Annual Research Review: Impact of advances in genetics in understanding developmental psychopathology

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It was hoped that diagnostic guidelines for, and treatment of, child psychiatric disorders in DSM-5 would be informed by the wealth of clinical genetic research related to neurodevelopmental disorders. In spite of remarkable advances in genetic technology, this has not been the case. Candidate gene, genome-wide association, and rare copy number variant (CNV) studies have been carried out for attention-deficit/hyperactivity disorder (ADHD), Autism, Tourette's Syndrome, and schizophrenia, with intriguing results, but environmental factors, incomplete penetrance, pleiotropy, and genetic heterogeneity, underlying any given phenotype have limited clinical translation. One promising approach may be the use of developmental brain imaging measures as more relevant phenotypes. This is particularly important, as subtle abnormalities in timing and expression of gene pathways underlying brain development may well link these disorders and be the ultimate target of treatments. Keywords: Developmental psychopathology, genetics, copy number variants, pre-natal diagnosis, nosology, prevention.

Introduction
Genetic technology is advancing so quickly that this review will probably be outdated before it goes to press. There have been impressive advances in our broader understanding of the genetics of psychiatric disorders, with potential for treatment, and ultimately prevention (Geschwind, 2011), but the relevance for diagnosis of childhood onset disorders remains unclear. This special issue on Nosology in Developmental Psychopathology provides a welcome opportunity to review the clinical impact of genetic studies with prediction for the future. The focus of this review is the implications of genetic research for the practice of child psychiatry generally, but we illustrate historic issues and current research trends across an array of disorders.

Advances in genetic technology have certainly had an impact upon research! As reviewed in this Journal in 2009 (Plomin & Davis, 2009), papers on the genetics of developmental psychopathology have been increasing exponentially. The number of publications have paralleled methodological advances from linkage to genome-wide association studies (GWAS) and copy number variants (CNVs) with whole genome sequencing (Roach et al., 2010) and stem cell studies (Marchetto, Winner, & Gage, 2010) now being carried out.

For this special issue on nosology, we restrict ourselves to the current impact on understanding diagnosis, treatment, and/or prevention of childhood onset disorders. Several lines of evidence make this question of great interest. It is increasingly accepted that subtle disturbances of brain development underlie the pathology of many mental disorders in adults as well as in children (Lewis & Levitt, 2002; Rapoport, Addington, Frangou, & Psych, 2005). It is hoped and predicted that advances in developmental brain imaging will provide intermediate phenotypes for genetic studies (Pine, Ernst, & Leibenluft, 2010). In addition, the dramatic advances in cytogenetic/genomic array-based diagnosis is of particular interest for developmental disorders, as most molecular-based brain morphological abnormalities are manifested in childhood (Epstein, Erickson, & Wynshaw-Boris, 2004).

Nosology is crucial for clinical practice. While there are no genetic guidelines planned for DSM-5, genetic findings have implications for diagnosis and treatment, or even prevention, that are of potential clinical interest. Given the challenges in psychiatry to identify measurable laboratory tests to diagnose disorders as in other branches of medicine, one anticipated outcome from the multitude of genetics studies has been that we would elucidate more genetically homogeneous subtypes of our current diagnostic categories. As we will demonstrate throughout this review, with a few rare exceptions, this is not yet the case.

Family, twin, and adoption studies have documented high heritability of several major childhood psychiatric disorders (Gupta & State, 2007; Lombraso, Pauls, & Leckman, 1994; Thapar, O'Donovan, & Owen, 2005). Nonetheless, genome-wide association studies, which examine the association between a particular allele and a diagnosis or trait within a population, have indicated that most common disorders (psychiatric and nonpsychiatric) are complex,

Conflict of interest statement: No conflicts declared.
involving large numbers of genes, each of small effect (Ku, Loy, Pawitan, & Chia, 2010; Risch & Merikangas, 1996). Given the high phenotypic variability associated with the best candidate genes in psychiatry (Wallace et al., 2010), such as disrupted in schizophrenia-1 (DISC1; Millar et al., 2000) and MECP2 (Zoghbi, 2003), or the best established CNVs, for example 22q11 deletions (Green et al., 2009), and the importance of environmental exposures (Hallmayer et al., 2011), our field has little reason to expect phenotypic specificity from a particular genetic variant. This is illustrated in Figure 1.

**Historic perspective**

Cytogenetic findings with respect to chromosomal imbalance such as trisomy 21 (Lejeune, Turpin, & Gautier, 1959) led to optimism regarding the genetics of specific behavioral syndromes (Skuse & Seigal, 2008). Utilization of classic cytogenetic techniques, such as high resolution G-banded karyotyping developed in the 1970s (Yunis et al., 1978), led to the identification of many microdeletion syndromes such as 15q11-q13 deletions responsible for Prader-Willi (Butler, Meaney, & Palmer, 1986), 17p11.2 deletions associated with Smith-Magenis (Smith et al., 1986), and 22q11 deletions causing DiGeorge and velocardiofacial syndromes (Greenberg, Elder, Haffner, Northrup, & Ledbetter, 1988). Over the next decade, continued efforts led to identification of genetic causes for Charcot-Marie Tooth and Angelman syndromes, among others (Mefford & Eichler, 2009). Also, fueling this optimism was the ability to detect single genes with strong causal influence on a variety of neurodevelopmental disorders such as Lesch-Nyhan syndrome, Tuberous Sclerosis, or Neurofibromatosis (Hebebrand, Scherag, Schimmelmann, & Hinney, 2010). Nonetheless, researchers are yet to definitively identify a causal variant for any of the more common, non-Mendelian psychiatric disorders.

Historically, linkage studies of psychiatric illnesses have had limited success in identifying risk genes, with a few exceptions such as NRG1 and DTNBP1 in schizophrenia (Stefansson et al., 2002; Straub et al., 2002). Recently, GWAS studies have had some success in identifying common single-nucleotide-polymorphisms (SNPs) that have small effects on risk, but heterogeneity is a major limitation for GWAS. In spite of evidence that attention-deficit/hyperactivity disorder (ADHD) is highly heritable, a meta-analysis of genome-wide association studies found no significant genome-wide associations, suggesting that the effects of common risk variants are very small (Neale et al., 2010). In contrast, linkage studies can detect a signal in a particular region that may be derived from many kinds of susceptibility variants including common SNPs, multiple rare variants, or CNVs which may occur in one or more genes in a region. A recent meta-analysis of 32 linkage studies, including 3255 pedigrees with schizophrenia and related disorders revealed suggestive evidence for linkage on 2q, 5q, and 8p (Ng et al., 2009). These regions had all been implicated previously (Lewis et al., 2003). Of note, one region that did not emerge from this analysis was the major histocompatibility complex (MHC) region on chromosome 6, which was highlighted in a series of recent GWAS studies (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009).

![Figure 1](https://example.com/image1.png) Neupropsychiatric phenotypes associated with copy number variations (CNVs). Reprinted with permission from the American Journal of Psychiatry (Copyright © 2010), American Psychiatric Association.
Disrupted in schizophrenia-1 is one of several schizophrenia risk genes (albeit with variable phenotype within the families) of current intense research interest because of its importance in brain development (Jaaro-Peled et al., 2009). *DISC1* contains two common nonsynonymous (i.e. changes amino acid) SNPs -Leu607Phe and Ser704Cys – that modulate facets of *DISC1* molecular functioning important for cortical development, fronto-temporal cortical anatomy in adults, as well as risk for diverse psychiatric phenotypes that often emerge during childhood and adolescence.

One promising approach may be the use of developmental brain imaging measures as more relevant phenotypes (Pine et al., 2010). In a recent study, Raznahan et al. (Raznahan et al., 2010) related *DISC1* genotype at Leu607Phe and Ser704Cys to cortical thickness (CT) in a large sample of healthy children and adolescents, aged 9–22, on whom magnetic resonance imaging brain scans had been acquired longitudinally. Rate of cortical thinning varied with *DISC1* genotype. Specifically, the rate of cortical thinning was attenuated in Phe-Carrier compared with Leu-Homozygous groups (in bilateral superior frontal and left angular gyri) and accelerated in Ser-Homozygous compared with Cys-Carrier groups (in left anterior cingulate and temporal cortices). Both SNPs additively predicted fixed differences in right lateral temporal cortex, which were maximal between Phe-Carrier/Ser-Homozygous (thinnest) versus Leu-Homozygous/Cys-Carrier (thickest) groups. These findings suggest that these SNPs influence risk for diverse phenotypes, in concert with other genetic and environmental factors, by impacting on the early maturation of fronto-temporal cortices and support a theme that subtle variations in structural and functional brain development will provide a frame for integrating diverse genetic findings.

Childhood onset disorders are not only caused in part by many genes of small effect but also, based on studies of schizophrenia and bipolar disorder, it is likely that a large proportion of the heritable risk is due to the interaction or combinations of hundreds or thousands of common variants, none of which contributes an individually measurable effect to risk (Craddock et al., 2008; Purcell et al., 2009). To date, there are few genes that have been replicated using linkage or GWAS for autism spectrum disorder, ADHD, or nonsyndromal mental retardation.

There is building evidence that some alleles are shared across psychiatric disorders (e.g., schizophrenia and bipolar disorder), and that there may be some very broad specificity for common alleles with respect to general disease category (e.g., psychiatric-nonpsychiatric); (Purcell et al., 2009; Williams et al., 2010). The small effect size of common alleles, and the prior probability that any chosen candidate gene or allele will be associated with a given phenotype is extremely low, and results with existing genome-wide techniques have been weak or inconsistent for other child psychiatric disorders such as obsessive-compulsive disorder and tourette syndrome (Gradon, 2010), as well as autism (State, 2010).

**Copy number variants**

Rapid advances in molecular genetic technology, particularly in DNA microarray technology, have greatly enhanced our ability to detect submicroscopic copy number variations (Beaudet & Belmont, 2008). These technologies, coupled with the dramatic decline in cost for running microarrays, have lead to a flurry of reports describing novel genomic syndromes over the past several years. CNVs are typically defined as a DNA segment of at least 1 kb in size, for which copy number differences have been observed in the comparison of two or more genomes. In addition to the somewhat surprising findings that many healthy individuals carry large segments of DNA that are either missing a copy or have gained an extra copy (Iafrate et al., 2004; Sebat et al., 2004), many specific regions have now clearly been associated with several neurodevelopmental phenotypes. There has been increasing interest in the rare variant (CNV) approach in child psychiatry.

The overlap across broad diagnostic categories, inheritance from a healthy relative (phenotypic heterogeneity/incomplete penetrance), and the convergence of multiple genetic etiologies on some basic syndromes (genetic heterogeneity) provide major insights about the biology of mental illness. Reports from multiple investigators of recurrent microdeletion of 16p11.2 in up to 1% of autistic patients (Weiss et al., 2008) has now been extended to include individuals with intellectual deficiency, language disorder, and schizophrenia (Mefford & Eichler, 2009). Intriguingly, while both duplications and deletions at 16p11 occur within autism (Weiss et al., 2008), duplications are more selectively associated with schizophrenia with differing associated head size/brain imaging measures (Mccarthy et al., 2009). The best known CNV in psychiatry, which confers a very high risk for psychopathology, is the deletion at 22q11 that has now been associated with language delay, psychosis, bipolar disorder, autism, and obsessive-compulsive disorder (OCD; Green et al., 2009).

Several studies indicate some shared susceptibility genes across schizophrenia and bipolar disorder (Moskvina et al., 2009; O'Donovan et al., 2008a; Purcell et al., 2009), although this does not appear to carry over for CNVs (Grozeva et al., 2007). An increased rate of rare de novo CNVs observed in autism and schizophrenia has been reported (Sebat et al., 2007; Stone et al., 2008; Xu et al., 2008), although other reports indicate that rare CNVs are often inherited from a healthy parent and therefore represent a partial risk rather than a highly penetrant etiologic factor (Walsh et al., 2008; Weiss et al., 2011).
Impact of advances in genetics

Future technologies E.G. whole genome sequencing and induced pluripotent stem cells

A myriad of new technologies will undoubtedly reveal many more novel rare syndromic disorders, particularly as the resolution and accuracy improves as the reality of whole genome sequencing becomes more typical. The association of the same rare CNVs with autism and schizophrenia is even more clear (Rapoport, Chavez, Greenstein, Addington, & Gogtay, 2009), as well as with epilepsy and mental retardation (O’Donovan, Kirov, & Owen, 2008b), possibly autism and Selective Mutism (State, 2011) leads to further erosion of phenotypic specificity in psychiatric genetics. We are left with the still vague model that any particular clinical diagnosis is determined by other yet to be discovered genetic, epigenetic, and environmental modifiers.

Identification of intermediate phenotypes closer to the biologic action of the genes would be extremely useful. Both childhood onset schizophrenia and autism have been shown to have abnormal brain development with premature increase in brain size for autism and premature cortical ‘pruning’ for schizophrenia (Rapoport et al., 2009), leading to a model that the underlying phenotype may involve dysregulation of genes affecting the timing rather than the pattern of cortical development. Crespi and others also have modeled the overlap between autism and schizophrenia (Crespi, Stead, & Elliot, 2010; McCarthy et al., 2009), which suggests that timing and/or pattern of early brain development should be explored in genetics studies.

Prenatal diagnosis – prevention

With the introduction of array comparative genomic hybridization (CGH) and SNP microarrays, diagnostic testing is readily available. Remarkably, the focus has shifted such that both phenotype-first and genotype-first approaches are in wide use. These techniques allow for broad screening of patient populations that largely (though not completely) replace classic cytogenetic testing. This has major implications for both prenatal screening and diagnostic testing. There is already change in the timing of risk assessment at some clinical sites.

While the risk of any one neurodevelopmental disorder will be very small, large scale population-based studies that ascertain subjects across a wide range of phenotypes will provide better information about the prediction of risk for developing any undesirable pathology from a given chromosomal anomaly. To date, the most compelling abnormality warranting genetic counseling is the 22q11 deletion, for which there is a high likelihood (albeit nonspecific) of developmental pathology. Any genetic testing will be controversial, either because of lack of sufficient scientific basis for clinical usefulness (Mitchell et al., 2010) or because of more general ethical concerns (Munger, Gill, Ormond, & Kirschner, 2007), and will remain a very personal decision.

Treatment

Pharmacogenetics studies investigate genetic associations of drug response, and there are some clear examples of success in all of medicine (Feero, Guttmacher, & Collins, 2010). While there have been a variety of studies relating risk genes to response to stimulant drugs (Polanczyk et al., 2005), these have had little practical relevance, but may be useful in understanding the physiologic response to stimulants. Other predictive studies in pediatric psycho-
pharmacology have not been realized and remain impractical.

In the 1960s, the basic laboratory work by Seymour Kaufman on phenylketonuria (PKU), a metabolic disorder that can lead to progressive mental retardation, brain damage, and seizures if left untreated, led to a preventive dietary treatment consisting of restricted phenylalanine intake, particularly during infancy and childhood (Friedman, Kaufman, & Kang, 1972; Kaufman, 1983; Kaufman et al., 1978). Since that time, no understanding of the mechanisms of syndromic neurodevelopmental disorders has led to prevention or successful symptom reversal. Nevertheless, the steady discovery of monogenic disorders and the resulting creation of mouse models for these disorders have led to treatment research in some syndromal childhood onset conditions. The best illustrations would be the ongoing treatment research in Fragile X syndrome (FXS).

Mutations in the FMR1 (fragile X mental retardation) gene can cause a variety of disabilities, including cognitive deficits, attention-deficit/hyperactivity disorder, autism, and other socio-emotional problems. In addition, individuals with the full mutation form distinct difficulties, including primary ovarian insufficiency, neuropathy, and the fragile X-associated tremor/ataxia syndrome (which is also sometimes seen in older premutation carriers). The cause of FXS is decreased or absent levels of fragile X mental retardation protein (FMRP) that are typically caused by full mutation (>200 CGG repeats) of FMR1 gene. Therefore, multigenerational family involvement is commonly encountered when a proband is identified with a FMR1 mutation.

Fragile X mental retardation proteins is a RNA binding protein that modulates dendritic maturation and synaptic plasticity through the inhibition of group 1 mGluR-mediated dendritic protein synthesis (Bagni & Greenough, 2005). Studies of metabotropic glutamate receptor 5 (mGluR5) pathway antagonists in multiple animal models of FXS have demonstrated benefits in reducing seizures, improving behavior, and enhancing cognition and correction of plasticity phenotypes. While most of the work is currently focusing on mGluR5, which is expressed most highly in the hippocampus, neocortex, and striatum, some work is also ongoing with mGluR1 which is expressed primarily in the cerebellum. The work in rodents showed a role for mGluR5 in regulating inhibitory and excitatory balance with anticonvulsant properties of mGluR5 antagonists. Human FXS patients have cognitive impairment, and often seizure disorder (Bear, 2005).

The ‘mGluR Theory’ of FXS is now being tested directly, and preclinical research suggests potential efficacy for anxiety, convulsions, pain, and migraine. Neuropsych Group plc recently reported results of a single dose trial with the selective mGluR5 antagonist, fenobam, in 12 subjects. Single doses of 150 mg were well tolerated with anecdotal reports of some efficacy (Berry-Kravis et al., 2009). As a result of pharmacologic problems, fenobam is not likely to be followed up for fragile X. However, phase II trials of novel mGluR5 antagonists are in progress for individuals with FXS (Berry-Kravis et al., 2009; Dolen, Carpenter, Ocaín, & Bear, 2010). While there are no detailed reports available yet, Novartis has just completed its phase II double blind trials (Harris, 2010), and Roche has recently initiated a similar trial with another novel mGluR5 agent. Lithium, also an indirect downregulator, or mGluR, was found helpful as an add-on treatment for 15 young males with FXS (Berry-Kravis et al., 2008). Finally, Seaside Therapeutics initiated a trial of a GABA-B receptor agonist (which inhibits glutamatergic signaling), but no data are available yet.

If any of these approaches prove to be clinically successful, it will be among the first useful clinical treatment applications of molecular genetics to child psychiatry. Based on the varied phenotype, however, even if successful, mGluR5 treatment is unlikely to narrow phenotypic definition.

Conclusions

In spite of the limitations that have been stressed throughout this review, there remains optimism about the ultimate application of molecular genetics for diagnosis and treatment of psychiatric disorders. No short-term application is anticipated. The path from gene discovery to treatment has been arduous, even for nonpsychiatric conditions such as cystic fibrosis. If risk can be calculated across disorders, the most immediate application of molecular genetics findings is the possibility of prevention of some disorders such as autism, intellectual disability, and very early onset schizophrenia, through prenatal genetic testing (Handyside, 2010). Clinical studies of each rare variant or point mutation site could provide additive benefit, reaching an overall level of possible prevention of up to 10% of nuclear autism when chip technology allows each individual syndrome screening to be carried out simultaneously (Miller et al., 2009; Shen et al., 2010). The low cost will permit a very large number of genomic regions to be queried (Lu et al., 2008; Van Den Veyver et al., 2009). Nonetheless, this is likely to remain a highly controversial area until these broader risk ratios are known and adequate genetic counseling can be implemented (Bassett, Scherer, & Brzustowicz, 2010).

Diagnostically, the data suggest that for the most part, phenotypic correlates will be very broad cutting across various neurodevelopmental, psychiatric and neurologic disorders. There is very great likelihood of a significantly impairing psychiatric disorder with a 22q11 deletion, for example, even though the risk of any one of five different disorders does not exceed
25%. Environmental effects have been underestimated (Hallmayer et al., 2011), and are also likely to be non-specific (Peen, Schoevers, Beekman, & Dekker, 2010).

There is a certain irony in the strong genetic link between autism and schizophrenia. Kanner originally thought that autism might be subsumed under schizophrenia (Kanner, 1943, 1962), but later changed his mind in light of reports by Rutter indicating that these were separate disorders (Rutter, 1972a,b). The now established genetic links between these diagnoses is of no immediate use to the practicing clinician. We, and others, have suggested that the field may eventually be unified by identification of abnormalities in timing or pattern of brain development at critical periods (Crespi et al.; Rapoport et al., 2009; Shaw et al., 2007; State, 2011). Current research on Huntington’s disorder shows abnormal brain developmental trajectories decades before onset of illness, suggesting patterns of early brain growth as targets for treatment development (Paulsen et al., 2010). As Bilguvar and others recently outlined, the advent of next generation sequencing together with evidence that mutations in a single gene or locus can effect divergent neurodevelopmental outcomes bring promise for future research (Bilguvar et al., 2010). For example, identification of a rare risk variant with varied developmental outcomes will allow studies of relatively small samples having considerable phenotypic heterogeneity.

Psychiatric nosology has been neither demeaned nor aided by progress in genetic research. Clinical descriptive diagnosis remains essential for clinical prediction and treatment. These genetic results ultimately may be useful in understanding broad underlying biologic risk, perhaps explaining diagnostic comorbidity, and even leading to conceptually new treatments targeting, for example, a more general normalization of brain development. The true role of molecular genetics in psychiatric (and other) disorders will be a major focus of health research for a long time to come.

Acknowledgements
This review article was invited by the journal, for which the principal author has been offered a small honorarium payment towards personal expenses.

This manuscript is based on material funded by the NIH.

The authors have declared that they have no competing or potential conflicts of interest.

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Key points
- The last two decades of genetic research neither denigrates nor informs DSM-5 Psychiatric Classification.
- Linkage and GWAS studies have diminished the optimism for genetic diagnosis of child psychiatric disorders.
- Studies of rare variants, particularly rare copy number variants have been more encouraging, but their rarity, varied penetrance, pleiotropy, as well as genetic and phenotypic heterogeneity of psychiatric syndromes limits the usefulness and understanding of these findings.
- There remains optimism that next generation sequencing, coupled with advances in measurement of brain development will enable greater in-depth long-term understanding of the genetic influence in psychiatric disorders.

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Accepted for publication: 13 September 2011
Published online: 8 November 2011