EDITORIAL

A Hot Spot of Genetic Instability in Autism

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Sixty-five years after Leo Kanner first described autism,[1] we are beginning to move beyond description of this clinically heterogeneous neurobehavioral syndrome toward a deeper understanding of its biologic complexity. In areas such as genetics and neuroscience, researchers have joined the search for objective measures to elucidate autism's pathogenesis.

It has become clear that the solutions to autism will be neither simple nor uniform among patients with various autistic syndromes. At least 60 different genetic, metabolic, and neurologic disorders have been associated with autism and involve approximately 10% of patients, whose clinical presentations frequently vary, even among those with known disorders.[2] For example, some (but not all) children with Rett's syndrome, the fragile X syndrome, Down's syndrome, fetal valproate embryopathy, or congenital rubella may also present with autism.

Each new objective finding expands the number of forms, or "autisms," like layers of an onion. This expansion occurred with the discovery of mutations in *MECP2* that cause Rett's syndrome.[3] After this discovery, the disorder was recognized as a singular entity with varied manifestations, rather than a form of autism. Likewise, boys with autism and the fragile X syndrome have been characterized as a subgroup of the latter disorder. Another promising approach has been to characterize the dysmorphic phenotypes found in 20% of children with autism, which will probably lead to the discovery of other genetic disorders.[4]

In this issue of the *Journal*, Weiss et al.[5] describe deletions and duplications at chromosome 16p11.2 that appear to be associated with approximately 1% of unexplained, idiopathic, and nonsyndromic autism. The phenotypic patterns and severity of autism varied among their 13 case subjects with deletions and 11 subjects with duplications and overlapped with findings of delays in motor and cognitive development and dysmorphic features. In the study subjects, there was a notable absence of developmental regression, which typically affects 40% of children with late-onset autism, usually between 14 and 24 months of age,[6] indicating that the 16p11.2 deletion or duplication events are mostly associated with autism of early onset.

The study by Weiss et al. supports the general notion that large, spontaneous deletions and duplications contribute to the molecular causes of autism.[7,8] That said, the only credible and novel association reported by Weiss et al. was that between autism and the 16p11.2 locus. Indeed, the authors report that they observed no additional de novo events in multiple unrelated cases, other than duplications at 15q13 (the region disrupted in the Prader–Willi and Angelman syndromes), which were described previously.[9,10] Last year, Sebat and colleagues[8] described a similar 16p11.2 deletion, along with many other candidate loci, on the basis of the screening of copy-number variants associated with autism.

What might explain the different results arising from these two screenings? Differences in the genotyping platforms, analytical methods, and study design seem to be likely contenders. However, Weiss et al. had a different burden of proof: they required that their mutation events be observed in multiple unrelated samples and be confirmed in replication studies.

The genomic region identified by Weiss et al. corresponds to 1 of approximately 150 regions of the human genome that are predicted to be

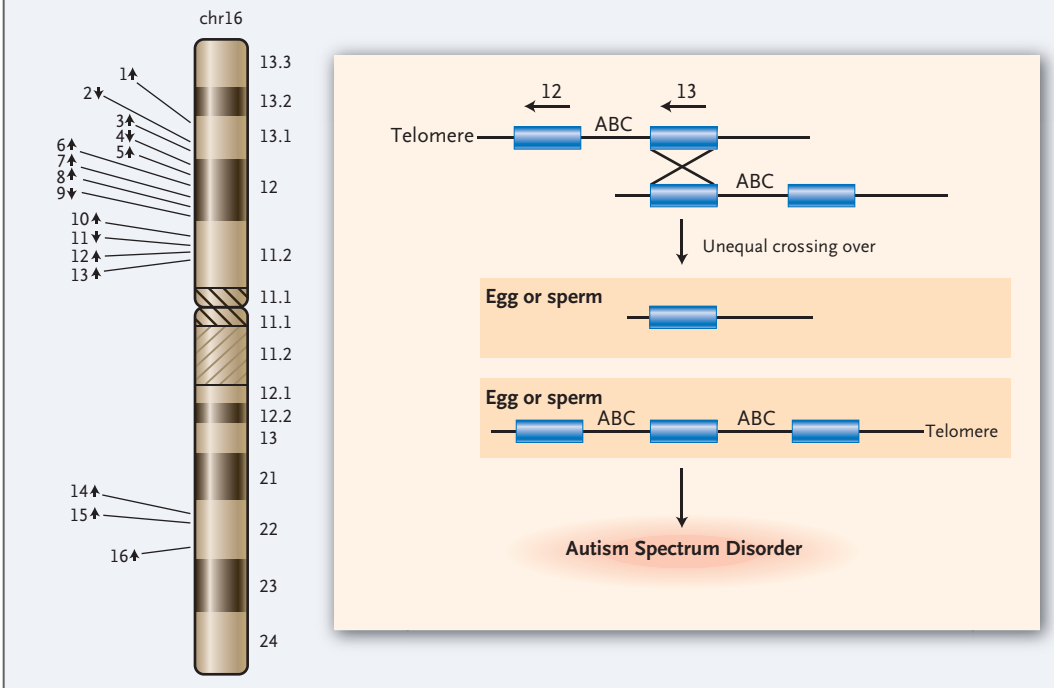

Figure 1. A Hot Spot of Genomic Instability Associated with Autism.

Interspersed duplication blocks (12 and 13) on 16p11.2 promote unequal crossing over during meiosis (two of four chromosomes are shown). Gametes are produced that either lack or carry a double dose of the critical interval. Dosage-sensitive differences of genes in the critical interval (A, B, C) probably increase the susceptibility to disease. There are more than 25 genes or transcripts in the critical interval (e.g., *DOC2A, QPRT,* and *TBX6*), as well as rapidly evolving genes in the flanking duplications.

"hot spots" for recurrent deletion and duplication.[11,12] The presence of large, highly similar duplications flanking the 16p11.2 region predisposes this particular portion of the chromosome to unequal crossing over during meiosis (Fig. 1). Consequently, although the parental DNA is normal, the unique sequence between these duplicated sequences becomes microduplicated or microdeleted in offspring.[13] The critical genomic segment described by Weiss et al. seems to be identical to a previously described de novo microdeletion in male monozygotic twins with mild mental retardation, aortic-valve abnormalities, and seizure disorder; no evidence of autism spectrum disorder was presented.[14] As in other diseases associated with genomic disorders (e.g., the velocardiofacial syndrome and schizophrenia), it is likely that the effect of the 16p11.2 deletion or duplication extends beyond autism and that variability in clinical manifestations depends on differences in genetic background. This theory is consistent with an observation made by Weiss et al. in two families: affected children inherited the 16p11.2 duplication from unaffected parents.

The short arm of chromosome 16 is exceptional from an evolutionary perspective because it is populated by an excess of duplicated segments that emerged relatively recently during evolution (less than 15 million years ago).[15] More than 16 blocks of segmental duplication are interspersed across the chromosome, and rearrangements among these blocks have been associated with various genomic disorders involving mental retardation, multiple congenital abnormalities, and autism. It is interesting that most of the duplicated sequences on chromosome 16 also carry copies of one of the most rapidly evolving gene families in the human species.[16] Both the gene family and the genomic architecture are specific to apes and humans, which is consistent with other reports[17] that from an evolutionary standpoint, autism may be a relatively "young" disease.

Will other hot spots of recurrent deletion and

duplication be identified that are associated with autism? The fact that deletion and duplication at 16p11.2 and duplication at 15q11.2 together account for approximately 2 to 3% of cases of autism warrants further study of spontaneous copy-number variation as a cause of this disease. More important, these examples highlight a different paradigm for the genetic basis of autism. Rather than being an inherited disease, autism may be the result of many independent loci that rarely delete or duplicate during gamete production. Collectively, such de novo events might contribute significantly to the disease and explain why few genetic loci have been confirmed with the use of traditional linkage-based approaches. A key factor in the search for additional large, highly penetrant structural changes will be the frequency of the new mutation event.[13] Regions such as 16p11.2 and 15q11.2 may be the tip of an iceberg, discovered first because the frequency of their de novo mutations is much higher than that of other autism-associated regions of de novo copy-number variation. It is possible that after much larger case–control groups have undergone genotyping, some of the 50 other large de novo events observed by Weiss et al. and other events described in recent studies will turn out to be specifically associated with autism. The discovery of significant associations for the rarer loci may require the screening of tens of thousands of DNA samples from patients rather than a few thousand samples. Deeper sample collection and new cost-effective genomic techniques may be needed to peel away the remaining layers of the onion.

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