Molecular genetic analysis of a cryptic unbalanced translocation in two siblings with autism

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We undertook molecular genetic studies on two siblings diagnosed with autism whose phenotypes vary drastically. The younger female is much more severely affected and has very little speech. The older male has some speech, but shows greater deficits in social behavior. At the time that the family members enrolled in the research study, blood samples were obtained from both the brother and sister for genetic analysis. Based on clinical testing prior to entering the research project in 2000, both siblings' chromosomes were visualized and believed to be normal. Recent microarray analysis using the Affymetrix Genome-Wide Human SNP Array 6.0 revealed abnormal copy number changes, showing that each sibling carries a duplication on chromosome 2 of approximately 5 MB of material derived from 2pter to 2p25.2. They also have a deletion that encompasses approximately 4 megabases and extends from the 12p telomere to the breakpoint 12p13.32. FISH analysis confirmed this to be an unbalanced translocation. The breakpoint on chromosome 2 occurs within 2p25.2. Within this duplicated region, one gene of interest is SNTG2, coding for syntrophin G2, a cytoplasmic peripheral membrane. The breakpoint on chromosome 12 occurs within 12p13.32.

We are conducting investigations into possible genetic causes of their differing phenotype. One hypothesis is that the siblings may have inherited a different haplotype along the non-deleted copy of chromosome 12; genetic variation in genes in this region may impact the phenotype. Analysis of SNP genotype data reveals that the siblings carry different alleles on the non-deleted copy of chromosome 12. Among the genes in this region is CACNA1C, coding for a subunit of a voltage-gated calcium channel. This gene has been implicated in other studies in autism and in bipolar disorder, in addition to heart disease.

Other possible genetic moderators of the phenotype include the presence of additional copy number variants, and differences in the size and location of regions of homozygosity, which may harbor recessive alleles that contribute to the phenotype. Among the most striking differences between the siblings is a region on chromosome 3 where the more severe female has a region of homozygosity stretching approximately 7 Mb. This region includes SMARCC1, coding for a SWI/SNF subunit believed to play a role in chromatin remodeling, as well as DOCK3, coding for a cell-signaling protein indicated in neurological disorders. She also carries a region of homozygosity on 14q23.1, also a region of interest in autism. SNP-based microarray data are powerful in their ability to detect both copy number and genotype variation that may impact the risk for complex genetic disease, and also moderate the severity of the phenotype.