ment to compare outcomes in auctions with secret versus public reserve prices, two common approaches used to auction goods on the Internet. They auctioned 50 matched pairs of Pokemon trading cards on eBay: one with a minimum bid of 30% of the card's book value, and one with a minimum bid of $0.05 and a secret reserve price equal to 30% of the card's book value. Keeping the reserve price secret reduced the probability of selling any card, the number of serious bidders in an auction, and the amount of the winning bid. Thus, contrary to the beliefs of many eBay sellers and to the predictions of models of rational bidder behavior, using secret reserve prices instead of public reserve prices actually lowers a seller's expected returns.

An example of a natural field experiment designed to measure key parameters of a theory is (*6*), where parameters associated with why people give to charities are estimated. In this study, Karlan and I worked with a private charity to explore the effects of different matching rates on charitable giving by soliciting contributions from more than 50,000 supporters. In one group, solicitees were informed that for every dollar contributed, an outside donor would match the contribution 1:1. A control group received no match, and other groups received more generous matching rates (such as 2:1 or 3:1). Simply announcing that a match is available increases the revenue per solicitation by 19%. In addition, the match offer increases the probability that an individual donates by 22%. These estimates shed light on a key parameter for fundraisers: how sensitive contributions are to the "price" of giving.

In the examples above, I have focused on natural field experiments; similar examples can be found for artifactual and framed field experiments. The various field experimental approaches, lab experiments, and econometric methods using naturally occurring data should be thought of as strong complements—much like theory and empiricism. Combining insights gained from each methodology will permit scholars to develop a deeper scientific understanding. For example, economists have shown that there is much to be gained from gathering data from a variety of settings, both controlled and uncontrolled. In those cases where behaviors are robust, the advice to policy-makers can be unequivocal. In other instances, behaviors might differ systematically, and developing theory to explain such discrepancies deepens our economic understanding. Similar gains can accrue within the sciences more broadly.

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GENETICS

Insights into the Pathogenesis of Autism

Genetic analysis of inbred families reveals genes associated with susceptibility to autism.

James S. Sutcliffe

Autism is a common developmental disorder that profoundly impairs the emergence of social behaviors and communication in children before 3 years of age. Repetitive, stereotyped, and obsessive-compulsive–like behaviors are also prominent features of the disorder (*1*), and are often accompanied by cognitive impairment, seizures or epilepsy, gastrointestinal complaints, disordered sleep, and other problems. Identifying risk factors for autism has become a high priority of scientists, lay groups, and parents of autistic children. On page 218 of this issue, Morrow *et al*. (*2*) add several more genes to a growing number of genetic abnormalities that correlate with susceptibility to autism (see the figure).

Twin and family studies demonstrate that the etiology of autism has a substantial genetic component. Current estimates of sibling recurrence risk—the likelihood that a younger sibling of an autistic child will also have autism—is greater than 15% (*3*–*5*). Comparing this to population rates of approximately 1 per 500 children for narrowly defined autism or 1 per 150 children for the more broadly defined autism spectrum disorders indicates a high degree of heritability in families.

Determining specific genetic changes that increase the risk of developing disorders like autism is extraordinarily complex (*6*) due to heterogeneity—different kinds of variation at many underlying genes are involved. One type of variation consists of rare disease-causing or highly penetrant mutations, and these have implicated specific biological processes. Similarly, common variation—usually discrete changes in DNA sequence—has been identified in autism, but only a few specific findings have been replicated. Other important clues to genetic factors in autism include abnormalities such as chromosomal translocations, inversions, and large deletions or duplications, which are more frequent in individuals that present clinically with dysmorphic features and severe cognitive impairment. Geneticists have long hypothesized that genes disrupted by chromosomal abnormalities in isolated cases may play a role in susceptibility to autism more broadly and have pursued experiments toward this end.

Recent advances in DNA microarray technologies have revealed a substantial etiological role for small losses and gains of DNA—so-called copy number variation—in autism (*7*–*12*). All individuals harbor this common form of genetic variation, which can be inherited from a parent or can arise as a sporadic event de novo. However, a large and growing number of deletions and duplications of DNA have been found in people with autism. As comparisons to control samples identify which variants are unique, more frequent, or equal in autism versus control cases, we will be better able to interpret the observed copy number variation.

Much discussion has focused on whether a copy number variant is inherited or arises de novo, with greater interpretive weight vis-à-vis disease association given to the latter. As with large chromosomal abnormalities, it may be that the disruption or dysregulation of gene expression underlies the risk or causal effect for a given copy number variant. Genes may be lost or an extra copy may be present on a given chromosome; genes flanking a DNA

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PUTATIVE AND KNOWN AUTISM-RELATED GENES	
Glutamatergic synapse function and/or neuronal cell adhesion	
FMR1[A,B]	Fragile X mental retardation 1
NLGN3[B]	Neuroligin 3
NLGN4[B]	Neuroligin 4
NRXN1[B,C]	Neurexin 1
SHANK3[B,C]	SH3 and mulitple ankyrin repeat domains 3
CNTNAP2[B,C,D]	Contactin-associated protein-like 2
PCDH10[C]	**Protocadherin 10**
CNTN3[C]	**Contactin 3**
Endosomal trafficking	
NHE9 (SLC9A9)[B,C]	**Na^+/H^+ exchanger isoform 9**
NHE6 (SLC9A6)[B]	Na^+/H^+ exchanger isoform 6
***DIA1* (c3orf58)**[C]	**Deleted in autism 1**
A2BP1[C]	Ataxin 2-binding protein 1
Neuronal activity regulation	
FMR1[A,B]	Fragile X mental retardation 1
MECP2[B,C]	Methyl CpG binding protein 2
***DIA1* (c3orf58)**[C]	**Deleted in autism 1**
PCDH10[C]	**Protocadherin 10**
NHE9 (SLC9A9)[B,C]	**Na^+/H^+ exchanger isoform 9**
A2BP1[C]	Ataxin 2-binding protein 1
UBE3A[B,C]	Ubiquitin protein ligase E3A
Implicated in related disorders	
FMR1[A,B]	Fragile X mental retardation 1
MECP2[B,C]	Methyl CpG binding protein 2
NHE6 (SLC9A6)[B]	Na^+/H^+ exchanger isoform 6
A2BP1[C]	Ataxin 2-binding protein 1
UBE3A[B,C]	Ubiquitin protein ligase E3A
Other functions	
EN2[D]	Engrailed homeobox 2
SLC6A4[B,D]	Serotonin transporter (SERT, 5-HTT)
MET[D]	Met proto-oncogene (c-Met, HGFR)
SCN7A[C]	**Na^+ channel, voltage-gated, type VII**
RNF8[C]	**Ring finger protein 8**

Genes implicated in autism pathogenesis. Genes have been implicated in autism (*1*, *2*) on the basis of different functions and forms of genetic variation, and also on their association with disorders that show features of autism. They share common or related pathways, as shown. A, genes showing triplet repeat expansion; B, genes with rare mutations or coding variants; C, genes with copy number variation or chromosomal abnormality; D, association of common alleles. Genes implicated from (*2*) are shown in bold.

deletion or duplication may be subject to dysregulation because of altered local chromatin structure or separation from key enhancer elements (which regulate gene expression). Thus, copy number variation is a major category of genetic risk for autism spectrum disorders, and is implicated in 10 to 20% (or more) of cases (*7*–*12*). The genetic heterogeneity of autism, however, greatly complicates the task of identifying genes that increase susceptibility to the disorder.

Morrow *et al.* use the powerful genetic technique of homozygosity mapping to identify autism genes. Geneticists have long taken advantage of the statistical power afforded by genetic analysis of families in which parents of affected individuals share a common ancestry (e.g., first cousins). Such consanguineous families, more common in the Middle East, are at substantially increased risk for autosomal recessive conditions [traits that are expressed when an individual is homozygous (has two identical copies) for a particular gene]. There is a growing recognition that inbred families are also useful in identifying genes for complex disorders, such as autism.

Morrow *et al*. use DNA microarrays to study numerous consanguineous families from the Middle East. By analyzing the inheritance of DNA throughout the genome in these pedigrees, they identify chromosomal regions that are inherited in common by the affected individuals who share the same two copies of these regions. These homozygous segments, which are heterozygous in the related parents, are likely to represent a causal or risk factor. In several of these families, the regions linked to the autism spectrum disorder and inherited "identical by descent" contained deletions. Thus, the affected individuals were completely deficient for the genes (or potential regulatory DNA) that lie within the deleted intervals. By extension, the absence of those gene products, and/or the possible altered expression of genes in the immediate vicinity of the deletion, is predicted to cause the autism spectrum disorder in that family.

An important question is whether a gene identified as causing disease in a single inbred family has any relevance to autism in nonconsanguineous families. In addition, establishing which gene (or genes) lies within or near a deleted interval—the disruption of which is causing the disorder—is not trivial. Here, a nice story is developed for one such region on chromosome 3q containing a large (~886 kilobase) deletion. A gene called *DIA1* (*deleted in autism1*; also known as *c3orf58*) encoding an uncharacterized protein is completely removed, whereas *NHE9* (*Na^+/H^+ exchanger 9*), a nearby gene encoding a membrane protein that exchanges intracellular H^+ for extracellular Na^+, remains intact but could be dysregulated. To assess the broader relevance of these genes in autism, Morrow *et al.* sequenced the coding regions of *NHE9* in affected subjects from nonconsanguineous U.S. families and found a loss-of-function mutation in one family. Similar mutations cause an epilepsy phenotype in mice, and for the related *NHE6* gene, they cause a phenotype with autistic symptoms and epilepsy. In addition, other variation is implicated, because a focus on autism families with epilepsy led the authors to observe a much greater number of coding variants in cases compared with controls. Taken together, these findings support dysregulation of *NHE9* as a contributing or causal factor in that family.

The most provocative observations from this study point to an important functional class of genes involved in autism susceptibility. The authors show that several of the genes identified in or likely affected by homozygous deletions are regulated by neuronal activity—that is, their expression changes in response to stimulation of neuronal activity. Because autism is a neurodevelopmental disorder, emphasis has been placed on prenatal development, which is guided by intrinsic gene-expression patterns. The brain continues to develop long after birth, however, and experience and environmental input play an important role in subsequent development. Synapses (connections between neurons) mature partly as a function of experience-dependent neuronal activity and of the gene-expression changes that accompany it. But if those genes are disrupted by mutation or copy number variation, that could suggest that the process of activity-regulated synaptic development itself is disrupted in some way. Indeed, this is the authors' hypothesis.

Dysregulation of synaptic development is an established idea in autism research. Although it is conceptually a big step, and the authors are cautious in their conclusions, the possibility that dysregulation of these genes results in disruption of synaptic development in response to early-life environment and experiences is an intriguing proposal, whose validity must await the results of further research.

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