Published in final edited form as:

Nature. 2008 August 14; 454(7206): 838–839. doi:10.1038/454838a.

AUTISM:

Family connections

Daniel H. Geschwind

Program in Neurogenetics, Department of Neurology, and at the Semel Institute, David Geffen School of Medicine, University of California, Los Angeles, 710 Westwood Plaza, Los Angeles, California 90095-1769, USA. dhg@mednet.ucla.edu

Abstract

Autism is a common neurodevelopmental syndrome with a strong genetic component. The study of autistic individuals whose parents are cousins highlights the genetic diversity of this condition.

Genetically complex human disorders, such as obesity and Alzheimer's disease, also occur in rare inherited forms — that is, a disease-causing mutation arises that can be passed on to the next generation. Studying such rare mutations is a powerful strategy for gaining insight into the mechanisms of the more common forms of a disease¹. This is especially true of autism, for which most associated gene mutations that have been identified are either rare or cause syndromic forms of the disorder^{2–6}. Reporting in *Science*, Morrow *et al.*⁷ describe their study of a large group of highly consanguineous families — families in which there were many marriages between cousins — to search for genes connected with increased susceptibility to autism.

To identify rare, disease-causing, recessively inherited mutations in consanguineous families, a technique called homozygosity mapping⁸ is used. In this technique, the genomes of a group of subjects with a certain disorder are searched for regions that they have in common and that are identical (homozygous) on both chromosomes of an affected individual. It is assumed that such regions are passed on from both parents, who shared a recent common ancestor. Homozygosity mapping has been successfully used to identify the genes responsible for certain inherited diseases, such as rare disorders of neural development, but it has not been widely applied to more common, complex genetic disorders.

Morrow *et al.*⁷ aimed to carry out homozygosity mapping to identify autism genes in children of consanguineous marriages. But consanguineous families in which several children have autism are hard to come by, and so the first challenge was to find and characterize such pedigrees.

The authors therefore established an impressive collaborative network throughout the Middle East and Eurasia (the Homozygosity Mapping Collaborative for Autism; HMCA), and identified 88 consanguineous families with autistic children. (It is common for cousins in Middle Eastern families to marry, and families tend to be large, so the search for inherited factors is that much easier.) The authors scanned the genomes of their subjects at high resolution for structural chromosomal anomalies such as deletions or duplications (also called copy-number variations, or CNVs).

Previous work^{3,9} has found that individuals with sporadic (non-familial) autism have a higher prevalence of *de novo* CNVs (those not observed in parents) than do those with inherited autism. Morrow *et al.* do not find such an increase in *de novo* CNVs in their subjects, but they do find an increase in inherited CNVs in HMCA families. This, along with

a low level of *de novo* events, is consistent with inherited, rather than sporadic, autism in these families.

The authors also identify six chromosomal regions in the HMCA subjects that harbour inherited, homozygous deletions ranging from 18 to 880 kilobases in size. The largest of these regions removes a gene of unknown function called *c3orf58*, and disrupts the promoter sequence of another gene, *NHE9*, which encodes a cell-membrane protein. The authors compared the sequence of *NHE9* in several hundred autistic subjects from non-consanguineous families and controls, and show that single base-pair mutations in the gene are associated with autism. Their finding therefore further supports a role for *NHE9* in increasing the susceptibility to this disorder.

The symptoms of autism include communication and social deficits, and restricted and repetitive behaviour. Clinical features can vary widely between individuals, and may include epilepsy or developmental regression after a period of apparently normal development. To simplify their analysis of *NHE9*, Morrow and colleagues focused on a subset of individuals who suffered from autism-associated epilepsy. It is thought that a subset of individuals who also have a particular additional disease feature (phenotype) in common might form a more genetically similar group. Unlike most of the autistic subjects without epilepsy, these individuals showed a more than fivefold increase in potentially harmful base-pair changes in the *NHE9* gene sequence, including a stop codon. Therefore, *NHE9* may be added to the list of genes that are associated with certain subsets of autism⁶.

Morrow and co-workers' observations⁷ raise some intriguing questions. Five of the six homozygous deletions identified in the HMCA subjects lie in regions outside the coding sequence of the implicated genes, and so are unlikely to disrupt the encoded protein sequence. Several of the deletions might disrupt presumptive regulatory regions, whereas another 320-kilobase deletion closest to the *PCDH10* gene, which encodes the PCD10 (protocadherin 10) protein, does not lie in a coding region or in a sequence of known function. The effect of these deletions on neighbouring genes, and any causal role in autism, therefore require further investigation. Also, the causal nature of the *NHE9* mutations, which result in potentially deleterious changes at the protein level, must be established, because similar changes are observed in control subjects, albeit less frequently.

The difficulty in identifying mutations that are definitely pathogenic is an emerging theme in common neuropsychiatric disorders. Morrow and colleagues' study demonstrates that studying consanguineous families is a fruitful path to identifying autism genes, but also that such analysis is more challenging than might initially have been expected. This is partly due to the underlying genetic heterogeneity of autism, a facet underscored by this study. The authors find that no single recessive mutation is associated with autism in more than one family, even in consanguineous families from the same geographic region.

Luckily, advances in DNA sequencing technology mean that even large genomic regions can be efficiently sequenced, and work to identify recessive mutations in single base pairs within the genomes of subjects from the HMCA group might already be under way. Sequencing shared regions in these families could be even more informative because many mutations in these regions are probably small — perhaps single base-pair mutations — and thus might more directly implicate specific genes.

Convergent evidence from other studies, including functional and gene -expression data, will be crucial in assessing the relevance of candidate genes to autism¹⁰. Morrow *et al.* embrace this notion, as their putative autism susceptibility genes represent diverse functional classes, which at face value do not suggest common molecular mechanisms. To provide a potential functional context, they show that three of the genes — either near (*PCDH10*) or

overlapping (*c3orf58* and *NHE9*) the deletions — are among a significant subset that is associated with a form of neuronal activity thought to be involved in learning and memory¹¹.

The authors suggest that investigating such genes might provide a way of unifying seemingly diverse molecular findings in autism. Given the nearly two dozen genes that are now associated with the disorder⁶, this should be a readily testable hypothesis. The way in which functional data relate to the core deficits of autism is not known, because many aspects of learning and memory are preserved in autistic children. The idea that autism might represent a general deficit in neuronal plasticity caused by changes in gene expression needs to be reconciled with the specificity of cognitive dysfunction observed in the condition¹², as well as the preservation of general intellectual ability in many individuals. This aspect highlights a central challenge of research in this area: connecting basic molecular pathways to the properties of complex neural circuits and cognition in humans. Spanning these diverse levels of function will require detailed analysis of the correlation between the genetic composition of individuals and their associated phenotype across the spectrum of autism disorders.

References

1. Peltonen L, Perola M, Naukkarinen J, Palotie A. Hum. Mol. Genet. 2006;15:R67–R74. [PubMed: 16651371]
2. Jamain S, et al. Nature Genet. 2003; 34:27–29. [PubMed: 12669065]
3. Sebat J, et al. Science. 2007; 316:445–449. [PubMed: 17363630]
4. Jacquemont ML, et al. J. Med. Genet. 2006; 43:843–849. [PubMed: 16840569]
5. Strauss KA, et al. N. Engl. J. Med. 2006; 354:1370–1377. [PubMed: 16571880]
6. Abrahams BS, Geschwind DH. Nature Rev. Genet. 2008; 9:341–355. [PubMed: 18414403]
7. Morrow EM, et al. Science. 2008; 321:218–223. [PubMed: 18621663]
8. Lander ES, Botstein D. Science. 1987; 236:1567–1570. [PubMed: 2884728]
9. Marshall CR, et al. Am. J. Hum. Genet. 2008; 82:477–488. [PubMed: 18252227]
10. Alarcón M, et al. Am. J. Hum. Genet. 2008; 82:150–159. [PubMed: 18179893]
11. Flavell SW, Greenberg ME. Annu. Rev. Neurosci. 2008; 31:563–590. [PubMed: 18558867]
12. Geschwind DH, Levitt P. Curr. Opin. Neurobiol. 2007; 17:103–111. [PubMed: 17275283]