Genetic clues to the biological basis of autism

Martha Turner, Gabrielle Barnby and Anthony Bailey

Autism, the prototypical pervasive developmental disorder, is characterized by impaired communication and social interaction, and by repetitive interests and behaviours. The core disorder probably affects around 5:10 000 individuals, of whom some three-quarters are male. Onset is in the first three years of life, and the disorder is associated with lifelong disabilities. Because of the clear evidence that idiopathic autism has a strong genetic basis, many groups are undertaking whole genome screens to identify susceptibility loci. We review the first results, and briefly consider the implications of molecular genetic findings for future research, diagnosis and management.

AUTISM (Box 1) is a behavioural syndrome that was, for many years, considered to have a psychogenic aetiology; the organic basis not being accepted until the associations with mental disability and epilepsy were demonstrated. The underlying abnormalities in brain development and function have still not been identified. The syndrome is sometimes associated with single gene disorders, most frequently the fragile X syndrome and **tuberous sclerosis**, and there are also case reports of autism co-occurring with a very wide range of cytogenetic abnormalities[1]. Nevertheless, a recognized medical aetiology can usually only be identified in a small minority of cases. The possibility that genetic influences might also be implicated in idiopathic cases was at first considered unlikely, as multiplex families (families containing more than one affected individual) are relatively uncommon. The realization that the low **recurrence risk** in fact represented a very high **relative risk** – as core autism is an uncommon disorder – led to a series of twin and family studies. The largest same-sex epidemiological twin study found a 60% concordance rate for autism in monozygotic (MZ) twin pairs compared with 0% among dizygotic (DZ) pairs[2] (Fig. 1), leading to a calculated heritability for the liability to autism of over 90%. The findings from the other twin studies are in keeping, and, together, the results suggest that autism is one of the most strongly genetic psychiatric disorders[2]. Szatmari *et al.*[3] have recently reviewed ten family studies of autism and calculated a pooled 2.2% rate of autism among the siblings of singleton autistic **probands**. When studies extended the phenotype to include Asperger's syndrome and other **pervasive developmental disorders** (PDDs), the rate rose to approximately 5% (Refs 3,4).

Some of the twin and family studies of autism also suggest that the behavioural phenotype extends beyond PDDs to include a range of related, but milder, social and language impairments – and possibly also behavioural rigidity[4]. Indeed, in the UK twin study, the concordance rate for a broader phenotype of social and/or language abnormalities (that included PDDs) was 92% in MZ pairs versus 10% in DZ pairs[2] (Fig. 1). The rate of these milder phenotypes is also elevated among the relatives of singleton **probands**, and, at present, it is unclear quite where the boundaries between pervasive developmental disorders and these milder phenotypes should be drawn[4]. Paradoxically, it was probably the presence of these milder phenotypes in some parents that first gave rise to the notion that autism had an environmental basis.

The search for susceptibility genes

Although the strong genetic predisposition to autism is no longer in doubt, identifying susceptibility loci is not straightforward (Box 2). In the absence of specific drug effects and detailed knowledge of the underlying pathophysiology, there are no very strong pointers to functional candidate genes. Of course, the well-established association with various medical disorders has been pursued but, for instance, no linkage has been found with the fragile X mental retardation 1 gene (*FMR1*) (Ref. 5). The finding of elevated platelet serotonin levels in perhaps a quarter of cases has prompted association studies of the serotonin transporter and various serotonin receptor genes with, so far, no

Martha Turner BA
Research Psychologist
MRC Child Psychiatry Unit, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, UK SE5 8AF.

Gabrielle Barnby BSc
Research Assistant
Wellcome Trust Centre for Human Genetics, Roosevelt Drive, Headington, Oxford, UK OX3 7BN.

Anthony Bailey* BSc, MB BS, MRCPsych, DCH
Clinical Scientist
MRC Child Psychiatry Unit, Institute of Psychiatry, De Crespigny Park, Denmark Hill, London, UK SE5 8AF.
Tel: +44 (0)20 7252 5756
Fax: +44 (0)20 7252 5107
***e-mail: Anthony.Bailey@iop.kcl.ac.uk**

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Box 1. Clinical features of autism (adapted from Ref. 23)

Qualitative impairments in reciprocal social interaction, including:
- Impairment in the use of nonverbal behaviours, including eye-to-eye gaze, facial expression, body postures and gestures.
- Failure to develop peer relationships.
- A lack of spontaneous seeking to share enjoyment, interests or achievements with other people.
- Lack of socio-emotional reciprocity.

Qualitative impairments in reciprocal communication, including:
- Delay in, or total lack of, language development.
- Impairment in the ability to initiate or sustain a conversation with others.
- Stereotyped and repetitive use of language, or idiosyncratic language.
- Lack of varied, spontaneous make-believe or social imitative play.

Restricted repetitive and stereotyped patterns of behaviour, interests and activities, including:
- Encompassing preoccupations with stereotyped and restricted patterns of interest.
- Apparently inflexible adherence to specific, non-functional routines or rituals.
- Stereotyped and repetitive motor mannerisms (e.g. hand or finger flapping or twisting).
- Persistent preoccupation with parts of objects.

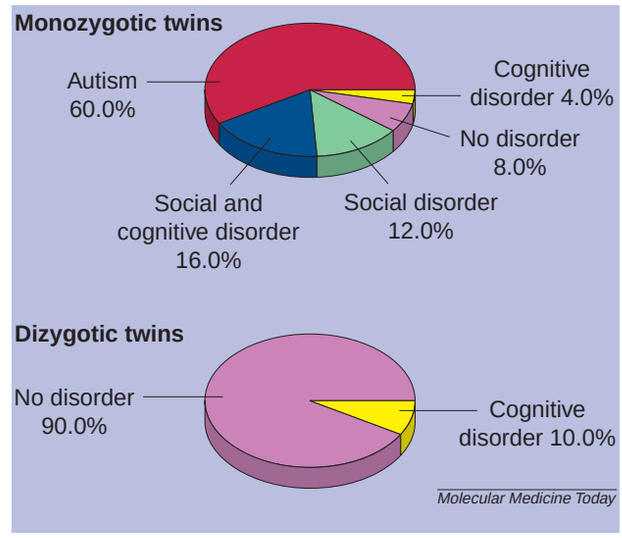

Figure 1. Twin concordance rates from a UK same sex epidemiological sample[2].

Box 2. Strategies for finding susceptibility loci

Candidate gene studies
Candidate studies examine genes that seem likely to be implicated in a disorder. Genes thought to be involved in relevant pathophysiological processes are known as functional candidates. Positional candidate genes are those within or close to cytogenetic rearrangements associated with the disorder. There are no very strong functional candidate genes for autism, although the genes involved in the serotonergic and GABA systems are potential functional candidates. Genes within duplications on proximal chromosome 15q are potential positional candidates.

Genome screens
In the absence of candidate genes some 300–400 highly polymorphic microsatellite markers, evenly spaced throughout the genome, are typed in an affected relative pair sample. Non-parametric or allele sharing linkage analysis is used to identify markers at which affected relative pairs share alleles more often than expected by chance. A statistically significant increase in sharing implies that the marker might be linked to a nearby susceptibility locus.

Association studies
Areas of suggestive linkage can be fine mapped using association strategies; these identify alleles that occur at significantly different frequencies in affected versus control samples. Commonly, the frequencies of parental alleles that are not transmitted to affected offspring are used as internal controls.

clear pattern of findings[6–8]. Indeed, as yet, there are no particularly strong leads from any of the case-control or family-based candidate-gene association studies, although the likelihood of genetic heterogeneity has not been systematically assessed.

With regard to positional candidates and regions, most attention has recently focused on the proximal portion of the long arm of chromosome 15 (Ref. 1): a region in which chromosomal duplications and other rearrangements are sometimes associated with an autistic phenotype with apparent **imprinting** effects. The presence of a cluster of γ-amino butyric acid ($GABA_A$) receptor genes in this area has partially fuelled this interest, but association studies in this region have so far yielded inconsistent results[8–10].

A complication for molecular genetic approaches is that the substantial difference between the concordance rates for autism in MZ and DZ twin pairs suggests that autism does not represent a single-gene disorder. The twin and family findings indicate a multi-locus disorder, with one model suggesting that 2–10 interacting genes are likely to underlie susceptibility[11]. Although some of the data support a model of **epistatic** interactions between a small number of loci, there is not really sufficient evidence to strongly support any particular hypothesized complex mode of inheritance. As autism is associated with several distinct medical disorders, genetic heterogeneity among idiopathic cases also seems likely, although phenotypic markers of potential heterogenity are limited[12].

The evidence from genome screens

In the absence of strong functional or positional candidates, and considerable uncertainty about the precise mode of inheritance, many groups have used an **affected relative pair design** combined with a whole genome screen. The approach uses highly polymorphic markers to identify chromosomal regions in which affected relative pairs (usually siblings) with autism or another PDD show more allele sharing than expected by chance, and can use non-parametric analysis (requiring no

knowledge about the mode of inheritance). The region or marker showing increased allele sharing can then be further examined for evidence of linkage or association.

In the past two years, four research teams have published their complete findings from a whole genome screen using an **affected relative pair design**. The first published screen, by The International Molecular Genetic Study of Autism Consortium (IMGSAC; http://www.well.ox.ac.uk/~maestrin/iat.html)[13], examined 99 affected relative pair families from six countries, and identified regions on six chromosomes (4, 7, 10, 16, 19 and 22) at which affected relative pairs showed increased allele sharing [multipoint maximum lod scores (MLS) >1 (where lod stands for log of the odds)]. The most significant findings were on chromosome 7q, with an MLS of 2.53 in all sib-pair families rising to an MLS of 3.55 when analysis was restricted to the largest subset of families: 56 pairs from the UK. The second most significant region was on chromosome 16p near the telomere, with an MLS of 1.51 in all families, and 1.97 in the subset of UK families.

In a genome-wide screen of 51 multiplex families from seven countries, Philippe and colleagues[14] identified 11 markers with an MLS > 0.6 (nominal $P < 0.05$), on chromosomes 2, 4, 5, 6, 7,10, 15, 16, 18, 19 and X. Using **multipoint analysis**, the most significant areas of sharing were on chromosome 6q (MLS = 2.23), 19p (MLS = 1.37), and 15q (MLS = 1.1). The area of elevated statistics on proximal 15q overlapped the 15q11–q13 region implicated in the cytogenetic rearrangements that are sometimes associated with an autistic phenotype. The authors calculated that, by chance, 13 of their 264 markers would have been expected to show significance at the 5% level. Nevertheless, four of the identified 11 regions (on chromosomes 2q, 7q, 16p and 19p) overlapped those identified by the IMGSAC (Ref. 13); the region on 7q giving an MLS of 0.83.

In a two-stage screen of 139 multiplex families in the USA, Risch and colleagues[15] (http://www-cap.stanford.edu/research/syndromes_disorders/autism/genetics.html) identified four chromosomal locations yielding a multipoint MLS > 1.0 on 1p, 7p, 17p and 18q. The most significant finding was on proximal chromosome 1p (MLS = 2.15), with the next most positive region on 17p (MLS = 1.21). The authors concluded that their findings were largely negative, and compatible with a genetic susceptibility to autism mediated by at least 15 loci of small effect. The potential susceptibility region on 7q identified by the IMGSAC (Ref. 13) gave an MLS of 0.62, rising to 0.93 at the next most proximal marker.

The Collaborative Linkage Study of Autism (CLSA; http://www.nemc.org/psych/autism1.htm)[16] identified three regions in 75 families in the USA showing a **multipoint heterogeneity** MLS > 2. Two of these regions were located on chromosome 13, with a peak at marker D13S800 (MLS = 3.0 using a recessive model), and a second peak between markers D13S217 and D13S1229 (MLS = 2.3). The third most significant area was consistent with the 7q region identified by the IMGSAC (Ref. 13), with a **multipoint heterogeneity** MLS of 2.2.

Potential susceptibility regions

The Duke University group's screen findings (http://www2.mc.duke.edu/depts/medicine/medgen/autism.html) have appeared in abstract[17] – with elevated statistics reported on chromosomes 1, 2, 3, 7, 18 and 20 – but they have published in full on susceptibility regions on chromosome 7q (Ref. 18) and 15q (Ref. 19). On 7q, linkage analysis was guided by their preliminary genome screen findings and an autism family in which three siblings inherited, from their mother,

Glossary

Affected relative pair design – A sample of families identified on the basis that each contains two or more affected individuals, usually siblings. Increased allele sharing between affected individuals within families can be tested using model-free or non-parametric statistical approaches.

Attention deficit hyperactivity disorder (ADHD) – Developmental disorder resulting in inattentiveness, impulsivity and hyperactivity.

Dyspraxia – A disability in the organization of movement resulting in poor co-ordination, that is usually associated with some degree of impaired performance on visuo-spatial cognitive tasks.

Epistatic – The interactions between genes (or their products) that influence gene expression.

Fragile X – The most common cause of congenital mental retardation, affecting 1 in 2000 children, caused by the expansion of a CGG repeat in the FMR-1 gene.

Imprinting – A phenomenon whereby the phenotype depends upon the parent of origin of the disease gene.

Linkage disequilibrium – The tendency of alleles at closely linked loci to be associated together. When alleles at two distinct loci occur together more frequently than expected from the known allele frequencies and the recombination fraction, the alleles are said to be in linkage disequilibrium.

Multipoint analysis – Testing for linkage between a disease and genetic markers by examining several markers simultaneously.

Multipoint heterogeneity – The calculation of lod scores under a dominant and a recessive model explicitly allowing for locus heterogeneity (i.e. clinically similar disorders that are caused by mutations at different genes or mutations at the same locus that can result in diverse conditions).

Pervasive developmental disorders (PDDs) – A group of disorders with onset in the first three years of life. They involve a combination of impairments in communication and reciprocal social interaction and stereotyped patterns of interests and behaviours. The disorders include autism, Asperger's syndrome (a similar condition that is not associated with language delay or general intellectual impairment), and a range of atypical or milder manifestations of the same triad of difficulties (Atypical Autism and Pervasive Developmental Disorder-Not Otherwise Specified; PDD-NOS). The prevalence for all forms of PDD is uncertain but probably at least 18 in 10 000.

Proband – The affected index case through which the family is identified.

Recurrence risk – Risk to subsequently born relatives of affected individuals of being affected themselves.

Relative risk (λ_r) – The frequency with which a disorder is diagnosed in the relatives of an affected person as a proportion of the frequency of that disorder in the population.

Tuberous sclerosis – An autosomal dominant disorder caused by major loci on chromosomes 9 and 16. It is characterized by skin lesions, benign tumours and neurological abnormalities, and is often associated with epilepsy and learning disabilities.

a paracentric inversion in the chromosome 7 candidate region, with the two male sibs affected by autism and their sister by a developmental language disorder[18]. In 76 multiplex families in the USA, a peak MLS of 1.77 was noted at marker D7S2527, with the adjacent region also showing positive statistics[18]. Some markers in the region also showed **linkage disequilibrium**, with the majority of the effect coming from the paternal contribution. On 15q, 14 markers were typed in 63 families in the region implicated by cytogenetic rearrangements, with an area of significance peaking at marker D15S217 (MLS = 1.31)[19], there was also some evidence suggestive of increased recombination in this region.

The findings from the whole genome screens illustrate some of the difficulties of identifying susceptibility loci in multilocus disorders: they have yielded an array of different loci with none reaching a lod score of 3.6 (Fig. 2; Box 3). Clearly, some findings are likely to be false positives, arising by chance because of the large number of analyses. Nevertheless, the extent to which all groups have identified increased allele-sharing in the region on 7q that showed significant linkage in the IMGSAC UK families[13] is encouraging (Table 1). Because idiopathic autism seems likely to be a genetically heterogeneous disorder[12], and because there are differences between groups in the characteristics of the multiplex families they have ascertained, it is questionable whether, at this stage, one should expect consistent and significant lod scores across samples. Moreover, in genetically complex disorders, different loci with additive effects are likely to be prominent in different samples simply by chance, and the sample size necessary for replication might considerably exceed that of the original sample[20]. Indeed, as yet, the sample sizes of all groups are still relatively modest. The precise locations of maximal linkage on 7q also differ between screens (Table 1). Although these discrepancies justify continued caution over the significance of the findings from the first five screens, they might simply reflect the extent to which location estimates can vary around a true locus. It is also possible, however, that more than one susceptibility locus lies in this area; indeed, a potential susceptibility locus for language disorder has already been identified proximal to the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) on 7q (Ref. 21). The findings on 15q, although less consistent, warrant further investigation, and there is also a potentially interesting convergence of findings on chromosome 2q.

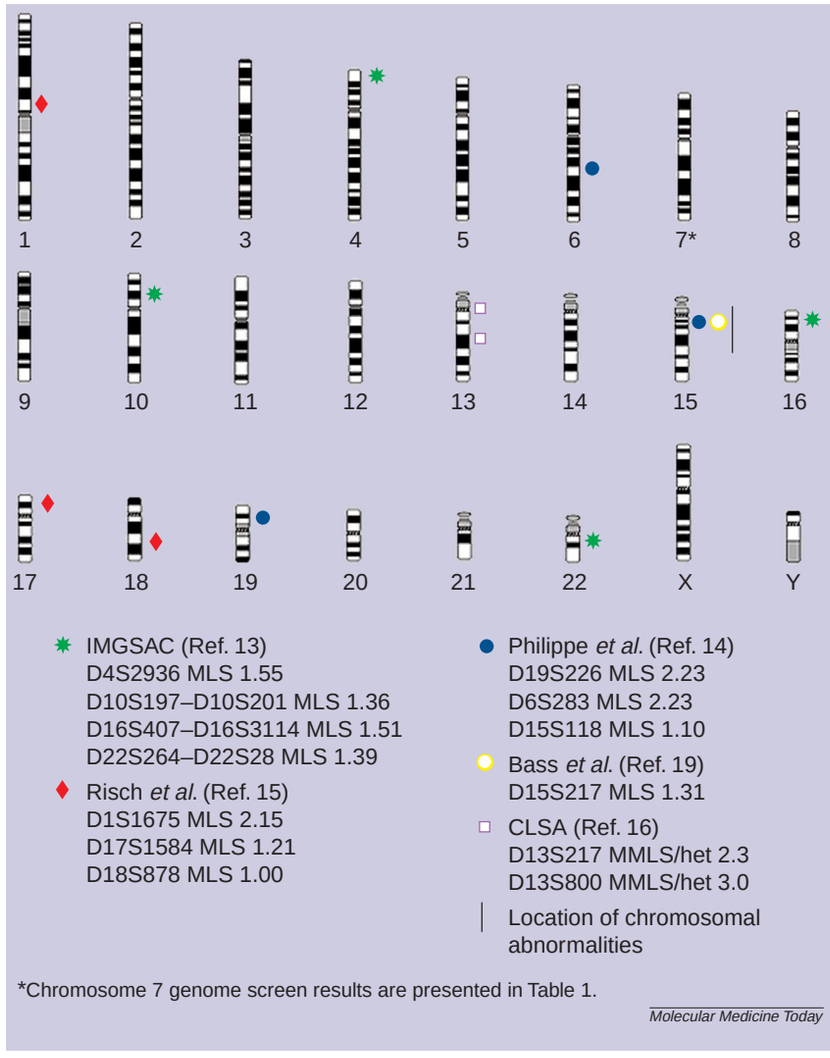

Figure 2. Autism genome screen results. Linkage findings from whole genome screens with MLS>1.00

Individual groups will be pursuing their promising linkages independently, but a meta-analysis of the whole genome-screen findings represents a complementary strategy for establishing significant linkage. For this to be a useful exercise, comparability of measures across studies is required, and preferably some hypotheses about how any systematic differences between samples might relate to the divergent linkage findings. That would provide a basis for combining genotyping data on larger, potentially more homogeneous, groups of cases. At present, however, there are no strong indications as to which phenotypic features might index genetic heterogeneity. The presence or absence of language[12], and IQ level, are obvious characteristics to use initially, although it is known that there can be considerable within-family variation in these features. Although combining data on more severely affected cases might appear an optimal strategy, it seems possible that genetic heterogeneity might be greater among cases associated with learning difficulties.

Future directions

Association studies

Promising regions of linkage can be investigated further using association strategies, and several groups are beginning to use this approach. Crucially, more easily available singleton samples can be used.

Box 3. Establishing significance in genome screens

Genome-wide scans involve multiple statistical tests, and correction must be made for the probability that significant excess sharing will occur at random somewhere in a whole genome scan. Setting the lod score threshold at 3.6 for a study of sibs and half sibs equates to a 5% probability of identifying a significant linkage at random[24]. In complex disorders, true susceptibility loci of relatively weak effect might not reach this level of significance. Replication of suggestive linkage by other groups in a genome-wide scan might point to true positive loci worthy of further study, although much larger sample sizes are required to replicate linkages in complex traits. When other laboratories test an area of previously identified suggestive linkage, correction must be made for testing a larger number of markers in a small region. If the findings from several studies conflict, this might reflect aetiological heterogeneity between samples or simply chance variation. A meta-analysis of all studies might eventually be necessary to establish significant linkage; this requires comparable diagnostic procedures across groups and pooling of the raw data on identical markers for reanalysis. Inevitably, for relatively rare disorders such as autism, this also requires international collaboration. Pooling of samples also provides the opportunity for analysing phenotypically similar subgroups of adequate size, or stratifying by risk factors. Of course, loci that confer a very modest elevation in risk and have common alleles might never show significant linkage; association studies provide an alternative way forward, although the need to correct for multiple testing remains.

Table 1. Multipoint scores on chromosome 7 from autism genome screens[a]

cM	Markers in region	MLS	Group	Refs
104.0	**D7S1813**	2.2	CLSA[b]	16
125.8	**CFTR**			
130.8	**D7S2527**	1.77	Ashley-Koch *et al.*	18
135.3		0.83	Philippe *et al.*	14
137.7	**D7S640**	2.01	Ashley-Koch *et al.*[c]	18
139.3	**D7S1804**	0.93	Risch *et al.*	15
144.7		2.53	IMGSAC	13
149.6	**D7S684**	0.63	Risch *et al.*	15
150.0	**GATA32C12**	0.8	CLSA[b]	16

[a]Abbreviations: MLS, maximum lod scores (where lod stands for log of the odds); CLSA, the Collaborative Linkage Study of Autism; IMGSAC, the International Molecular Genetic Study of Autism Consortium; MMLS/het, multipoint heterogeneity MLS; NPL, nonparametric linkage.
[b]MMLS/het score.
[c]Multipoint NPL analysis.

Because of the very rapid progress in mapping the human genome, information about brain-expressed candidate genes in regions of linkage is increasingly available, and allelic variants can be tested directly for association. This approach complements screening for single nucleotide polymorphisms (SNPs) in narrowed regions of **linkage disequilibrium**. So far, molecular genetic research has focused on the core phenotypes: autism and related pervasive developmental disorders. Although this represents a sensible initial strategy, it does not make full use of the information available from other family members, and accurate characterization of other first-degree relatives in multiplex families will be an important next step.

Functional genomics

The promising convergence of some findings from the published whole genome screens and cytogenetic abnormalities raises the possibility that the first autism susceptibility locus might be identified in the near future. An immediate task will be to establish the biochemical function of the gene, if that is not already known. The molecules with which the gene product interacts and the linked biochemical pathways will themselves become potential targets for candidate gene studies. It will also be possible to undertake gene expression studies using the small number of postmortem brains that are currently available. Hopefully, molecular genetic insights will offer clues to the underlying neurophysiology.

Animal models

The generation of relevant animal models of genetic susceptibility represents an important step from the identification of genes to knowledge of their function in the developing organism. The expectation is not that a model of complex human behaviours can be generated, but rather that the influences of susceptibility loci on brain development and neurophysiology can be studied. Animal models have already proved useful in modelling single gene disorders, but their applicability to multigenic disorders, where each locus has only a limited effect, is uncertain. Monogenic models have, however, been developed to mimic multifactorial diseases. There is a mouse model (NOD) that simulates human insulin dependent diabetes mellitus, and a digenic animal model, using offspring from a cross between a mouse heterozygous for the *patch* mutation with a mouse homozygous for the *undulated* mutation[22], has been developed for the study of spina bifida occulta. It is possible that these types of approach might also be useful in autism, and breeding experiments could make it possible to bring different combinations of genes together. The overall usefulness of this approach is likely to depend, however, on the extent to which it is possible to develop models that reflect the potentially subtle changes in gain or loss of function relevant to oligogenic disorders. Of course, the major challenge for a molecular biological understanding of autism is to identify and understand those factors that influence phenotypic expression. Twin studies have hinted at the possible range of phenotypic expression, but the underlying mechanisms are obscure. Thus, it is not known if substantial phenotypic variability reflects some type of genetic instability, gene–environment interaction, or simply chance.

Epidemiology

Understanding phenotypic expression will also require returning to family data to establish the extent to which single susceptibility loci underlie either individual or multiple components of the extended autism phenotype. Genetic epidemiological approaches will also be necessary to estimate gene frequency, penetrance and attributable risk in the general population, as well as to establish the extent to which susceptibility loci contribute to variance in relevant personality traits. In the

longer term, the approach to identifying any putative environmental risk factors is likely to be determined by what is known about gene function and the timing of gene expression during development. Establishing the relationship between different genetic predispositions, prognosis and the development of secondary complications – such as epilepsy – will ultimately require longitudinal studies.

Genetic applications

Improving diagnosis

One of the main benefits of identifying susceptibility genes for autism will be an improved understanding of the relationship between genotype and phenotype. Although core autism is well-defined and easy to diagnose behaviourally, our understanding and recognition of children at the boundaries of PDDs is much less developed. As susceptibility loci for autism begin to be cloned, some of this genetic information might be useful in resolving current diagnostic uncertainties. For example, genetic information could be helpful in identifying phenotypic differences between language disorders that arise on the basis of autism susceptibility loci and those that have a different genetic basis, and possibly also a better long-term outcome. Another example concerns children with Asperger's syndrome, who sometimes receive a primary diagnosis of **attention deficit-hyperactivity disorder** (ADHD) or **dyspraxia** before their pervasive social difficulties are eventually recognized. Of course, accurate diagnosis of the relatively milder phenotypes is a prerequisite for accurate genetic counselling.

Genetic counselling

A potentially early application of a better understanding of the aetiology of autism will be the prospect of improved genetic counselling to parents of autistic children who want information about the risks of having further affected children, and to other family members who are concerned about having an autistic child themselves. Current **recurrence risk** estimates are based on empirical recurrence rates among siblings. At the individual level, the immediate applicability of research findings will depend heavily on whether already identified loci seem to be implicated in that family and what is known about the risk attributable to each locus. In the longer term, a better understanding of genetic mechanisms should enable increasingly more accurate advice to be provided.

Pre-natal and pre-symptomatic testing

At present, it is unclear whether the current interest in pre-natal testing for monogenic disorders will eventually apply also to autism and related complex disorders. Obviously, the potential to test for the presence of a high-risk genotype could significantly influence genetic counselling to affected families. Nevertheless, the complex gene interactions that are suspected to underlie autism suggest that testing is unlikely to be a straightforward issue. In particular, the apparent non-deterministic nature of the genetic influences – as evidenced by the substantial degree of phenotypic variability – means that knowledge that an individual carries one or more of the susceptibility genes for autism might not strongly predict a particular outcome. Moreover, it is possible that susceptibility loci also contribute to traits that are beneficial – for instance, elevated IQ or single-mindedness.

There might be genetic variants of autism for which testing could be viewed as potentially more useful. That situation might arise if a particular genetic predisposition was strongly associated with a severely disabling disorder, a particular disease course, or the development of complications such as epilepsy. Genetic knowledge might then predict the need for particular environmental, behavioural or medical interventions.

The outstanding questions

- In what proportion of cases are the current most promising susceptibility loci implicated?
- Are genes affected by cytogenetic rearrangements also implicated in idiopathic cases?
- Will knowledge of the function of the first cloned gene aid in the identification of other susceptibility loci?
- How do environmental or random factors influence gene expression?
- How will identification of susceptibility genes improve treatment?

Management

Presently, there are no specific drug therapies for autism, and the mainstay of management is appropriate educational provision and behavioural intervention. Although particular symptoms, such as repetitive behaviours, can be ameliorated somewhat by pharmacotherapy, the core social difficulties seem relatively unresponsive to medication. Current drug therapies rely on altering neurotransmission without understanding the underlying neurophysiological abnormalities. With increased knowledge of the function of susceptibility genes, it might be possible to develop specific drug therapies using animal models. Improvements in our neurophysiological understanding might also offer insights into minimizing the developmental regression that affects perhaps a third of children, usually in the second year of life, and could perhaps also be relevant to prevention of, or more effective treatments for, epilepsy. An increased understanding of abnormal brain function is also likely to influence the development of new psycho logical treatments. Finally, in the longer term, there is the exciting possibility that molecular genetic insights will help to identify mechanisms that influence phenotypic outcome, possibly very early in development.

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