacting protein 1 gene (*CYFIP1*), one of the four annotated genes in this region, might be the responsible disease gene because it serves functions important for neurodevelopment. CYFIP1 (also known as Sra1) is a protein that mediates the repressive action of the fragile X mental retardation protein (FMRP) on dendritic protein synthesis in response to glutamatergic synaptic activity [14].

A single gene directly implicated in autism and schizophrenia is contactin (CNTN)-associated protein-2 (*CNTNAP2*). Five recent studies report the identification of *CNTNAP2* as a genetic susceptibility factor in autistic patients by linkage, association, resequencing and CNV analysis [10,15–18]. The *CNTNAP2* gene is not new in the arena of neuropsychiatry. It was identified as the gene interrupted by a translocation in a family with the Gilles de la Tourette syndrome and obsessive compulsive disorder [19] although it was recently refuted as the disease gene [20]. However, homozygous mutation of *CNTNAP2* causes

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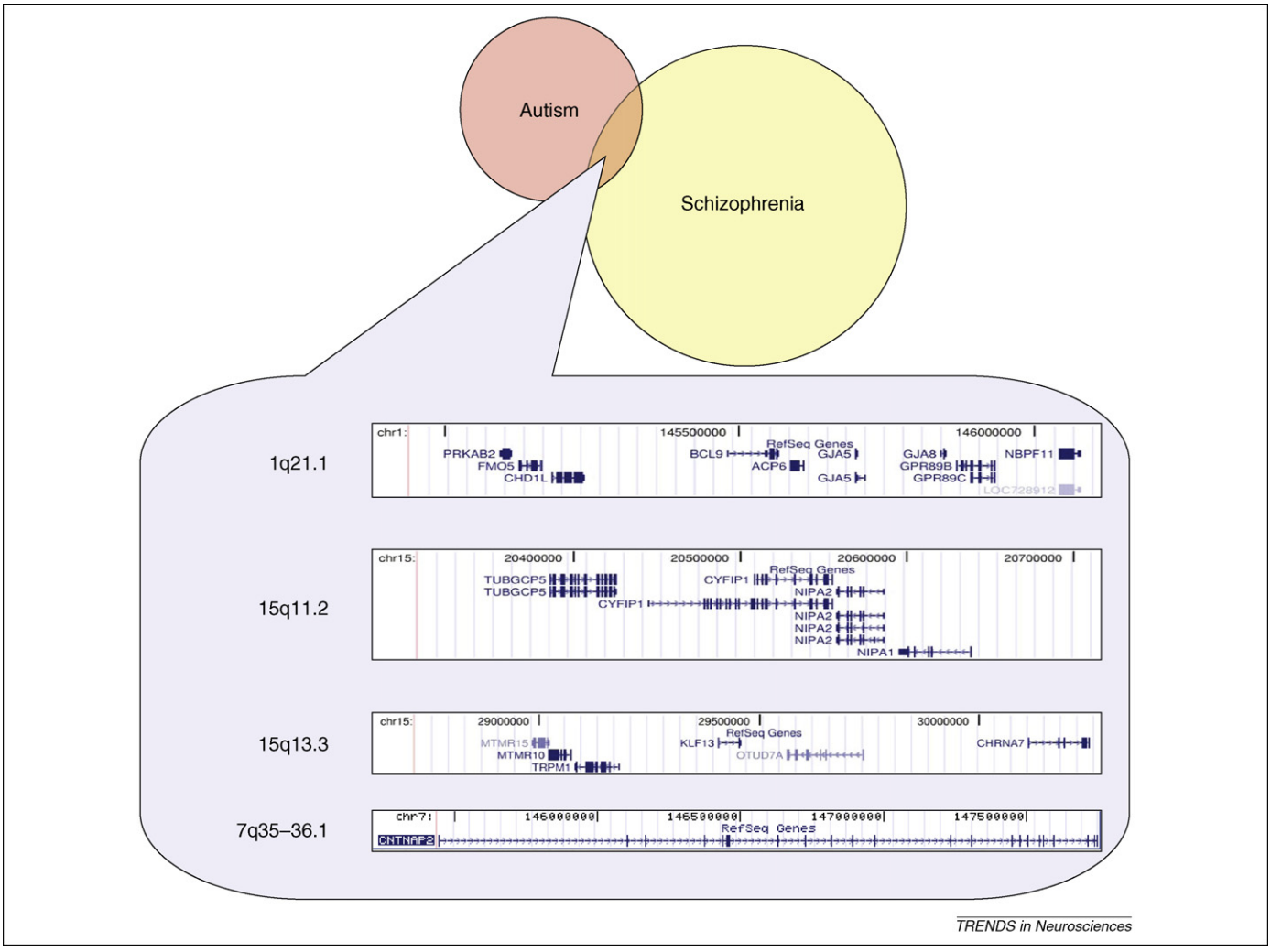

Figure 1. Genotypic overlap of autism and schizophrenia. Both autism and schizophrenia are neurodevelopmental disorders with high heritability. They are considered to be separate disorders each with a broad spectrum and differentiated phenotypically by clinical criteria. Recently, recurrent copy number variations (CNVs) in chromosomal regions and in single genes have been found in cases with autism and with schizophrenia that are the same. Three microdeletions at 1q21.1, 15q11.2 and 15q13.3 have been associated with schizophrenia [8,9] and encountered as CNVs in autistic patients. These CNVs are rare but recurrent (<0.3%). *CNTNAP2* is a gene interrupted by deletions in autism and schizophrenia. These findings indicate that the domains of autism and schizophrenia might have a genetic overlap in which these genetic factors reside and that a shared aetiology between autism and schizophrenia might exist. The microdeletions and the *CNTNAP2* gene are depicted by genomic organization and RefSeq gene content as provided by the UCSC human genome browser (http://genome.ucsc.edu).

cortical dysplasia-focal epilepsy, a syndrome of congenital epilepsy with neuropsychiatric co-morbidities [21]. Recently, *CNTNAP2* has also appeared as a haploinsufficiency in schizophrenia. Two studies reported internal and overlapping deletions in the *CNTNAP2* gene [9,22]. Polymorphisms in *CNTNAP2* in children associated with typical specific language impairment [23]. These novel findings put the gene product CNTNAP2 (also known as Caspr2), and the contactin system of which it is part of, in the limelight of the genetics of neuropsychiatric disorders.

The contactin system

CNTNAP2, a member of the neurexin family, is encoded by an extraordinarily large gene on chromosome 7q35–36.1. CNTNAP2 is a single-pass transmembrane protein with multiple protein-interaction motifs typical of the neurexins: epidermal growth factor repeats, laminin globular domains, an F5/8-type C domain and a putative PDZ-binding site. There are five *CNTNAP* genes in the human genome. CNTNAPs complex with CNTNs, which are neural recognition proteins of the immunoglobulin cell adhesion molecule (IgCAM) superfamily that link to the extracellular neuronal membrane through a glycosylphosphatidylinositol anchor. There are six CNTNs in human and mouse. CNTNAP2 complexes with CNTN2 (also known as TAG-1). Complexes of CNTNs and CNTNAPs function as receptor-signaling units and are thought to mediate neuron–glial cell interactions, neuronal migration and dendritic orientation [24]. It is likely that these cellular functions are the actors causing anomalies in neurodevelopment if molecular functions are subject to loss or gain.

Moreover, other members of the CNTN family have also been identified in autism: *CNTN3* (also known as *BIG-1*), *CNTN4* (*BIG-2*), *CNTN5 (NB-3)* and *CNTN6 (NB-2)* [10,25]. Notably, the *CNTN4* gene was disrupted in multiple pedigrees with autism and has also been implicated in the 3p deletion syndrome characterized by developmental delay [25,26]. *CNTN3* was also found to be associated with autism [5], and CNVs in *CNTN5* and