Late Breaking Chromosomes

Copy Number Variations, Like Accidents, Often Come in Pairs

A proverb says: ‘accidents, like..., often come in pairs’. In medical genetics ‘accidents’ would be the genetic alterations underlying clinical phenotypes. A decade of genome-wide segmental aneuploidy screening has revealed thousands of loci with copy number variations (CNVs) in patients as well as in healthy individuals [Iafrate et al., 2004; Zhang et al., 2006; Hochstenbach et al., 2011]. CNVs can be subdivided into 2 types. First, CNVs flanked by segmental duplications, which occur frequently in the entire human population and are, therefore, termed recurrent CNVs [Coe et al., 2012]. Second, CNVs, with more or less unique breakpoints, which are scattered throughout the human genome and occur with highly variable frequencies in different populations. Recurrent CNVs are a challenging class of ‘accidents’ in medical genetics because of their relatively high frequency of occurrence in both healthy individuals and in patients selected on the basis of different classes of phenotypes, such as developmental delay, epilepsy, autism, or schizophrenia [Poot et al., 2011]. Therefore, the possible phenotypic contribution of a single recurrent CNV in the genome of a patient seems to be limited [Poot et al., 2010a, 2011].

Recurrent CNVs in region 16p11.2 encompass 24 genes and occur at a frequency of 0.3–0.7% in patients with various developmental disorders, such as autism, developmental delay, epilepsy, schizophrenia as well as in healthy individuals [Weiss et al., 2008; Bijlsma et al., 2009; McCarthy et al., 2009; de Kovel et al., 2010; Rosenfeld et al., 2010; Shinawi et al., 2010; Mefford et al., 2011]. In 18 out of 77 patients with 16p11.2 CNVs, Rosenfeld et al. [2010] found intellectual, speech and language delays as the most consistent clinical phenotypes. In an independent study, Shinawi et al. [2010] found speech and lan-

guage delays and, additionally, cognitive impairments in 27 out of 45 patients with 16p11.2 CNVs. In 2 recent studies, 3 patients with 16p11.2 CNVs and developmental verbal dyspraxia, a.k.a. childhood apraxia of speech, were reported [Newbury et al., 2013; Raca et al., 2013]. While all 16p11.2 CNVs in the 3 patients had occurred de novo, the third patient, who had also received a diagnosis of pervasive developmental disorder not otherwise specified (PDD-NOS) according to DSM IV, inherited an additional duplication in the chromosomal region 6q22.31 [genome coordinates from 123,527,545–124,311,813 (GRCh37/hg19)] from his clinically normal mother. This CNV was novel and did not overlap with any known CNVs in the Database of Genomic Variants [Newbury et al., 2013]. This duplication covers 2 genes: the entire coding region of triadin (*TRDN*; OMIM 603283), a ryanodine-sensitive calcium channel expressed in cardiac and skeletal muscle and the first exon of sodium/potassium-transporting ATPase subunit beta-1-interacting protein 2 isoform 2 (*NKAIN2*; OMIM 609758). Truncation of *NKAIN2*, due to a translocation, has been described in patients with developmental delay and complex neurological impairments [Bocciardi et al., 2005; Yue et al., 2006]. Since both the duplication of *TRDN* and the truncation of *NKAIN2* were inherited from his healthy mother, they can, by themselves, not be a sufficient cause of the childhood apraxia of speech phenotype of the patient.

To explain the highly variable phenotypic outcome of recurrent and unique CNVs and other forms of gene disruptions, several mutational mechanisms can be envisaged. First, a CNV does not occur alone, but may, in concert with other unique or recurrent CNVs, contribute to complex disorders [Girirajan et al., 2010]. Different combinations of recurrent CNVs found among patients with different clinical phenotypes may aid in explaining the clinical variability among some of these developmental

disorders [Girirajan et al., 2012]. The case reported by Newbury et al. [2013] clearly fits into the 2-site CNV model for developmental disorders [Girirajan and Eichler, 2010].

A second mechanism may be the inheritance of 2 different, but overlapping, CNVs from 2 healthy parents [Hochstenbach et al., 2012]. Searching for gene mutations by transmitted deletions in a cohort of 20 cases, a single patient with severe mental retardation, lack of speech, microcephaly, cheilognathopalatoschisis, and bilateral hearing loss was found to have inherited 2 losses overlapping with respect to a single gene. Thus, the patient carried a loss of both alleles of the highly conserved heat shock factor binding protein 1 (*HSBP1*) gene [Hochstenbach et al., 2012].

A third mechanism may be perturbation of networks of epistatic interaction between genes by pairs of CNVs [Leblond et al., 2012; Poot, 2013]. A fourth, related mechanism may be the loss of binding sites for transcription factors, such as *FOXP2* due to a deletion covering intron 1 of *CNTNAP2*, as has been reported in a single patient with delayed development of speech and autism [Poot et al., 2010b]. Whatever the underlying mixed mutational mechanism(s) may be, comprehensive genotyping of patients with developmental phenotypes such as childhood apraxia of speech appears mandatory [Newbury et al., 2013]. At any rate, 'diagnostic fatalism,' i.e. halting all further genotyping after a single CNV or mutations in a single gene have been found, should be avoided [Poot et al., 2011].

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