The genetics of neurodevelopmental disease

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The term neurodevelopmental disorder encompasses a wide range of diseases, including recognizably distinct syndromes known to be caused by very rare mutations in specific genes or chromosomal loci, and also much more common disorders such as schizophrenia, autism spectrum disorders, and idiopathic epilepsy and mental retardation.After decades of frustration, the past couple of years have suddenly seen tremendous progress in unravelling the genetics of these common disorders. These findings have led to a paradigm shift in our conception of the genetic architecture of common neurodevelopmental disease, highlighting the importance of individual, rare mutations and overlapping genetic aetiology of various disorders. They have also converged on specific neurodevelopmental pathways, providing insights into pathogenic mechanisms.

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Introduction

A lot can go wrong in the development of a human brain. The staggeringly complex circuitry that constitutes the substrate of the mind requires an equally complex network of genes to orchestrate its self-assembly. Mutations affecting any of a wide range of cellular processes can lead to altered neurodevelopment and result in neurological or psychiatric disease. In some cases, the effects are quite specific, as in the link between mutations in genes controlling asymmetric cell division and microcephaly [1], in genes affecting the guidance of specific axonal tracts which lead to very distinctive neurological syndromes [2] or in genes controlling cell migration which underlie various cortical malformations [3].

Many neurodevelopmental mutations, however, result in a diffuse and variable presentation of psychiatric or neurological symptoms, which by themselves are not sufficiently specific to recognise a distinct aetiology. Individual disorders are often diagnosed instead on the basis of additional characteristic phenotypes, such as typical facial morphology (e.g. Down syndrome or Williams syndrome), somatic markers (e.g. neurofibromatosis and tuberous sclerosis) or diagnostic magnetic resonance imaging findings (e.g. for cortical malformations). More and more commonly, however, karyotypic or molecular genetic tests, such as those for Fragile X or Rett syndrome, are being used to directly determine the underlying cause and diagnose patients with a specific genetic syndrome. Depending on one's definition of neurodevelopmental, there are hundreds to thousands of such Mendelian syndromes, each very rare.

The term neurodevelopmental disorder is also used to refer to disorders that are really quite common in the population, however, including schizophrenia (SZ, ~1%), autism spectrum disorders (ASD, nearly 1%), epilepsy (~0.85%) and mental retardation (or intellectual disability, ~2%). After decades off rustration, the past couple of years have suddenly seen tremendous progress in unravelling the genetics of these disorders. This review will focus on these recent findings and their implications for the genetic architecture and pathogenic mechanisms of common neurodevelopmental disorders.

The genetic architecture of common neurodevelopmental disorders

Although research into epilepsy and mental retardation has mainly proceeded on the model of genetic heterogeneity and has been very successful in defining rare genetic syndromes, research into psychiatric disorders largely took a different route. Despite seminal findings of very rare mutations predisposing individually to SZ (e.g. DISC1 [4]) or ASD (e.g. NLGNs [5]), these fields largely turned to a common disease/common variant (CD/CV) model where disease is thought to be caused by the inheritance in any individual of a combination of a large number of common variants. The reasons for the rejection of heterogeneous Mendelian inheritance in the case of SZ have been discussed elsewhere and can now be seen to have been based on unfounded assumptions ([6•], but see [7] for a conflicting analysis).

The CD/CV hypothesis was the foundation of genome-wide association studies (GWAS), the idea being that if common variants predispose to illness, even only in combination with other alleles, this should be detectable as an increase in allele frequency in disease cases versus controls, ifl arge enough numbers are compared. Such studies have now been completed, with many thousands

of subjects, and the primary conclusion is stark: there are no common variants that confer even a modest (> 1.2-fold) statistical increase in risk of SZ [8,9••,10,11], ASD [12,13] or epilepsy [14•].

On the other hand, a wealth of individual, rare mutations have recently been identified that predispose to ASD, SZ, epilepsy, mental retardation and other disorders. This has been made possible by the development of array-based technologies for comparative genomic hybridisation [15] that can detect deletions and duplications of chromosomal segments, or copy number variants (CNVs). Two seminal papers by Jonathan Sebat and colleagues found that CNVs, especially those affecting genes involved in neurodevelopment, are enriched among patients with ASD [16] or SZ [17••]. The realization that CNVs could also be detected through the analysis of genome-wide SNP data quickly led to the mining of GWAS datasets for this kind of mutation, providing additional support for the involvement of such mutations in common neurodevelopmental disorders [18,19,20••,21,22], including ADHD [23•], mental retardation [24•,25•] and epilepsy [26•,27•].

These findings demonstrate that common disorders can be caused by rare and recent (often de novo) mutations of large effect, which are likely rapidly selected against [28•]. CNVs of course are just the most readily detectable class of mutation and analyses in other Mendelian disorders show that they typically constitute only 10 15% of pathogenic mutations. Consistent with this, sequencing of individual genes has also revealed a large number of rare or private point mutations likely to be causal or strongly contributing to disease [29,30,31•,32•,33]. It should also be emphasized that while the association of de novo CNVs with disease implies dominant effects, recessive causes of these disorders are also common they have, however, with some exceptions (e.g. [34••]), been less amenable to the discovery of specific loci.

Overlapping genetic aetiology

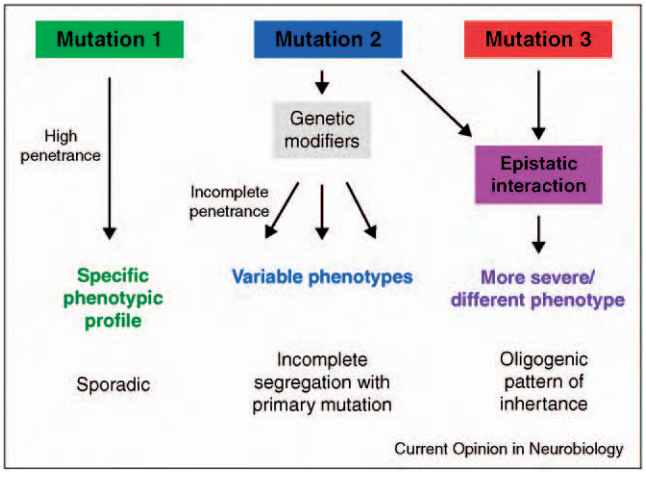
One of the surprises from this research has been the finding that many of the more common, recurrent CNVs and a number of single-gene mutations predispose not to one specific 'disorder' or diagnostic category, but to many [35,36•,37••,38]. This suggests a fundamental aetiological overlap between what have largely been defined clinically as distinct disorders. This conclusion is in agreement with the recognized fluidity of diagnoses in individual patients over time and is also supported by large-scale epidemiological studies which have shown individual and familial comorbidity between SZ, ASD, epilepsy, bipolar disorder, major depression, ADHD and other psychiatric diagnoses (e.g. [39,40,41•]). Thus, while an individual's risk of SZ is increased 10-fold if they have a sibling with SZ, their risk of bipolar disorder or autism or epilepsy is characterised by incomplete penetrance for particular disorders and variable expressivity.

From genotype to phenotype

The sources of phenotypic variability include both additional genetic and non-genetic factors. Non-genetic factors must play important roles in the ultimate expression of many phenotypes, as demonstrated by the fact that concordance rates for monozygotic twins for any of these disorders are substantially below one hundred percent. Phenotypic expression may be strongly affected by various environmental factors, second 'hits', such as head injuries or febrile seizures in the development of epilepsy, psychosocial stressors or other experiential factors. However, there is also likely a crucial contribution from intrinsic, stochastic developmental variation, which is evident in normal development and increased when the system is perturbed by mutation. Distinct phenotypic states may thus result as the end-points of divergent developmental trajectories [42].

Genetic context is also expected to have a large influence on the expression of phenotypes associated with a

Figure 1



Genetic heterogeneity in neurodevelopmental disorders. Several types of mutation are shown. Mutation 1 is of high penetrance and predisposes strongly to a particular profile of symptoms (e.g. trisomy 21). Such mutations will tend to arise de novo in sporadic cases, due to their serious effects on reproductive fitness. Mutation 2 is of lower penetrance and variable expressivity and its effects are modified by the presence of additional variants in the genetic background. Mutation 2 could still be considered the primary causative mutation, in the sense that without it, the patient would not be expected to show psychiatric or neurological symptoms (e.g. DISC1 translocation). The modifier loci, which could include common variants (most obviously the Y chromosome), would not cause disease in the absence of some such primary mutation. In the third case, Mutation 2 and Mutation 3 are present in the same individual and show strong epistatic interactions. Either mutation may be capable of causing some set of symptoms alone but the combined effect may be more severe or qualitatively different (e.g. multiple recurrent CNVs). This situation would lead to a more

Table 1

Synaptic genes recently implicated in common neurodevelopmental disorders. Genes are included if their products are localized to the synapse, if mutations have been seen in multiple cases, either within or across disorders, or mutations have been seen in multiple members of a gene family or in genes encoded interacting proteins, and if the gene is not already associated with a defined syndrome. Mutations in many additional genes with other functions are not included nor are CNVs where the effect has not been localized to a specific gene. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; BD, bipolar disorder; DD, developmental delay; E, epilepsy; MD, major depression; MR, mental retardation; OCD, obsessive compulsive disorder; SZ, schizophrenia; TS, Gilles de la Tourette's syndrome

Gene	Location	Associated phenotypes	Nature of mutation(s)	Protein Aliases	Protein function	Protein interactions	References
APBA2	15q13.1	ASD, SZ	CNVs	Mint2	Synaptic adaptor protein	NRXNs	[9••,18,37 ••,56]
ASTN2	9q33.1	ASD, SZ	CNVs		Neural recognition molecule		[9••,57][a]
CNTN3	3p12.3	ASD	Homozygous deletion	BIG 1	Axon guidance, synapse formation	CNTNAPs, PTPRG	[34••]
CNTN4	3p26.3	ASD, DD	CNVs, translocation	BIG 2	Axon guidance, synapse formation	CNTNAPs	[57][a]
CNTN5	11q22.1	SZ	CNVs	NB 2	Axon guidance, synapse formation	CNTNAPs	[51]
CNTNAP2	7q35	ADHD, ASD, E, OCD, SZ, TS	CNVs, point mutations	Caspr2, Nrxn4	NRXN family member	CNTNs, ADAM22, synaptic scaffolding proteins	[18,23 •,27 •,30,35][a]
CNTNAP4	16q23.1	E	CNV	Caspr4	NRXN family member	CNTNs	[27•]
CNTNAP5	2q14.3	ASD	CNV	Caspr5	NRXN family member	CNTNs	[58]
CYFIP1	15q11.2	ASD, E, SZ,	CNVs, small deletions		Activity dependent translation	FMR1	[9••,18,19,21,27 •][a]
DISC1	1q42.2	ASD, BD, MD, SZ	Translocation, point mutations, CNVs		Multiple, including synapse development	NDE1, PDE4B, many others	[4,29]
DLG1	3q29	ASD, MR, SZ	CNVs	PSD93	Synaptic scaffolding	Many synaptic proteins	[17••,18][a]
DLG2	11q14.1	ASD, SZ	CNVs	PSD95	Synaptic scaffolding	Many synaptic proteins	[17••,18,22][a]
DLGAP2	8p23.3	ASD, MR, SZ	CNVs		Synaptic organisation	DLG proteins	[20••,37 ••,49 ••]
ERBB4	2q34	SZ	CNVs		Cell migration, inhibitory synapse formation	NRG1	[17••], unpublished data
LRFN5	14q21.1	ASD, DD, SZ	CNVs, translocation	SALM5	Synapse formation	PSD95, RTN3	[47][a]
NDE1	16p13.11	ASD, E, MR, SZ	CNVs, small deletions		Cell migration, synaptically localised	DISC1, LIS1	[9••,18,21,25 •,27 •][a]
NLGN1	3p26.31	ASD	CNVs		Excitatory synapse formation	NRXNs, SHANKs	[57]
NLGN3	Xq13.1	ASD	Point mutations		Inhibitory synapse formation	NRXNs, SHANKs	[5]
NLGN4X	Xp22.31	ASD, MR, TS	CNVs, Point mutations		Synapse formation	NRXNs, SHANKs	[5,20 ••][a]
NRXN1	2p16.3	ASD, SZ, TS	CNVs, point mutations		Synapse formation	NLGNs, LRRTMs	[18,36 •,37 ••,56,57][a]
PCDH9	13q21.32	ASD	CNV		Synapse formation		[20••]
PCDH10	4q28.3	ASD	Homozygous deletion		Synapse formation		[34••]
PCDH19	Xq22.1	E, MR, ASD, SZ	CNVs, point mutations		Synapse formation		[49••][a]
SHANK2	11q13.4	ASD, MR	CNVs, point mutations		Synaptic scaffolding	NLGNs, Homer	[32•,49 ••]
SHANK3	22q13.3	ASD, SZ	CNVs, point mutations		Synaptic scaffolding	NLGNs, Homer	[20••,31 •,37 ••][a]
SLITRK1	13q31.1	OCD, TS	Inversion, point mutations		Synapse formation	14 3 3 proteins	[59][a]
SLITRK2	Xq27.3	SZ	Point mutations		Synapse formation		[33]
SLITRK6	13q31.1	E	CNVs		Synapse formation		[27•]
SYNGAP1	6p21.3	ASD, MR	CNVs, point mutations		Synaptic RasGAP		[49••][a]
TSPAN7	Xp11.4	ASD, MR, SZ	CNVs, point mutations		Synapse formation	Integrins	[20••,33,37 ••][a]
UBE3A	15q11.2	ASD, E, SZ, Angelman syndrome	CNVs, point mutations		Ubiquitination, activity dependent synapse development	Arc, many others	[18,19,21,46,57]

[a] Not all supporting references could be included.

particular mutation. It is certainly the norm for all phenotypes in animal models to show large modifying effects of genetic background and epistatic interactions which can be complex and unpredictable [43•]. Such effects are also typical of even the most classically defined 'Mendelian' disorders, such as cystic fibrosis and retinitis pigmentosa [44]. Figure 1 illustrates a number of scenarios for how such genetic interactions may be manifested and how they will affect patterns off amilial inheritance.

Segregation within families may often be imperfect, even in cases where there is strong statistical support from population studies that an individual recurrent mutation is associated with risk of a disorder. First, not all carriers of the mutation will have a particular disorder (this is expected under incomplete penetrance/variable expressivity). Second, and quite unexpectedly, the presumed pathogenic variant may be absent from some affected individuals in the family [37••,45•,46,47]. This suggests that there are at least two independently segregating mutations in some families and raises the possibility that they may interact.

One recent study directly illustrates this kind of effect. Evan Eichler and colleagues found numerous instances of a microdeletion at 16p12.1 in a large cohort of patients with developmental delay/intellectual disability with congenital malformation [48••]. They also found a strong enrichment for the presence of some second-site CNV among 16p12.1-carriers in this cohort. Those individuals with a second 'hit' showed a more severe phenotype and in cases where the second CNV was associated with a known syndrome, these patients showed distinct phenotypic features. In cases where the 16p12.1 deletion was inherited, retrospective analysis of the carrier parent identified high rates ofl earning disabilities, psychiatric diagnoses and seizures, demonstrating a wider range of phenotypic expression than in the screening cohort. Patients carrying other recurrent, inherited CNVs also showed enrichment for a second hit. Similar observations have been made in autism [49••] and epilepsy [27•]. Thus in many cases, inheritance of these disorders, like most Mendelian disorders, may be effectively oligogenic.

Convergence on neurodevelopmental pathways

Perhaps the most striking finding from recent genetic studies has been the convergence on genes involved in neurodevelopment [17••,23•,27•,33,37••,49••,50,51], particularly in aspects of synaptogenesis. A partial list of such 'synaptic' genes with mutations found in disease cases is given in Table 1 . These include a greater-than-expected number of mutations affecting multiple members of particular gene families (e.g. CNTN, CNTNAP, DLG, NLGN, SHANK, and SLITRK), or genes whose protein products directly interact or perform related functions (NRXN1 NLGNs SHANKs ; DISC1 NDE1 ; NRG1 ERBB4). Deep sequencing of several of these genes in cases (including CNTNAP2 , DISC1 , SHANK2 and SHANK3) has identified additional point mutations, further strengthening the case for their pathogenicity [29,30,31•,32•].

This is not to imply by any means that all the genes identified have roles in synaptic processes mutations in a huge number of other genes with diverse cellular functions can cause neurodevelopmental disease. Nor is altered synaptic development the only cause of pathogenic disruptions in neuronal networks epilepsy can, for example, also arise due to defects in ion channels or in cell migration during cortical or hippocampal morphogenesis. Nevertheless, disruptions in synaptic processes certainly seem to be one common route by which neurodevelopment can be compromised in a way that can lead to psychiatric disturbances.

We are now in the remarkable position of having gone, in the space ofj ust two or three years, from having identified only a handful ofl oci with causative mutations for these common conditions to a list that is too long to usefully publish in toto Modelling these mutations in animals is beginning to provide insights into pathogenic mechanisms (e.g. [52,53••,54••]) and to suggest points of phenotypic convergence across different mutations.

The future is now

The arrival of affordable whole-genome sequencing now promises to reveal the full spectrum of mutations associated with these diseases and to further delineate the relevant molecular pathways. As well as a 'forward genetic' approach based on sequencing cases, it will be equally important to do 'reverse genetics' to define the range of possible phenotypes that can arise when gene X is mutated. This will be most readily achieved in family studies where all mutation-carriers can be identified and phenotyped, regardless of clinical status. Obtaining evidence that any particular mutation is causative will thus depend on careful phenotyping and the definition of what it is one thinks it is causing.

Many traditional diagnostic categories evidently represent umbrella terms for collections of genetically heterogenous syndromes, which will likely be increasingly defined by genetic lesion (e.g. [24•,55•]). For clinical geneticists, knowledge of the genetic aetiology in each case may provide meaningful distinctions in genetic risk of great importance to individuals and their families. The ultimate hope is to use genetic discoveries to learn enough about the underlying neurobiology to generate novel and patient-specific therapeutic approaches for these common and devastating disorders.

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