FEATURED ARTICLES

Pair of a kind

Neuroscience Gateway (January 2008) | doi:10.1038/aba1803

Researchers identify two mutations associated with autism spectrum disorders.

What if your hunt through the haystack turned up not one but two needles? Robust autism spectrum disorder (ASD)-associated gene mutations have been difficult to identify. Now researchers report two independent genetic defects associated with ASD in recent articles in *the New England Journal of Medicine* and *the American Journal of Human Genetics*.

ASDs may be distinct diseases with several common features, including stereotyped behaviors and impairments in communication and social interaction. Distinct genes might be involved in different ASDs.

People with ASD show increased gene copy-number variation relative to the general population, and chromosomal abnormalities, like Prader-Willi and Angelman syndromes, account for nearly 10% of ASD. Weiss *et al.* aimed to identify regions of genetic instability associated with ASD. They report 593 kb deletions and duplications on chromosome 16p11.2 in people with ASD. The carrier frequency of 16p11.2 aneuploidy was approximately 1% and 0.01% in people with and without ASD, respectively, suggesting that these mutations increase the risk of autism 100-fold, according to the authors. This chromosomal region contains syntaxin 1B, which is important in neurotransmission, and several integrins, which are important in neural development, suggesting that disruption of these genes may be involved in certain types of ASD.

Are there other genes involved in autism? Previous genome-wide association studies identified ASD-associated mutations in members of neuregulin and neurexin families, which bind to each other and are important in the differentiation of pre- and postsynaptic sites, respectively. In 2006, researchers identified a mutation in the neurexin family member *Contactin-associated protein-like 2 (CNTNAP2)* that associated with severe autism with seizures in an Amish pedigree. Now Alarcón *et al.*, Arking *et al.* and Bakkaloglu *et al.* report that mutations in *CNTNAP2* associate with other types of ASD.

Language deficits and delays are common features of autism. Alarcón *et al.* previously identified a 10 cM region of chromosome 7 that associated with language delays in people with ASD. In the current study, the authors tested 2758 single-nucleotide polymorphisms (SNPs) on chromosome 7. Only SNPs in *CNTNAP2* associated with delayed speech in people with ASD.

Arking *et al.* and Bakkaloglu *et al.* report that *CNTNAP2* mutations associate with narrowly and broadly defined autism, respectively. Arking *et al.* identified *CNTNAP2* in a genome-wide association

study of genes associated with strictly defined autism (often referred to as classic or type I autism), excluding other ASDs. In contrast, Bakkaloglu *et al.* found an inversion of chromosome 7 that disrupted *CNTNAP2* in a person with mental retardation and autism-related behaviors. The authors sequenced *CNTNAP2* coding exons in 635 and 942 people with and without ASD, respectively. They found 13 *CNTNAP2* mutations unique to people with ASD, 8 of which either were predicted to disrupt *CNTNAP2* expression or were in conserved regions of the gene.

Each of the three groups of authors identified different autism-associated mutations in the *CNTNAP2* gene, suggesting that like chromosomal region 16p11.2, *CNTNAP2* may be particularly susceptible to autism-related mutation. Identification of these and other autism-related mutations will help differentiate ASDs from one another and may improve ASD diagnosis and treatment.

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1. Alarcón, M. *et al.* Linkage, association, and gene-expression analyses identify *CNTNAP2* as an autism-susceptibility gene. *American Journal of Human Genetics* **82**, 150–173 (2008). | [PubMed](#) |
2. Arking, D. E. *et al.* A common genetic variant in the neurexin superfamily member *CNTNAP2* increases familial risk of autism. *American Journal of Human Genetics* **82**, 160–164 (2008). | [PubMed](#) |
3. Bakkaloglu, B. *et al.* Molecular cytogenetic analysis and resequencing of *Contactin associated protein-like 2* in autism spectrum disorders. *American Journal of Human Genetics* **82**, 165–173 (2008). | [PubMed](#) |
4. Weiss, L. A. *et al.* Association between microdeletion and microduplication at 16p11.2 and autism. *New England Journal of Medicine* (2008) doi: 10.1056/nejmoa075974. | [Article](#) |