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Review

The Genetics of Child Psychiatric Disorders: Focus on Autism and Tourette Syndrome

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Investigations into the genetics of child psychiatric disorders have finally begun to shed light on molecular and cellular mechanisms of psychopathology. The first strains of success in this notoriously difficult area of inquiry are the result of an increasingly sophisticated appreciation of the allelic architecture of common neuropsychiatric and neurodevelopmental disorders, the consolidation of large patient cohorts now beginning to reach sufficient size to power reliable studies, the emergence of genomic tools enabling comprehensive investigations of rare as well as common genetic variation, and advances in developmental neuroscience that are fueling the rapid translation of genetic findings.

In many ways it is truly the best of times.

However, as excitement justifiably mounts that the field is finally gaining a scientific foothold, a survey of recent findings points to both continuing and emerging challenges. The early application of mature genomic technologies that are providing unequivocal, if not comprehensive, insights into the contribution of common variants to common medical conditions (Altshuler et al., 2008) have so far not revealed definitive findings in child psychiatry, reinforcing the conclusion that the genetics of these disorders are particularly difficult to decipher; current gene discovery efforts in a number of childhood and adult disorders are challenging the biological relevance of the psychiatric diagnostic nosology, and the ability to leverage advances in neuroscience promises to remain both a blessing and a curse: on the one hand, the contribution of neurobiological data to clarifying genetic findings and driving translational efforts is indispensible. At the same time, the lure of substituting biological plausibility for accepted standards of evidence in genetic or genomic analyses, coupled with the rapid accumulation of massive amounts of sequence and structural variation in affected individuals, risks a proliferation of extremely intriguing, but ultimately misguided, neurobiological narratives.

This review will aim to address both sides of the coin: the tremendous promise as well as the challenges facing child psychiatric genetics. The first three sections will address the changing conceptions of the allelic architecture of common disorders, the attendant emerging focus on rare variation in child psychiatry, and the causes and consequences of an increasing reliance on case control association methodology. The review will then turn to consider gene discovery efforts in two paradigmatic childhood disorders: autism and Tourette syndrome, focusing on recent finding, their roles in illuminating pathophysiological mechanisms, and the likely future of human genetic endeavors in these areas.

The Allelic Architecture of Child Psychiatric Disorders

Relatively early in the history of genetics of common child psychiatric disorders it became clear that writ large these did not obey simple Mendelian expectations. This consensus led to the ascendance of the ''common variant common disease hypothesis'' (CVCD) as the predominant paradigm in the field (Chakravarti, 1999; Reich and Lander, 2001; Risch and Merikangas, 1996): The expectation was that any given common allele (defined here as 5% or greater population frequency) would carry moderate effects and was likely to be neither necessary nor sufficient to lead to the clinical phenotype. Indeed the notion was that a combination of risk alleles would contribute to the emergence of pathological traits falling at the extremes of a population distribution. Consistent with this view is the notion that family members will tend to demonstrate subclinical manifestations of a phenotype of interest due to the presence of some, but not all, risk alleles and that one of the primary objectives of human genetic research would be to account for all or most of these common genetic risks shared by the population. The combination of the CVCD paradigm along with steadily increasing estimates of the number of genes anticipated to play a role in neuropsychiatric disorders led to the related conclusion that association methodologies, demonstrating that a particular common allele was overrepresented in the population of affected individuals, would be the most powerful and profitable avenue to gene discovery.

A convergence of the common variant paradigm with the technical feasibility of genotyping one or a small number of common alleles led to a plethora of candidate gene association analyses throughout the 1990s and into the early part of this century. Indeed for many years, the study of child psychiatric genetics was essentially synonymous with this approach. Unfortunately, the reliability of these studies proved to be poor (Hirschhorn et al., 2002; Lohmueller et al., 2003). To those outside the field, a steady stream of plausible but routinely contradictory findings began to cast doubt on the entire enterprise.

However, over the past few years, the emergence of highly reproducible associations from genome-wide association (GWAS) studies across a variety of medical fields has clarified many of the reasons for these difficulties (Altshuler et al., 2008; Manolio, 2010): first, the effect size of common alleles

contributing to common disorders is, by and large, much smaller than previously anticipated; second, the prior probability that any chosen candidate gene or allele will be associated with the phenotype of interest is extremely low, even given the most plausible biological hypotheses. This reality that has been underscored by the very small number of previously suspected loci that have been confirmed by unbiased genome wide analyses. Finally, the methodological confounds to association studies, particularly attending case control approaches, are more problematic than initially suspected.

With regard to this last point, several key issues are particularly relevant: for example, the degree to which subtle differences in ancestry among cases and controls, known as population stratification, could derail analyses was appreciated but the methods available initially to control for this confound were rudimentary and later found to be inadequate. The presumption that grouping by observable characteristics or self-reported ethnicity would be sufficient was incorrect. Fortunately, the large amount of variation now detected by genome-wide genotyping allows for precise matching of cases and controls. And while there remains some debate over how thoroughly even these methods can protect against this confound (McClellan and King, 2010), there is little question that the failure to address ancestry in a rigorous fashion contributed to the large number of nonreplicated studies. Similarly, candidate gene analyses often tended to underestimate the impact of pedestrian confounds such as genotyping error or batch effects.

These difficulties are of more than historical interest: a surprising number of studies continue to underestimate these issues; while the problem of population stratification is acknowledged (Tost et al., 2010), few "imaging genomic" studies, those aimed at investigating the relationship between genetic variation and functional or structural neuroimaging phenotypes, use methods that would be considered state-of-the-art within the genetics community to control for this, and even contemporary GWAS studies may still fall prey to cryptic technical artifacts (Sebastiani et al., 2010). Importantly, as will be discussed below, a key consideration for the future is that as many fields, including child psychiatry, increasingly employ case-control methods to study the contribution of rare alleles, similar liabilities must be anticipated in the analyses of both copy number variation and next generation sequencing data.

The Ascendance of Rare Variant Approaches in Child Psychiatry

Despite the clear numerical predominance of common variant studies in child psychiatry, rare variant approaches have a long history in the field and recent interest in these strategies has risen dramatically. This has been a consequence of an increasing recognition of the relevance of early rare variant findings, the development of CNV and next-generation sequencing platforms, and a consensus that GWAS studies have identified only a small proportion of the anticipate genetic risk for common disorders and that the "missing inheritance" may be accounted for in part by rare alleles (Goldstein, 2009; Manolio et al., 2009).

Before addressing specific findings in autism and Tourette syndrome, it is worthwhile to differentiate between two complementary but distinct approaches to conceptualizing rare variant analyses: i.e., "outlier" strategies versus methods based on a rare variant common disease (RVCD) hypothesis.

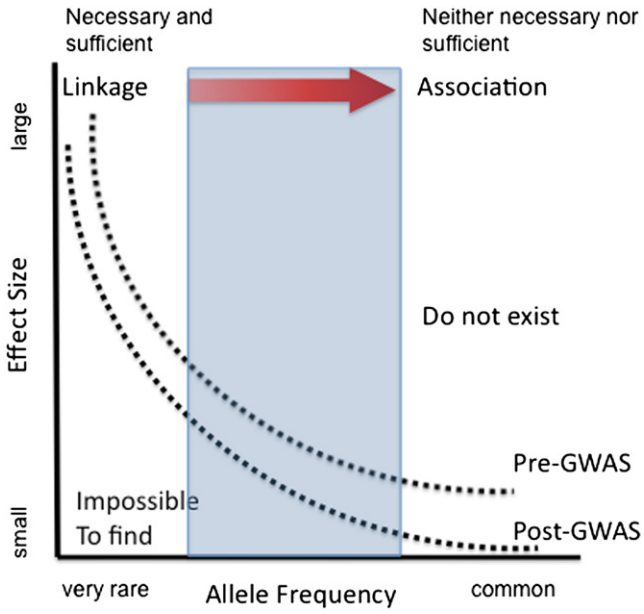

Figure 1. Relationship between Allele Frequency and Effect Size
The upper dotted curve shows the hypothesized relationship of allele frequency (x axis) to effect size (y axis), prior to genome-wide approaches to association, and the lower curve represents the shift resulting from data emerging from GWAS studies. The blue box highlights the likely contribution to ASD of low-frequency alleles carrying risks that are greater than those conferred by common alleles, but not of the scale identifed in rare Mendelian disorders. The red arrow at the top of the diagram represents the shift toward association approaches that is required to identify variants that are neither necessary nor sufficient for the emergence of a phenotype.

The rationale for outlier studies is that some, potentially very small, proportion of the allelic architecture for a complex disorder will be accounted for by low frequency variants of large effect, including Mendelian forms of a condition. This view is based on the notion that, particularly for early onset disorders, natural selection will tend to ensure a predictable, inverse relationship between allele frequency and effect size (Figure 1). This approach tends to disaggregate common phenotypes: disorders are not attacked writ large but with a focus on finding often extremely rare examples that promise to shed light on biological mechanisms relevant to more common examples of the phenotype. This emphasis poses an important contrast to at least the initial rationale for common variant studies by prioritizing traction with regard to pathophysiology over the effort to clarify population genetic risks.

This outlier approach is entirely consistent with but differs somewhat from studies based on a rare variant common disease (RVCD) hypothesis. Specifically, in contrast to the minimalist expectations regarding the role of rare variation in common disorders reflected in outlier studies and the tendency for these to focus on the extremes of a phenotypic spectrum, the RVCD paradigm posits specifically that rare variants will carry a significant portion, if not the majority, of population risk for a common disorder. This RVCD hypothesis has been recently pursued

through a growing number of CNV analyses and via deep sequencing studies of, for example, blood pressure regulation (Ji et al., 2008), cholesterol, and lipid metabolism (Cohen et al., 2004; Johansen et al., 2010) and autism (Bakkaloglu et al., 2008). With the advent of next generation sequencing, such studies promise to proliferate dramatically.

Already, these types of studies have engendered an important reevaluation of the manner in which rare variation may contribute to common disease: historically, rare variation has been synonymous with alleles of very large effect (Figure 1). Indeed, given the methods previously employed to detect rare disease alleles, most discoveries involved Mendelian inheritance, with the attendant demonstration that within the pedigrees being studied, the offending rare allele was necessary and largely sufficient to lead to the phenotype of interest. However, just as has been the case with common variants, recent studies suggest that rare alleles may be carrying smaller than anticipated effects without evidence of being necessary or sufficient to confer a phenotype (Bucan et al., 2009). A key corollary relates to the relationship between the effect size of a given allele, its frequency in the population, and the available methods to detect and confirm the relationship to disease (Figure 1). As common variant findings refocus expectations on alleles with extremely small risks, the spectrum of genetic effects anticipated for rare alleles necessarily expands, resulting in a shift in the approaches that would be required to identify this contribution.

The Utility and Pitfalls of Genetic Association

As a consequence, association studies in general, and case-control designs in particular, promise to play a major role in addressing the genetic risks in child psychiatry despite the emerging emphasis on rare variants. While this observation may seem self evident, the tendency to interpret rare variant findings based on vestigial expectations derived from Mendelian disorders can be quite powerful. There is a strong innate skepticism that tends to accompany the observation of rare mutations that are neither necessary nor sufficient to confer a phenotype, as for instance when a putative disease-related rare mutation is not always shared by affected siblings (Bucan et al., 2009; Kumar et al., 2008; Weiss et al., 2008).

An increasing reliance on case-control analyses will also result as a consequence of the emerging ability to detect de novo variation on a genome wide scale. While such mutations may carry very large risks, linkage analyses are not plausible given the nature of the variation. Moreover, the prior conventional wisdom that de novo losses of coding segments provided prima face evidence for disease causality has been definitively laid to rest (Iafrate et al., 2004; Sebat et al., 2004). Consequently, carefully controlled case-control analyses will be required to confirm the relevance of many de novo variants, particularly in those instances in which the penetrance of a given mutation is not 100 percent.

Of course, there is little reason to expect that the types of confounds attending common variant association studies will be any less pressing for rare sequence and structural variation. For example, power will certainly remain a critically important issue: the ability to detect association is a function both of effect size (larger for rare variants) and allele frequency in the study population (smaller for rare variants). This tradeoff suggests that some rare variants carrying modest effects will be impossible to detect given inherent limitations in sample sizes that can be consolidated.

Moreover, in the case of CNV analyses, typing error may be considerably more problematic using current array-based methods compared to SNP genotyping or sequencing due to limitations in prediction accuracy and confirmation methods; in addition, there is considerable sample-to-sample variability and a clear liability toward batch-effects even when using identical CNV platforms at differing times or at different laboratories. A recent elegant study identified these and several other less obvious method-associated technical challenges confronting CNV analyses (Craddock et al., 2010).

Similarly, population stratification, though initially downplayed in studies of rare structural variants, clearly has the potential to confound results (Merikangas et al., 2009). Finally, given the expectation of a very high degree of allelic heterogeneity and the possibility that individual mutations will be fleetingly rare, approaches to association will likely require cumulative counts of variations at a given gene, i.e., an analysis of mutation burden or mutation skew (Bakkaloglu et al., 2008; Cohen et al., 2004, 2006; Ji et al., 2008; Johansen et al., 2010). In these instances, given the large amount of neutral rare variation in the genome, the differentiation of functional from incidental mutations may be critical to confirm true association (Ji et al., 2008). And this can be a challenging enterprise: the human genome tolerates a tremendous amount of what would have previously been presumed to be clearly deleterious variation (Iafrate et al., 2004; Sebat et al., 2004), and recent evidence suggests accurate interpretation of the impact of particular alleles will be dependent on specific knowledge of the biology of the gene(s) and protein(s) in question (Ji et al., 2008).

The Impact of Next-Generation Sequencing

A comprehensive discussion of new genomic technologies is beyond the scope of this review. However, it is important to note that next-generation sequencing is already offering unprecedented opportunities to investigate genetic variation, gene expression, and epigenetic phenomenon. With regard to gene discovery, the ability to comprehensively identify both sequence and structural variants in large numbers of individuals promises to revolutionize the understanding of the allelic architecture and the specific genetic contributors to childhood neuropsychiatric disorders.

While the manner in which these technologies will be most effectively harnessed remains to be seen, several observations are warranted here: first, while there is little question that next-generation sequencing will empower large-scale case-control studies of rare variation, the field is also likely to see a reemergence of pedigree-based genetic studies. Already, sequencing the human exome has been shown to be a powerful approach to mapping rare mutations in the setting of tremendous phenotypic heterogeneity and within pedigrees that would have previously been too small to support traditional linkage analyses (Bilgüvar et al., 2010); these developments bode well for outlier approaches to common complex disorders. More generally, either multiply-affected families or apparently sporadic pedigrees may well offer the most expedient means to sort through

and prioritize the massive amounts of rare variation identified via next generation sequencing.

Finally, while the excitement about these new approaches is well justified, it is also a certainty than even the most exhaustive catalog of genetic variation will leave many questions unanswered and likely serve as only a first important step in illuminating the complex interplay of experience, environment, and biology in influencing normal and pathological brain development.

Autism and Autism Spectrum Disorders

Autism spectrum disorders are a group of syndromes characterized by fundamental deficits in social communication and language development and accompanied by highly restricted interests, stereotyped repetitive behaviors, or both. The canonical presentation is defined by deficits in all three areas, whereas disorders along the spectrum include significant social impairment with or without evidence of impairment in other domains. (Volkmar et al., 2009).

The evidence for a genetic contribution to ASD is very strong, based on family and twin studies (Bailey et al., 1995; Folstein and Rutter, 1977), the overlap of ASD with known genetic disorders (Fombonne et al., 1997), and recent molecular data (addressed below). There is a strong male predominance (Volkmar et al., 2004). Despite ambitious efforts aimed at identifying common and rare alleles, the number of genes or loci that are accepted as carrying definitive risk remains small and not immune from debate. In contrast, the list of intriguing and plausible candidates (see http://www.mindspec.org/auTSb.html) is proliferating exponentially, a phenomenon that can make deciphering the current literature quite difficult.

The absence of specific and sensitive biological markers for ASD, and the consequent reliance on syndromic categorization and subjective assessment presents predictable challenges, as it does in all areas of psychiatry (Volkmar et al., 2009). These issues extend well beyond the scope of the current discussion; however, a key phenomenological question that bears directly on the interpretation of the autism genetics literature involves the overlap of ASD and intellectual disability (ID), which is present in approximately 70% of individuals meeting full diagnostic criteria for autism (Chakrabarti and Fombonne, 2001), and approximately 45%–50% when one considers the entire range of ASD diagnoses.

It is important to note here that there is little debate that social impairment and cognitive delay are readily distinguishable in individuals with mild to moderate ID. While this differentiation becomes less reliable in cases of severe to profound delay, debate over this co-occurrence runs deeper than simple diagnostic uncertainty and reflects a historical interest in identifying specific risks for autism as opposed to ''general disruptions of brain development.'' This issue is similarly present with regard to the study of individuals with ASD and seizure, present in 10%–25% of individuals with autism (Volkmar and Pauls, 2003), and is particularly relevant to the study of syndromic autism i.e., ASD in the context of a known genetic syndrome or observed in individuals presenting with marked dysmorphology, structural brain abnormalities, or other evidence of a genetic syndrome but absent a known cause.

In part, these questions reflect an ongoing debate regarding whether social disability, characterized in the context of known genetic disorders, is identical to that observed in idiopathic ASD (Moss and Howlin, 2009), an issue that may sometimes be difficult to resolve given the challenges inherent in designing blinded studies of syndromes characterized by distinctive physical features. However, there is a second line of reasoning, based on twin and epidemiological data, that contends that the high rate of ASD in individuals with ID among clinically ascertained populations is an epiphenomenon resulting from a normal distribution of autism traits in the population which is made manifest by relatively poor ''compensatory mechanisms'' in individuals with ID (Figure 2A). This view proposes that discovery efforts in cases of overlapping ID and ASD will identify genes for the former, that a different set of genes underlie social functioning, and that the optimal strategy for gene discovery with regard to autism would focus on the population of ASD without intellectual disability (Skuse, 2007).

While these debates are ongoing, several considerations deserve mention: first, in addition to the increasing application of standardized instruments and blinding methods to enhance the diagnostic reliability of ASD in the context of known syndromes, the not infrequent detection of syndromic mutations in individuals with idiopathic ASD is evidence that these variations may lead to behavioral phenomenon that are, for all practical purposes, indistinguishable from idiopathic ASD (e.g., the absence of a known genetic syndrome or clear evidence of a monogenic disorder). Moreover, given that autism and related conditions are syndromic diagnoses and manifestly not unitary biological entities, there would seem to be little question that individuals that are rigorously characterized with ASD have ASD.

The more difficult questions of whether it is worthwhile to search for variants contributing to ASD in the context of ID and to pursue the biology of rare syndromes in an effort to understand autism remain contested. As noted above, a central rationale for outlier strategies is that a genetic variation that is definitively identified as causing or contributing to ASD regardless of co-occurring conditions offers potential traction with regard to cellular and molecular mechanisms of pathogenesis, at least in those cases. The question of whether this biology is generalizable remains to be demonstrated. However, there is solid evidence supporting the use of identical strategies in other common complex and heterogeneous conditions (Ji et al., 2008; Romeo et al., 2009). Moreover, as discussed in more depth below, current evidence already points to some convergence in the molecular mechanisms implicated through the study of syndromic forms of ASD and those suggested by genes that have the shown the strongest evidence so far for contribution to idiopathic ASD (Bourgeron, 2009; Toro et al., 2010). Finally, the observation that identical mutations may lead not only to ID and ASD, but to schizophrenia and possibly other neuropsychiatric disorders (addressed below) would seem to argue for a model based on the pleiotropy of genes underlying fundamental neuronal processes (Figure 2B), a phenomena that is highlighted by recent findings from our group with regard to the genetics of structural brain disorders (Bilgüvar et al., 2010).

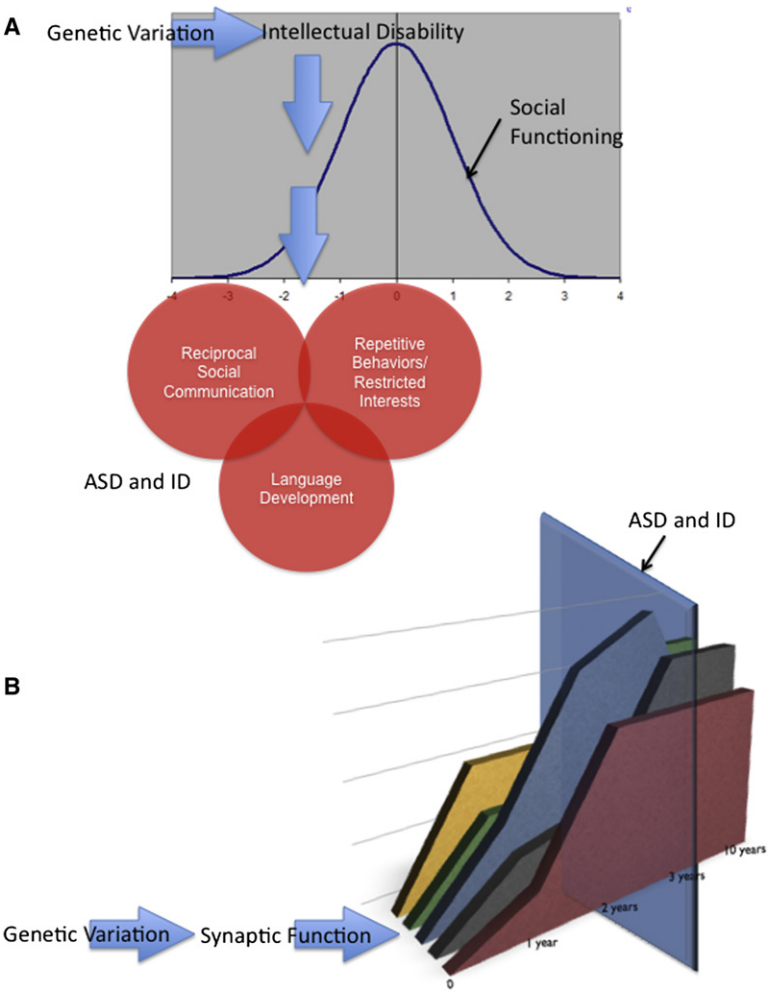

Figure 2. Two Models of the Overlap of ASD and ID

(A) This model represents a view well articulated by Skuse (2007) that the study of syndromic ASD, or ASD in the presence of ID, is more likely to identify genes related to intellectual impairment. Co-occuring ASD is a thought to be largely the consequence of a reduced compensatory capacity in individuals with ID. In this view, ASD characteristics are normally distributed in the population and are determined by a distinct set of genes. Given this model, the pursuit of ASD loci should focus on individuals who do not have ID. In the graph, the units on the x axis are standard deviations of a hypothetical measure of social functioning. An alternative model (B) focuses on the idea that mutations or variations in "ASD" genes alter fundamental cellular and molecular mechanisms in the CNS (noted here in shorthand as "synaptic function") as opposed to determining higher-order processes such as cognition or social function, that these perterbations set the stage for a developmental course that is reflected in trajectories across mutiple domains of CNS function, and that these trajectories will be influenced both by "inciting" genetic events as well as other genetic, epigenetic, and environmental processes. This model would suggest that the early vulnerability confered by genetic variation could ultimately be manifested in a wide variety of clinical diagnoses crossing categorical boundaries. In this case, the identification of rare highly penetrant alleles would point to biology that is relevant to a wide range of observed clinical outcomes including ID and ASD. In the graph, the x axis reflects time and the colored bars represent hypothetical trajectories in multiple areas of cognitive, linguistic, and behavioral functioning.

Early and Rare Variant Findings

These debates bear substantially on the interpretation of the results of gene discovery efforts. An observer inclined to compartmentalize syndromic ASD or ASD coincident with ID would likely contend that the field awaits definitive identification of a risk locus. Someone holding the alternative perspective would likely mark the cloning of the *Fragile X Mental Retardation Protein* (*FMRP*) as the first autism gene, given a longstanding and well-documented excess of the ASD phenotype observed in boys carrying canonical mutations and the repeated observation of *FMRP* mutations identified in cohorts of individuals with idiopathic ASD (Brown et al., 1986; Fombonne et al., 1997; Harris et al., 2008; Hernandez et al., 2009; Levitas et al., 1983).

A number of other well-defined syndromes have either been found to have a greater than expected frequency of individuals with ASD or to have core features that overlap with ASD or both (Hoffman and State, 2010). Among the substantial list, in addition to fragile X, the data for an appreciably increased prevalence of mutation carriers among cases of idiopathic ASD is so far best established with regard to tuberous sclerosis (Smalley, 1998; Smalley et al., 1992). Similarly, the overlap among defining features of syndromes such as Angelman or Rett, and ASD provides a complementary approach to studying the biology of autism. The contribution of these and other rare syndromes to the development of neurobiological models of pathogenesis is discussed in ensuing sections.

The first rare coding mutation in individuals with putative idiopathic ASD was identified in the neuronal adhesion molecule, Neuroligin 4X (Jamain et al., 2003). Based on the prior identification of recurrent deletions on the X chromosome in affected individuals, Thomas Bourgeron's lab sequenced genes within the interval in 36 sibling pairs and 122 trios and found a truncating frame-shift mutation in *NGLN4X* arising de novo in an unaffected mother and transmitted to two brothers, one with Asperger syndrome and the second with "typical" autism. Shortly thereafter, mapping of a multigenerational pedigree affected with both ID and ASD by an independent group led to the discovery of a segregating truncating mutation, nearly identical to the initially reported *NLGN4X* mutation (Laumonnier et al., 2004).

Over the ensuing half-decade, this finding has been further supported by convincing evidence for recurrent de novo mutations in individuals with ASD in *SHANK3* a postsynaptic scaffolding molecule that forms a complex with neuroligins and falls within the 22q13.3 microdeletion syndrome region (Figure 3; Durand et al., 2007; Gauthier et al., 2009; Lim et al., 1999; Moessner et al., 2007). Moreover, recurrent de novo mutations in other interacting molecules, including *NRXN1* (Kim et al., 2008; Szatmari et al., 2007) and *SHANK2* (Berkel et al., 2010; Pinto et al., 2010b), functional data showing a role for neuroligins in the establishment of both excitatory and inhibitory synapses (Chubykin et al., 2005; Graf et al., 2004; Scheiffele et al., 2000),

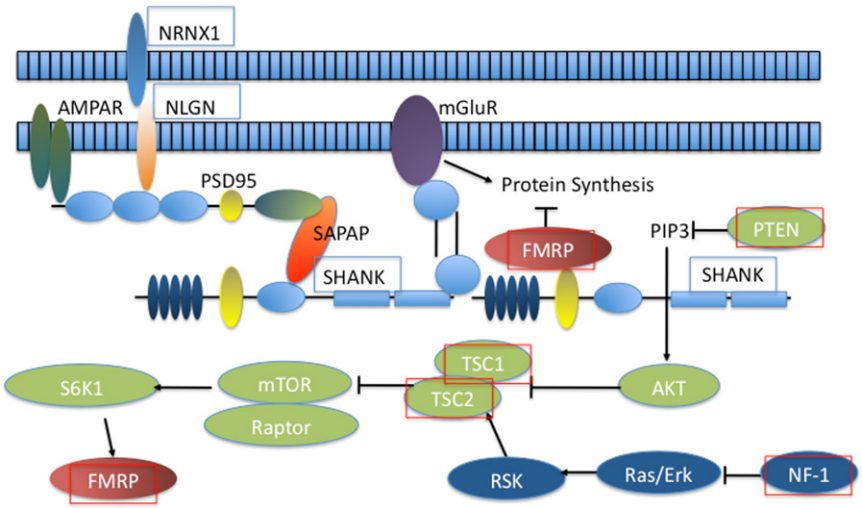

Figure 3. Rare ASD Variants in Genes Encoding Synaptic Proteins

The drawing shows a highly selected and simplified view of the excitatory synapse highlighting genes strongly implicated via rare variant studies of idiopathic ASD (blue boxes) and those identified through the study of syndromic ASD (red boxes).

and interesting, but less conclusive genetic (Jamain et al., 2003) and model systems data (Chadman et al., 2008; Tabuchi et al., 2007) with regard to the closely-related molecule *NGNL3*, have placed *NLGN4X* among the most widely accepted genetic findings in idiopathic ASD.

Over the last several years a rapidly expanding list of rare mutations have been described in affected individuals, representing so many genes in fact that an exhaustive assessment is not feasible here. However, only a small number yet have the property of being observed in rigorous studies by multiple independent investigators. Among these, in addition to *NGLN4X*, *SHANK3*, and *NRXN1*, the neuronal adhesion molecule CNTN4 has been identified by our lab and others via molecular cytogenetic mapping of de novo rearrangements and CNV analyses (Fernandez et al., 2004, 2008; Glessner et al., 2009; Roohi et al., 2009); and, quite recently, *SHANK2*, was identified both through the identification of de novo disruptive mutations in one patient with ID and another with ASD (Berkel et al., 2010) as well as via a large-scale CNV analysis (Pinto et al., 2010a).

A review of the data regarding another neuronal adhesion protein, encoded by the gene *Contactin Associated Protein 2*, provides a useful example of the state of the field at present, with intriguing findings falling just short of definitive evidence: the molecule was first identified as having a role in developmental delay through homozygosity mapping of a rare recessive frame-shift mutation in the Old-Order Amish population (Strauss et al., 2006). The report involved a syndrome of intractable epilepsy accompanied by clinically diagnosed autism. Shortly thereafter, independent reports provided evidence for variations in *CNTNAP2* in idiopathic ASD. The mapping of a rare de novo chromosomal rearrangement by our lab disrupting this locus in a simplex ASD pedigree and the subsequent identification of multiple rare transmitted, missense substitutions at highly conserved positions in affected multiplex families (Bakkaloglu et al., 2008), the simultaneous findings by two independent groups of common variant association (Alarcón et al., 2008; Arking et al., 2008), and a subsequent report of interaction of CNTNAP2 and FOXP2 along with a association of a common *CNTNAP2* allele in language impairment (Vernes et al., 2008) generated strong interest in this gene and led to its characterization by some authors as a confirmed idiopathic ASD locus.

However, while the initial mapping of a rare recessive mutation was quite compelling, the question of whether and how either common or rare variation in this gene contributes to nonsyndromic ASD remains open. For example, the mutation burden analysis conducted by our lab was suggestive, showing an approximately 2-fold increase in very rare missense variants in cases versus controls. However, as noted in the initial publication, the results did not reach statistical significance apart from a single recurrent transmitted allele for which population stratification could not be ruled out as a confound. Moreover, the study lacked the ability to reliably differentiate functional from incidental mutations in cases and controls. The two simultaneous common variant association studies identified different alleles that carried risk for differing phenotypes: one involving the diagnosis of ASD and the other mapping a language quantitative trait locus identified in individuals with ASD. Subsequently, only one of three published GWAS studies in ASD provided any support for association of *CNTNAP2* with the diagnosis of ASD and this was quite modest (Anney et al., 2010). Finally, the link to specific language impairment though statistically significant and based on a strong a priori hypothesis was nonetheless identified through a candidate gene association study and replication has yet to be attempted in a genome-wide analysis.

This characterization is not meant to call into question the rigor of the aforementioned studies or to detract from interest in *CNTNAP2*. The presence of multiple lines of evidence emerging nearly simultaneously from independent groups conducting state-of-the-art studies is unusual in the field and many of the outstanding questions have simply not yet been tested adequately to allow for independent replication. Nonetheless, this summary highlights issues that are reflective of the state of the science with regard to many of the most intriguing findings in ASD genetics both with regard to common and rare variants: underscoring the question of the relationship of syndromic findings to common forms of the disorder and highlighting the challenges posed by sample size, power, phenotypic heterogeneity, ancestral matching, and distinguishing functional from neutral alleles.

Copy Number Variation

Prior to the advent of high-density microarrays and the ability to detect submicroscopic variations in chromosomal structure, multiple recurrent chromosomal abnormalities were identified in individuals with ASD. The most common and highly penetrant

are maternally inherited duplications of chromosome 15q11–13 (Baker et al., 1994; Hogart et al., 2010). Rare recurrent deletions at 2q37, 1q21, 22q11, and 22q13, among others, have also been identified in affected individuals (Bucan et al., 2009, #4635; Lauritsen et al., 1999, #5538).

The importance of *submicroscopic* copy number variation for ASD was first reported by Michael Wigler's lab through the identification of a marked excess of de novo variations in affected singleton probands (10%) compared to probands from multiplex families (3%) or unaffected controls (1%) (Sebat et al., 2007). A subsequent genome-wide CNV study (Marshall et al., 2008) confirmed a several fold increase in these events, and suggested a cumulative frequency of approximately 5–10 percent in the simplex ASD population. However, another recent large-scale study, while identifying de novo variations in 5.6% of simplex ASD probands, did not find a difference compared to probands from multiplex families (5.5%) (Pinto et al., 2010a). The reasons for the variability observed in this third study have not yet been clarified, although even prior to these results, a hypothesis emerged that the increased frequency identified by Sebat et al. (2007) might apply particularly to large events, and consequently, that the increasing resolution of array platforms might tend to obscure some differences between groups.

The initial study by the Wigler lab also included a description of a 16p11.2 de novo deletion and, subsequently, two groups nearly simultaneously found a significant association of recurrent de novo CNVs, including both deletions and duplications (Kumar et al., 2008; Weiss et al., 2008), at this locus in idiopathic ASD, reporting on partially overlapping samples. The finding was confirmed in a subsequent genome wide investigation of structural variation (Marshall et al., 2008). Among the three other recent large-scale CNV studies, the 16p11.2 finding was not replicated in one due, in part, to the finding of a higher than reported rate of 16p11.2 CNVs in the control group (Glessner et al., 2009) and in two others, an independent assessment was precluded by extensive sample overlap with the previously reported cases (Bucan et al., 2009; Pinto et al., 2010b). Interestingly, a recent study of 4284 individuals with ID and multiple congenital anomalies found 16p11.2 CNVs in 0.3% of cases, consistent with that seen previously among ASD cohorts (Bijlsma et al., 2009), and providing further evidence for wide ranging phenotypic manifestations emerging from 16p11.2 variations (discussed below).

The 16p11.2 data serve as an important example of the manner in which current findings are challenging notions regarding rare variant contributions to ASD. All four deletions families reported by Kumar et al. (and described again in Weiss et al.) included two affected children, and in three of these pedigrees, only one of the affected siblings carried the de novo CNV. As noted, based on Mendelian expectations, the observation that within multiple small pedigrees the large de novo deletion was not necessary for the phenotype would raises eyebrows. Indeed, commenting on the lack of 16p11.2 replication in their CNV analysis, Glessner and colleagues write that their results "…indicate that CNVs at the 16p11.2.2 locus may not be sufficient to be causal variants in ASD." (Glessner et al., 2009) In fact, none of the reports of 16p11.2 provided evidence suggesting that the variant is uniformly necessary or sufficient to lead to ASD. The issue addressed by these studies is whether this CNV confers risk. The aforementioned studies and our own preliminary data from a CNV analysis of nearly a 1000 simplex families, provides mounting evidence that it does.

Recent CNV studies have also provided interesting data regarding other previously identified and novel loci. Glessner et al. (2009) replicated findings at 15q11–13 and 22q11.21, as well as *NRXN1* and *CNTN4*. As noted, they did not identify a significant difference in cases versus controls for 16q11.2 nor did they observe an association of CNVs at the *SHANK3* locus. Their analyses further highlighted multiple novel loci that were found to cluster via gene ontology analyses in the ubiquitin pathway and among molecules categorized as being involved in neuronal development. Pinto et al., in addition to reporting evidence for *SHANK2* almost simultaneously with a report by Berkel et al. (2010) identified several additional novel loci and provided strong evidence for X linked inherited deletions of *DDX53-PTCHD1*, with 7 reported males among the cases and none among 4964 controls. Their pathway analyses highlighted genes involved in cellular proliferation, projection, and motility, and GTPase/Ras signaling (Pinto et al., 2010b).

Common Variants

Similar to other child psychiatric disorders, the ASD genetics effort was initially characterized by a focus on idiopathic forms of the syndrome, an early inability to identify evidence for single gene inheritance and, subsequently, a widespread preoccupation with the CVCD hypothesis, investigated via nonparametric linkage and candidate gene association studies (Veenstra-Vanderweele et al., 2004).

With regard to nonparametric linkage, the largest study to date included 1181 multiplex families (Szatmari et al., 2007) and, along with a dozen others using similar approaches, did not identify highly significant evidence for linkage or result in the mapping of a common variation that accounted for the linkage signals identified. It should be noted that these studies are theoretically capable of identifying either common or rare disease alleles. They evaluated affected sib pairs for regions of the genome shared among family members more often than would be expected by chance and consequently have the advantages of not requiring an a priori specification of a mode of inheritance and of being robust to allelic heterogeneity.

A likely explanation for the lack of definitive results is the much greater than anticipated degree of locus heterogeneity observed in ASD. Particularly in light of the modest sample sizes employed, a great diversity of genes all contributing to ASD would tend to obscure evidence for excess sharing at any given locus. However, as noted previously, with the advent of next generation sequencing, a reemergence of linkage analyses of all types is imminent, given both the ability to comprehensively interrogate very large intervals and to leverage families for gene discovery that would have been too small to be useful using standard approaches.

With regard to common variants, despite considerable challenges and a host of nonreplicated associations, several studies conducted just prior to the GWAS era resulted in notable findings. These included the identification of *EN2* (Benayed et al., 2005, 2009), the *MET* oncogene (Campbell et al., 2006; Jackson et al., 2009), and *CNTNAP2* (Alarcón et al., 2008; Arking et al., 2008; Vernes et al., 2008). All three have shown some evidence

for replication but continue to be the subject of debate. This is due in part to their absence from the most promising results emerging from recent genome-wide association studies, though as noted below, there is considerable uncertainty regarding the current validity of this metric.

As with other areas of medicine, GWAS have emerged as the gold standard for the identification of common alleles carrying small effects and three relatively large studies in autism have recently been completed. The first included 780 families and an additional 1204 probands and identified significant association of ASD to an intergenic region of chromosome 5p14.1 mapping between the neuronal adhesion molecules *Cadherin 9* and *Cadherin 10* (Wang et al., 2009). The second involved a cohort of 1031 families and found association to a SNP near the gene *Semaphorin 5A* (Weiss et al., 2009) and a third used a discovery cohort of 1558 individual and found genome-wide evidence for association at the *MACROD2* locus (Anney et al., 2010). As a likely reflection of both the heterogeneity of ASD and the challenge of identifying alleles of very modest effect, none of these studies confirmed the others' findings.

While the field certainly hoped for replication of identical SNPs across these samples, the data are nonetheless consistent with similar studies of complex conditions. Despite cohort sizes that would be considered large for child psychiatry, none of these studies were well powered to replicate findings from the others (Anney et al., 2010). In addition, a comparison of these results with the candidate gene studies mentioned above underscores additional questions regarding both the impact of phenotypic heterogeneity and the best approach to addressing this problem. Both the *MET* and *CNTNAP2* literature provide evidence that association is robust either within a specific subgroup of affected individuals or with an endophenotype as opposed to a categorical diagnosis.

There has been a long-standing interest across all of psychiatry in leveraging endophenotypes, phenomena that fall along the path from genetic variation to the syndromal clinical presentation. This is understandable given the clear limitations inherent in categorical diagnostic approaches. The identification of more homogenous, biologically relevant, and heritable entities would seem virtually guaranteed to empower genetic studies and aid in the identification of risk alleles. The challenges in ASD, and for other neuropsychiatric phenotypes, include the difficulty in identifying relevant phenomenon a priori and the related confound of multiple comparisons if a variety of possibilities are examined through the course of a study. Moreover, it is worth noting in the instances where loci contributing to ASD have been most convincingly demonstrated that similar or identical rare mutations appear to confer a very broad range of phenotypes. These results suggest that the effective "distance" between variations in the sequence or structure of the DNA and resulting brain phenotypes may be quite large. Indeed, it is difficult to imagine in retrospect what endophenotype would have been useful to detect these mutations, though admittedly the situation may be different for common versus rare variants. Finally, it is worth noting that in other areas of medicine, common variant discovery has been highly successful even for heterogeneous disorders using a combination of clinical diagnoses and large cohorts. Given the magnitude of effects identified in those studies and those so far suggested by the initial GWAS in ASD, it is clear that the field is just now approaching the sample sizes necessary to begin to answer the question of common variant contributions. One thing is certain: as definitive replicated common variants are identified, the ability to then clarify relevant endophenotypes and a range of genotype-phenotype correlations will be dramatically enhanced.

Molecular Findings and Diagnostic Boundaries

As suggested above, one of the most interesting and thought provoking recent observation in the field has been the wide range of neuropsychiatric manifestations that now appear to emerge from identical rare variants. Indeed the conceptual challenge of integrating the co-occurrence of ID and ASD pales in comparison to that posed by the possibility that functionally identical mutations may lead to ASD, ID, seizure disorder, schizophrenia, ADHD, Tourette syndrome, OCD, or some combination of the above. Nonetheless data both from structural and sequencing studies suggests this may be the case: For example, 22q11.2 deletions, have long been implicated in the risk for psychosis in addition to the evidence with regard to ASD (Guilmatre et al., 2009; Vassos et al., 2010); CNVs at 16p11.2 have been observed in individuals with schizophrenia (Weiss et al., 2008), a finding that has been solidly supported by a large case control association analysis (McCarthy et al., 2009) and de novo mutations in *SHANK3* have been identified in individuals with schizophrenia as well as those with ASD (Gauthier et al., 2010). Structural variations at *CNTNAP2* have been reported not only in ASD and schizophrenia but Tourette syndrome as well (Friedman et al., 2008; Verkerk et al., 2003), and this overlap has also been observed with regard to *NLGN4X* (Lawson-Yuen et al., 2008).

At present the data pointing to overlapping risks for schizophrenia and ASD at the 16p11.2 locus is particularly compelling (McCarthy et al., 2009), with the prevailing hypothesis that duplications predispose to schizophrenia and a variety of other developmental outcomes including ASD, while deletions do not seem to play a prominent role in the risk for psychosis. The prospect of any shared molecular mechanisms is somewhat ironic. Autism was initially conceptualized as a form of childhood psychosis, but with advances in standardized diagnostic approaches, this idea was rejected (Volkmar and Pauls, 2003). While there is some overlap between ASD and the social withdrawal seen in individuals with schizophrenia, the natural history of the latter is quite distinctive versus the early onset that defines ASD, as are the positive symptoms of schizophrenia: auditory hallucinations and delusions have not been described as more common among individuals with idiopathic ASD.

Not surprisingly, the suggestion of convergence among so many developmental neuropsychiatric disorders opens the door to a variety of interesting debates. As suggested above, the notion of diagnostic substitution has been raised, but this would seems unlikely to explain all of the recent data given the range of signs and symptoms involved and the strikingly distinct developmental profiles. Of course, given the demonstration of incomplete penetrance for most of the implicated variants, it is also likely that some of the observations are incidental findings. This possibility underscores the importance of the type of large-scale association analysis reported by McCarthy et al.

(2009) as precisely the methodology that will be required to provide clear answers to these questions. Finally, as noted, the apparently broad range of phenotypic outcomes emerging from what appear to be identical mutations also poses some interesting challenges to the model that suggests the overlap of ID and ASD is a reflection of genes for the former uncovering the normal distribution of ASD traits in the population (Figure 2A). These observations would seem more consistent with a model of highly pleiotrophic effects of mutations influencing fundamental neurobiological processes (Figure 2B).

Emerging Neurobiological Models

At the molecular level, evidence in favor of this notion has begun to converge at the synapse. The identification of *NLGN4X* mutations and the independent findings of rare variants in *NRXN1*, *SHANK3*, and *SHANK2* have further focused attention on the function of neuroligin-neurexin complex and related molecules in the post synaptic density (PSD), a specialized region of the excitatory synapse (Figure 3).

Perhaps most interestingly, this data converges with the evidence pointing to a key role for the fragile X mental retardation protein at glutamatergic synapses (Bear et al., 2004; Huber et al., 2002; Nakamoto et al., 2007). The elaboration of this biology has led to an intriguing hypothesis: that the cognitive and social phenotypes may be mediated through deficits in plasticity relating to long-term depression and that this process is potentially reversible via targeting of metabotropic glutamate receptors or related signaling cascades (Bear et al., 2004; Dölen et al., 2010). The notion, supported by recent model systems data (Chang et al., 2008; Dölen et al., 2007), that fragile X syndrome may reflect a dynamic ongoing process and be amenable to intervention throughout the life span is now being translated into clinical trials in individuals with fragile X as well as with idiopathic ASD.

The intersection of studies of syndromic and idiopathic autism has also focused attention on the PI3K-AKT-mTOR pathway. As noted, there is strong evidence that rare mutations in *TSC-1/TSC-2* increase the risk for ASD; the data in this regard for *NF-1* and *PTEN* are also convincing (Butler et al., 2005; Buxbaum et al., 2007). These molecules point to the rapamycin-sensitive mTOR-raptor complex, a key regulator of protein synthesis and cell growth. Further, binding of hepatocyte growth factor to the *MET* oncogene results in activation of a variety of signaling cascades, a process that is regulated in part by PTEN. These findings point to two intriguing possibilities: first, that targeting of this pathway, as is feasible with rapamycin and other compounds, may provide a novel avenue for treatment (Ehninger et al., 2009; Ehninger et al., 2008), and second, that the data may converge with the biology implicated by fragile X to further refine the understanding of the molecular mechanisms leading to human developmental disorders (Narayanan et al., 2007; Sharma et al., 2010).

Of course, the question of whether the pathways implicated by syndromic ASD, which anchor both the mGluR and mTOR hypotheses, may have broader relevance for idiopathic ASD remains open. Ongoing studies, both to further elaborate basic neurobiology and to address the issue in the clinic, will help provide the answers. What is indisputable is that the conceptual transition reflected in these efforts is remarkable: the notion that intellectual disability and ASD associated with *FMRP* or *TSC-1* mutations *may* not set in stone early in development represents a seismic shift in thinking regarding the opportunities to treat these conditions and underscores the transformative potential of the interplay of human genetic findings and basic neurobiology.

A third area of possible traction in the neurobiology of ASD relates to *CNTNAP2*. As noted, the initial genetic evidence implicating homozygous truncating mutations in ID, seizures, and ASD was quite strong. Moreover, the investigators who mapped the locus in Old-Order Amish had the unusual opportunity to examine pathological specimens, due to surgical intervention for the severe epilepsy phenotype. The gross morphological abnormalities included temporal lobe dysplasia, evidence of abnormal cortical migration, and dysmorphic pyramidal neurons. Given many remaining uncertainties regarding the function of CNTNAP2 in the CNS and some evidence for the presence of the protein at the synapse (Bakkaloglu et al., 2008), overlap with the previously described pathways has not been ruled out. Equally interesting, however, is the suggestion, based on the expression of CNTNAP2 in postmitotic neurons in the developing human cortex and the aforementioned pathological data, that subtle abnormalities in cortical migration or organization might be an independent avenue to ASD.

When viewed in a more global sense, the recent large-scale studies of ASD have begun to suggest other interesting possibilities; the use of pathway analysis to integrate the very large amount of rare variation emerging from CNV studies has pointed to the ubiquitin pathway, neuronal adhesion molecules and those involved in cellular proliferation, projection, and motility, and GTPase/Ras signaling. A review of the data on 16p11.2 and other specific recurrent CNVs is also focusing attention on dosage sensitivity in conferring risk and shaping developmental outcomes (Toro et al., 2010). The further pursuit of these types of leads will be helped tremendously by additional definitive genetic findings that allow for prioritization among the various possibilities, lend greater specificity to testable hypotheses, and provide a clear link to the human phenotype.

Tourette Syndrome

The history of the genetics of Tourette syndrome (TS) has been similar in many respects to that described for autism and related conditions. However, in contrast to the tremendous attention focused on gene discovery in ASD and the voluminous literature, particularly over the last 5 years, the scale of the TS genetics effort has been relatively modest. The types of resources that have facilitated a high level of productivity in other areas of psychiatry and clinical neuroscience, including large patient cohorts and widely accessible biomaterials are just now beginning to be consolidated. Nonetheless, several recent genetic findings have provided promising leads regarding molecular mechanisms, cytogenetic and CNV data point to the important contribution of rare variants, and the first large-scale GWAS study will soon be completed.

TS is defined by the persistence of unwanted, brief, repetitive, nonrhythmic motor movements and vocalizations. It is a prototypical developmental disorder with an age of onset of between 3 and 8 years (mean ~7 years) and a tendency toward

considerable improvement as individuals reach adulthood (Bloch et al., 2006). While the diagnosis requires only the presence of both vocal and motor tics, the vast majority of individuals who present clinically suffer from other psychiatric syndromes: up to 50% of TS probands suffer from obsessive compulsive disorder (do Rosário and Filho, 1997; Ghanizadeh and Mosallaei, 2009); 50%–90% have co-occurring attention deficit hyperactivity disorder (Burd et al., 2005; Freeman, 2007; Ghanizadeh and Mosallaei, 2009; Leckman, 2003; Roessner et al., 2007; Stewart et al., 2006), and there is an apparently increased risk for both depression and anxiety apart from OCD (Coffey et al., 2000; Kurlan et al., 2002). These high rates of comorbidity are likely a consequence of a combination of selection bias (as epidemiological studies suggest that only a small percentage of individuals with tics or TS present to clinic); the possibility of a shared genetic liability as has been best documented for OCD (Pauls, 2001), and the possibility of a shared neurobiological substrate among these conditions. Typically, individuals with a TS spectrum disorder, meaning TS, chronic tics (either motor or vocal), or tics with OCD are considered to be affected for the sake of genetic studies. In addition, within TS pedigrees, family members with OCD alone are often included as affected individuals.

Genetic Findings

Twin data, though cumulatively representing a small number of studies and subjects, suggests a significant genetic contribution to TS. Monozygotic twin concordance rates are estimated at 50%–77% compared to 10%–23% for dizygotic twins (Price et al., 1985), with the range dependent on whether TS spectrum conditions are included. However, despite a longstanding consensus that genetics plays a key role in disease etiology, there are, as of yet, no confirmed, replicated genetic risk factors for TS and related conditions.

Early studies focused on large multigenerational pedigrees that seemed to point to single gene autosomal-dominant inheritance (Baron et al., 1981; Curtis et al., 1992; Kidd and Pauls, 1982; Pauls and Leckman, 1986). However, over time, as the techniques for mapping Mendelian disorders reached maturity, no TS locus was identified and a high rate of bilineal inheritance was noted (McMahon et al., 1996); this hypothesis was abandoned. Subsequent segregation analyses (Hasstedt et al., 1995; Kurlan et al., 1994; Walkup et al., 1996) led to the current characterization of TS as a complex, heterogeneous genetic disorder.

By the late 1990s, the lack of results from parametric analyses resulted in a shift toward nonparametric linkage. In 1999, The Tourette Syndrome Association International Consortium for Genetics reported a study of 92 affected sib pairs which resulted in multipoint maximum-likelihood scores of > 2 on chromosomes 4q and chromosome 8 (Tourette Syndrome Association International Consortium for Genetics, 1999). However, when the study was extended to 238 sib pairs and 18 large families, evidence for linkage in these regions diminished, and suggestive evidence emerged on chromosome 2p (Tourette Syndrome Association International Consortium for Genetics, 2007). Several other linkage studies have resulted in LOD scores either approaching or reaching statistical significance (Breedveld et al., 2010; Curtis et al., 2004; Mérette et al., 2000; Paschou et al., 2004); however, as of yet, only one, described in more detail below, has led to the identification of mutations altering the structure or function of transcripts mapping within or near these intervals.

Common variant candidate association studies have been widely employed and a variety of biologically plausible candidate genes have been assessed, including various dopamine receptors, the dopamine transporter, noradrenergic transcripts, tyrosine hydroxylase, *SLC6A3*, and a several serotonergic genes (Barr et al., 1996; Brett et al., 1995; Chou et al., 2004). These efforts involved samples sizes that would now be considered inadequately powered to detect common variant risks of plausible magnitude. Not surprisingly, they have not yet resulted in consistent and reproducible findings.

While the search for common alleles has predominated, there has also been a steady effort to evaluate the contribution of rare alleles, almost entirely reflected in outlier studies. Many of these were reported prior to the CNV era and involved mapping of de novo chromosomal abnormalities: For example, Petek et al. (2001) reported a de novo duplication disrupting *IMMP2L* (*inner mitochondrial membrane protein 2L*) and four independent studies described rearrangements at the chromosome 18q22 region with breakpoints mapping approximately within 1 Mb of each other. However no missense or nonsense mutations been identified in *IMMP2L* or in 18q22 transcripts, though the number of screened individuals has been very small.

Two similar findings are notable for their overlap with the ASD literature: An insertion of chromosome 2p21–p23 at 7q35–q36 was found to disrupt *CNTNAP2* in three affected individuals from one family (Verkerk et al., 2003), and Lawson-Yuen et al. (2008) reported a pedigree with a transmitted *NLGN4X* deletion involving exons 4, 5, and 6. The proband had autism as well as motor tics, while his sibling who also carried the deletion was diagnosed with TS and ADHD. The carrier mother was reported to have a learning disorder, anxiety, and depression. Again, large-scale sequencing of TS probands has not been reported for either transcript.

In a study from our laboratory that has become the subject of some contention, Abelson and colleagues (2005) reported a de novo chromosome 13 inversion in a sporadic TS pedigree mapping 350 kb from the transcript *Slit and Trk-like, Family Member 1* (*SLITRK1*). Subsequent sequence analysis of 174 unrelated probands revealed a single nucleotide deletion predicted to result in a prematurely truncated protein that segregated with TS and trichotillomania (compulsive hair pulling) (TTM) in the small family in which it was identified. Two independent occurrences of a rare single base change (var321) in a highly conserved region of the *SLITRK1* 3′UTR, corresponding to the binding site for the microRNA hsa-miR-189, were also identified. In vitro methods were used to demonstrate the functional consequences both of the coding and 3′UTR variations and haplotype analysis was performed to test whether the UTR variants were independent. Screening of more than four thousand controls resulted in a nominally significant association with TS ($p = 0.0056$).

Subsequent genetic studies of *SLITRK1* have yielded inconsistent results. Resequencing of individuals with TS has not revealed additional obviously pathogenic coding mutations (Chou et al., 2007; Deng et al., 2006; Zimprich et al., 2008). A common variant candidate gene study in a small cohort found significant association (Miranda et al., 2009) and several rare

missense mutations restricted to individuals with TTM were identified in (Zuchner et al., 2006); however, the small sample size of the former and the absence of a bona fide mutation burden analysis is the latter limited the conclusions that could be drawn from either study.

Two publications have specifically evaluated the rare variant var321 (Keen-Kim et al., 2006; Scharf et al., 2008). Given the extreme low-allele frequency, neither had the sample size necessary to conduct meaningful statistical analyses. However, both noted that the variant, while present in affected family members, appeared to be neither necessary nor sufficient for TS in some of these pedigrees and both found a high proportion of affected families of Ashkenazi descent that carried var321, leading to the contention that our initial report was an incidental finding confounded by population stratification.

As discussed above, the criteria implicitly employed in these studies would be appropriately applied to alleles purported to carry Mendelian risks but provides little evidence for or against association of var321. Moreover, our laboratory subsequently tested the hypothesis that population stratification due to occult Ashkenazi ancestry led to the initial finding (O'Roak et al., 2010). Using a combination of genome-wide genotyping data, a multidimensional scaling analysis and dense haplotype mapping we found no evidence to support the conclusion that occult ethnicity confounded our results. Instead the additional data provided further evidence that the two instances of var321 seen in the initial probands were on distinct haplotypes, suggesting either recurrent independent mutations or the sharing of an ancient allele by affected individuals, with either alternative providing additional support for the association with TS.

To date, only a single genome-wide study has been published of structural variation and this included 111 individuals (Sundaram et al., 2010). Despite careful attention to potential confounds including population stratification and batch effects, the small sample size limited the ability of the authors to arrive at definitive conclusions. However, recurrent CNVs were identified at loci previously implicated in ASD and schizophrenia, including *NRNX1* and the chromosome 1q21 region.

Finally, a recent study from our laboratory used parametric linkage to identify a rare functional nonsense mutation in the gene segregating with TS in a dense pedigree (Ercan-Sencicek et al., 2010). A family with a father and eight offspring meeting DSM-IV-TR criteria for TS and no evidence for bilineal inheritance was mapped using parametric linkage. Genome-wide analysis identified a single region reaching the maximum theoretical LOD score for the pedigree (Lod = 2.1). Sequencing of all genes within the interval led to the discovery of a single rare coding mutation, a premature termination codon (W317X) in the gene *L-histidine decarboxylase* (*HDC*), the rate-limiting enzyme in histamine biosynthesis. Given experimental evidence for incomplete or absent nonsense-mediated decay, and the knowledge that the wild-type (wt) HDC protein forms an active homodimer, the mutant protein was evaluated for possible dominant negative effects, and this was confirmed in in vitro studies.

Genetic Findings and Emerging Models

Given the paucity of specific genetic findings, the ability of gene discovery efforts to define molecular models remains limited, and a comprehensive consideration of the data regarding neuroanatomical studies of TS is beyond the scope of this review. Briefly, attention has been focused on the cortical striatal-thalamo-cortical circuitry that mediates the integration of movement, sensation, emotion, and intention. This long-standing interest is supported by analogy to other movement disorders, model systems studies, and neuroimaging data, and recent neuropathological findings pointing to abnormalities in straital cholingeric and GABAergic interneurons (Kalanithi et al., 2005; Kataoka et al., 2010).

There has also been a longstanding focus in the TS field on dopaminergic (DA) neurotransmission. In addition to analogies to other movement disorders, this interest is driven in part by the clinical observation that DA blockade is the most effective and reliable pharmacological means in the current armamentarium to transiently reduce tics (Scahill et al., 2006). Moreover DA agonists may engender tics and other stereotypes in individuals both with and without TS. However, neither genetic or neuroimaging studies have so far been definitive and overall the nature of the molecular mechanisms underlying TS remain elusive (Harris and Singer, 2006; Singer, 2005).

As noted, strong genetic findings in TS are limited and consequently the relevance of the biology of isolated outlier cases remains uncertain: *SLITRK1* has been pursued on several fronts. Our laboratory in collaboration with Angeliki Louvi reported on the conserved and developmentally regulated pattern of expression of SLITRK1 in CTSC circuits, highlighting both mRNA and protein expression in cholinergic interneurons and the striosomal compartment (Stillman et al., 2009); Kajiwara and colleagues (2009) found evidence that the previously noted regulation of neurite outgrowth (Aruga and Mikoshiba, 2003) is mediated by binding to 14-3-3 molecules; and Katayama et al. (2010) described an anxiety phenotype and evidence for increased noradrenergic neurotransmission in the mouse knockout. A particularly intriguing recent result has been the finding of excessive grooming, a putative obsessive-compulsive phenotype, in the mouse knockout of the closely related molecule, *SLITRK5* (Shmelkov et al., 2010).

The identification of a highly penetrant mutation in the gene *L-histitide Decarboxylase* (*HDC*) in a dense pedigree with TS provides a separate but potentially direct link to prior hypotheses regarding the involvement of DA pathways in TS: histaminergic (HA) neurotransmission is mediated by four known G protein-coupled receptors; HA in the CNS is known to modulate arousal, cognition, movement, and behavior, and while the biological implications are not yet clear, both histamine 2 (H2R) and histamine 3 (H3R) receptors are enriched in the human and rodent striatum (Haas et al., 2008). H3R is of particular interest as it acts as a presynaptic autoreceptor on HA containing projection neurons, with activation leading to decreased synthesis and release. It also functions as a presynaptic receptor on non-HA-containing neurons, regulating a variety of neurotransmitters, including DA and serotonin; and as a postsynaptic receptor that has been shown to colocalize with and modulate signaling through both D1 and D2 receptors in the striatum.

While HDC null mice are viable and exhibit no structural brain abnormalities, they have shown decreased brain HA and increased sensitivity to stereotypic behaviors upon administration of DA agonists (Kubota et al., 2002). Such stimulant-induced

movements, including rearing, sniffing, and biting have previously been proposed as a model of human tics (Saka and Graybiel, 2003). Taken together, these data point to the possibility that decreased HA synthesis and/or release in the CNS, whether mediated by *HDC* mutation or other processes, could predispose to or augment tics. Consistent with this hypothesis, studies of selective H3R antagonists and inverse agonists which increase histaminergic neurotransmission have been shown to moderate the effects of stimulants in rodent models (Fox et al., 2005), although a very recent study has called the extent of the effect into questioned (Burban et al., 2010).

Finally, H3R compounds have already entered early clinical trials, have a reportedly favorable side effect profile, and are being evaluated for a variety of neuropsychiatric indications. The convergence of the human genetic and model systems data and the potential availability of clinically useful compounds being investigated in related psychiatric conditions suggests a surprisingly direct avenue to test empirically the generalizabilty of the biology implicated by gene discovery in a single highly unusual pedigree.

Summary, Conclusions, and Future Prospects

The foregoing has highlighted both the tremendous promise as well as the considerable challenges that continue to face the study of the genetics of child psychiatric disorders, and ASD and TS in particular.

With regard to ASD, this review points to several overarching conclusions: (1) that despite notable progress, many current findings are not yet as definitive as in other areas of medicine; (2) that some of this uncertainty reflects the tremendous locus heterogeneity of this syndrome as well as the inherent difficulty in establishing association of rare alleles—either those that are de novo or conferring moderate risks; (3) that it would be entirely premature to minimize the importance of common variant studies, as ASD samples are just now reaching a point where well-powered analyses can realistically investigate the contribution of common alleles carrying plausible risks; and (4) that even a relatively small number of unambiguous genetic findings, whether with regard to common or rare variants, hold the potential to elaborate relevant molecular mechanisms.

With regard to TS, the conclusions are quite similar, but, as noted, the field has been comparatively slow to leverage emerging technologies due to limited patient resources. Nonetheless, the findings to date point to overlapping risks with other neurodevelopmental disorders, a theme that is extending across all of psychiatry. Moreover, the recent HDC findings from our group highlight a more general theme regarding the opportunities that may be afforded by simultaneous rapid progress across scientific disciplines. Given parallel advances in neurobiology and pharmacology, the speed with which genetic findings may be found to translate into clinically relevant investigations also promises to accelerate.

Finally, the review has focused on the promise that gene discovery has to drive neurobiological studies yielding novel insights into the molecular mechanisms of child psychopathology. As noted throughout, this has so far been most notable with regard to syndromic presentations and outliers, the challenges of arriving at a necessary level of certainty regarding genetic findings in idiopathic ASD and TS remains considerable. At the same time, the tools necessary to do so are clearly present. The consolidation of very large samples, the ability to feasibly query every base of the human exome and the imminent ability to do so cross the entire human genome, the maturation of proven methods to confirm association in multigenic complex disorders, and the manner in which new technologies are empowering both pedigree-based and case-control studies, all suggest that the optimism that characterizes the field is well founded.

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