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Distinct disorders affecting the brain share common genetic origins

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Abstract

Over the last few years, large cohorts of patients with distinct brain disorders of neuropsychiatric and neurological origin have been analyzed for copy number variation. Surprisingly, the same genetic abnormalities were found in cohorts of patients affected with mental retardation, autism, or schizophrenia.

Introduction and context

Copy number variation in brain disease

According to recent estimates, 5-12% of our genome is in a non-diploid state [1-3]. Copy number variation (CNV) discovery was enabled by the development of array-based techniques that detect chromosomal abnormalities at a resolution that may exceed that of traditional karyotyping under a light microscope by orders of magnitude. Initially, bacterial artificial chromosome arrays were used with a resolution in the megabase range but these were gradually replaced by oligonucleotide arrays with a resolution in the 10- to 100-kilobase range, thus enabling the detection of detailed CNV maps of the human genome. Broadly speaking, CNVs fall into two categories: the common ones that occur in a significant proportion of the general population and the rare ones that have been detected at a much lower frequency. The common CNVs are generally assumed to play an important role in the natural variation between individuals, including disease susceptibility, whereas the rare ones may cause disease.

It is well established that CNVs are responsible for at least 10% of all cases of mental retardation [4], predominantly defined by an intelligence quotient of two standard deviations below the mean. Many of the rare CNVs identified are unique and have been reported only once. Whether these are pathogenic depends on a number of factors, including *de novo* occurrence, size of the deletion, and gene content. In contrast, recurrent CNVs are found in multiple unrelated patients, usually with common clinical manifestations [5]. Recurrent CNVs are mostly flanked by low copy repeats (LCRs), referred to as segmental duplications (Figure 1).

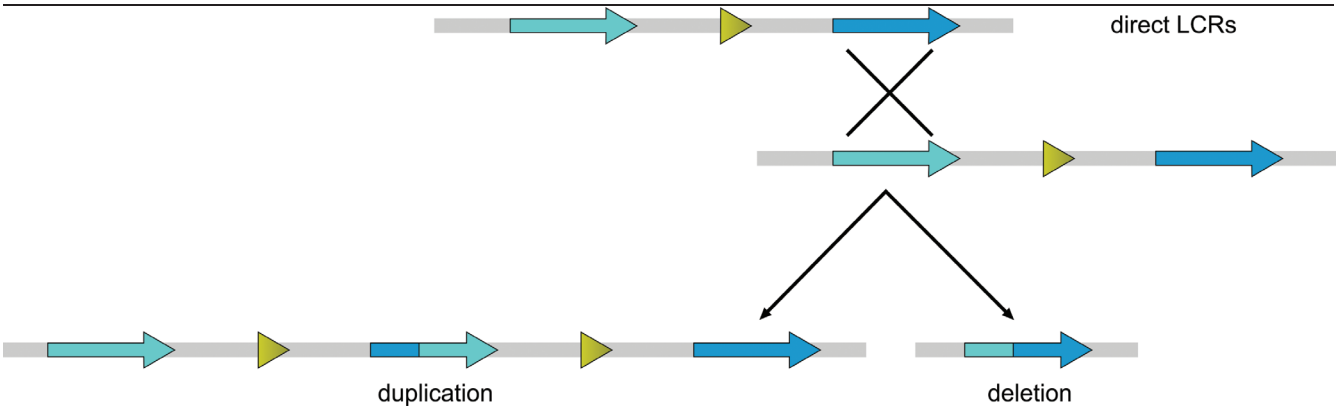
Over the past two years, cohorts of patients with disorders distinct from mental retardation were analyzed for CNV. Surprisingly, CNVs at specific chromosomal regions that are involved in mental retardation, including 1q21.1, 15q11-13, 16p11.2, 17p12, and 22q11.2, also appeared to be associated with autism (qualitative impairments in social interaction and communication) and schizophrenia (a psychotic disorder involving impairments in the perception of reality) (Figure 2). Moreover, the chromosomal regions encompassing the neurexin 1 (*NRXN1*) and the contactin-associated protein-like 2 (*CNTNAP2*) genes are also implicated in the three named disorders.

Major recent advances

Copy number variation discovery in autism and schizophrenia

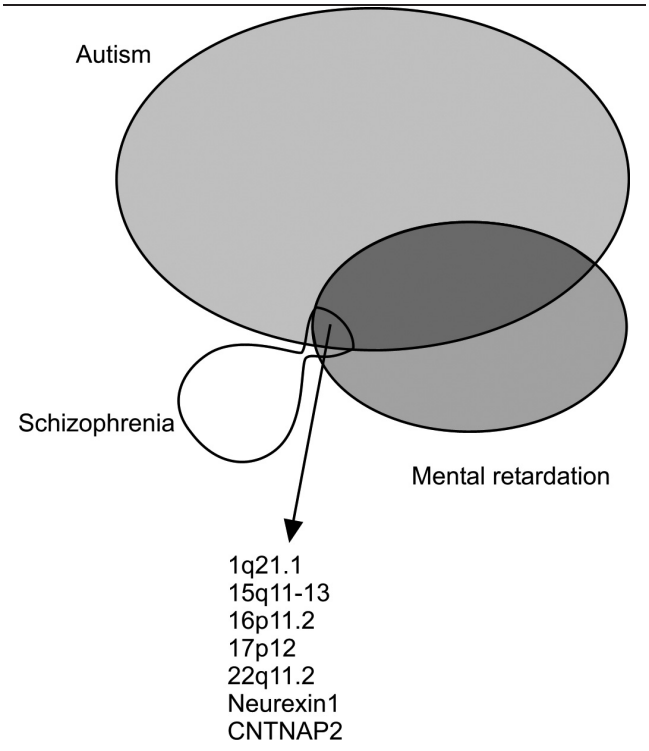
Deletions of the chromosomal region 1q21.1, between two breakpoints (bps) defined as 3 and 4, were initially described with a wide range of pediatric phenotypes, including mild to moderate mental delay and dysmorphic

Figure 1. Non-allelic homologous recombination



Schematic representation of the non-allelic homologous recombination process, generating deletions as well as their reciprocal duplications by unequal alignment of homologous chromosomes. LCR, low copy repeat.

Figure 2. Schematic overview of genetic overlaps between mental retardation, autism spectrum disorders, and schizophrenia



Copy number variations that cause mental retardation disorders overlap, to some extent, with those that cause autistic spectrum disorders and even with a few that cause schizophrenia. CNTNAP2, contactin-associated protein-like 2.

features, microcephaly, cardiac abnormalities, and cataract [6]. The reciprocal microduplication was found predominantly in patients who presented with autism or autistic features [6,7]. At the same time, 1q21.1 bp3-bp4 microdeletions were identified in 0.25% of patients with schizophrenia but in only 0.02% of controls [8-11].

The chromosomal 15q11-13 region has a complex molecular architecture containing five LCR sequences or breakpoints, and in addition this chromosomal region is subject to genomic imprinting. Paternal deletions of the region between bp2 and bp3 result in Prader-Willi syndrome whereas maternal deletions of the same region result in Angelman syndrome [12]. Patients with an extended bp1-bp3 deletion present with a more severe form of the disorder and more commonly display autistic features. Maternal duplications of the bp2-bp3 region cause a clinically variable neurodevelopmental disorder frequently associated with autism [13]. In fact, this duplication, found in 1-3% of patients, is the leading known cause of this disorder. Deletions and occasionally duplications of the 15q13.3 bp4-bp5 region were found in patients with a highly variable degree of mental handicap, frequently including autistic features [14-16]. The same bp4-bp5 deletion was also one of the more frequently observed CNVs associated with schizophrenia [9]. The intermediate bp3-bp4 region seems of little clinical significance.

A 16p11.2 deletion was found initially in monozygotic twins with mild mental retardation and multiple congenital anomalies [17]. Subsequently, a strong association between the same microdeletion as well as the reciprocal microduplication and autism was reported [18-21]. The microdeletion is also found occasionally in controls, but with a 100-fold lower frequency. In addition, the microdeletion/duplication is a risk factor for schizophrenia [8,10].

But the abovementioned CNVs are not the only abnormalities associated with mental retardation, autism, and schizophrenia. A duplication of chromosome 17p12 is generally associated with Charcot-Marie-Tooth disease type 1A (CMT1A) but is also occasionally found in mentally handicapped or autistic populations [7,22]. A deletion of the same chromosomal region increases the risk for schizophrenia by a factor of 10 [23]. One of the most frequent microdeletion syndromes, the 22q11.2 deletion, is associated with developmental delay in nearly 50% of patients. However, the same deletion is also found in autistic patients as well as in schizophrenic patients [8,11,24]. The phenotype of the reciprocal duplication is highly variable [25]. In addition, rearrangements involving the *NRXN1* gene on chromosome 2p16 and the *CNTNAP2* gene on chromosome 7q35 have been found in patients with mental retardation, autism, or schizophrenia [7,8,10,26-31]. Both genes are members of the larger neurexin superfamily involved in cell-cell interactions in the nervous system [32]. In contrast to the CNVs mentioned above, the deletions in these cases were highly variable in size.

Future directions

Unexplained clinical heterogeneity

Thus, several CNVs appear to cause a series of clinically heterogeneous brain disorders, including mental retardation, autism, and schizophrenia. Penetrance of these CNVs may vary and in some cases the abnormalities are inherited from seemingly unaffected carriers. Such inherited CNVs are better seen as risk factors than as a causative factor *per se*. For instance, penetrance of the 16p11.2 duplication in schizophrenia is estimated to be 30-50%. In other words, carriers of this microduplication have an 8- to 24-fold increased risk of becoming affected [33], in range with that of other genomic aberrations taking away one copy of 1q21.1, 15q13 bp4-bp5, or *NRXN1* [8,9,34]. While this overview focuses on mental retardation, autism, and schizophrenia, it has to be mentioned that many of the CNVs discussed above have also been associated with a broad range of additional phenotypes, most notably attention deficit hyperactivity disorder, epilepsy, and different psychiatric disorders, including bipolar and major depressive disorder. Interestingly, both the 16p11.2 microdeletion and the 1q21.1 microduplication are associated with a combination of autism and relative macrocephaly. An increased head circumference in infancy has been reported in patients with autism [35], suggesting a possible relationship between neurodevelopmental disorders and brain volume.

Interpretation of the clinical heterogeneity requires a greater understanding of how the CNVs lead to disease. For the most part, the disease resulting from a CNV is presumably due to an underexpression or overexpression of the genes in the deleted or duplicated region, respectively. In addition, it is possible that the deletion unmasks a recessive mutation on the other allele. However, imprinting, gene interruption, gene fusion, position, and transvection effects may also play a role in determining clinical heterogeneity and disease penetrance. In addition, it is possible that environmental variation of any kind influences the phenotype, but additional genetic factors could also play a role. The human genome is highly variant in both CNV content and single-nucleotide polymorphisms. Otherwise neutral genetic differences between individuals, in combination with the abovementioned CNVs, might determine whether the patient presents with mental retardation, autism, or schizophrenia. The only known example of such modifying genetic alterations at present is a recurrent 16p12.1 microdeletion that modifies neurobehavioral phenotypes [36]. The presence of this microdeletion in addition to a second pathogenic CNV manifests clinically as mental retardation. Perhaps the analysis of new cohorts with an even larger number of samples might help us to identify additional modifiers unknown as of yet. Alternatively, studying the CNV in animal models with a much more controllable genetic background seems attractive [37]. Thus, although some of the genetic origins of neurodevelopmental disorders are now beginning to be understood, many discoveries need to be made before we will begin to understand the common pathways leading to each of these disorders.

Abbreviations

bp, breakpoint; CNTNAP2, contactin-associated protein-like 2; CNV, copy number variation; LCR, low copy repeat; NRXN1, neurexin 1.

Competing interests

The author declares that he has no competing interests.

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