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Autism Spectrum and Obsessive–Compulsive Disorders: OC Behaviors, Phenotypes and Genetics

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Abstract

Autism spectrum disorders (ASDs) are a phenotypically and etiologically heterogeneous set of disorders that include obsessive–compulsive behaviors (OCB) that partially overlap with symptoms associated with obsessive–compulsive disorder (OCD). The OCB seen in ASD vary depending on the individual's mental and chronological age as well as the etiology of their ASD. Although progress has been made in the measurement of the OCB associated with ASD, more work is needed including the potential identification of heritable endophenotypes. Likewise, important progress toward the understanding of genetic influences in ASD has been made by greater refinement of relevant phenotypes using a broad range of study designs, including twin and family-genetic studies, parametric and nonparametric linkage analyses, as well as candidate gene studies and the study of rare genetic variants. These genetic analyses could lead to the refinement of the OCB phenotypes as larger samples are studied and specific associations are replicated. Like ASD, OCB are likely to prove to be multidimensional and polygenic. Some of the vulnerability genes may prove to be generalist genes influencing the phenotypic expression of both ASD and OCD while others will be specific to subcomponents of the ASD phenotype. In order to discover molecular and genetic mechanisms, collaborative approaches need to generate shared samples, resources, novel genomic technologies, as well as more refined phenotypes and innovative statistical approaches. There is a growing need to identify the range of molecular pathways involved in OCB related to ASD in order to develop novel treatment interventions.

Introduction

Family and twin studies indicate that autism spectrum disorders (ASD) have a strong genetic component [Bailey et al., 1995; Folstein & Rutter, 1977; Folstein & Rosen-Sheidley, 2001; Gupta & State, 2007; Veenstra-Vander-Weele & Cook, 2004]. It is also clear that ASD are etiologically heterogeneous. This heterogeneity can markedly reduce the power of gene-localization methods, including linkage analysis [Alcais & Abel, 1999; Gu, Province,

Todorov, & Rao, 1998; Zhang & Risch, 1996]. Some of the core features of ASD (e.g. phrase speech delay and repetitive behaviors) may themselves be familial traits [Freitag, 2007; Kolevzon, Smith, Schmeidler, Buxbaum, & Silverman, 2004; Ronald et al., 2006a; Ronald, Viding, Happe, & Plomin, 2006b; Silverman et al., 2002; Yrigollen et al., 2008] and may thus be useful phenotypes for identifying ASD-related genes.

Obsessive–compulsive behaviors (OCB) are one of the behavioral phenotypes that have shown the greatest promise for identifying different ASD-related phenotypes based on cross-sectional and family-genetic, linkage and association studies [Bejerot, 2007; Bejerot, Nylander, & Lindstrom, 2001; Bolton, Pickles, Murphy, & Rutter, 1998; Buxbaum et al., 2004; Cath, Ran, Smit, van Balkom, & Comijs, 2008; Cullen et al., 2008; Ivarsson & Melin, 2008]. At the surface, this would naturally lead to questions concerning the heritability of obsessive–compulsive disorder (OCD) and the possibility that some of these behaviors might be shared in common across OCD and ASD. Following this reasoning, it is clear that twin and family-genetic studies suggest that genetic factors play a role in the transmission and expression of OCD [Pauls, 2008]. Although earlier studies have indicated that the vertical transmission of OCD in families is consistent with the effects of a single major autosomal gene [Cavallini, Pasquale, Bellodi, & Smeraldi, 1999], it is likely that there are a number of vulnerability genes involved. Similar to ASD, etiologic heterogeneity may be reflected in phenotypic variability, making it highly desirable to dissect the OCD, at the level of the phenotype, into valid quantitative heritable components.

Questions are increasingly being raised concerning the degree to which the OCB seen in many individuals with ASD are related to their social difficulties [Mandy & Skuse, 2008]. Nevertheless, there remain major questions concerning the precise nature of the OCB seen in ASD and whether and how closely they resemble those seen in OCD. We undertake this review with the firm belief that identifying genetic risk factors for ASD, OCB, and related phenotypes and characterizing their role in early brain development will be important for understanding the molecular pathogenesis of ASD, as well as for defining methods for better diagnostics, and developing therapeutic approaches [Abrahams & Geschwind, 2008]. In order for this goal to be achieved, common phenotypic measurements are needed. Consequently, the question of “what phenotype is being evaluated” will be a key focus as we review the available data concerning the broader ASD phenotype [Bolton et al., 1998; Cath et al., 2008; Piven, Palmer, Jacobi, Childress, & Arndt, 1997].

Clinical Phenotypes

A major issue in considering the phenotypic overlap between ASD and OCD concerns the degree to which the behaviors and mental states described as “compulsive” or “obsessional” are really the same across the two sets of disorders. Terms used to describe the OCB seen in ASD include: repetitive interests, behaviors, and activities [Bodfish, Symons, Parker, & Lewis, 2000; Charman & Swettenham, 2001; Mandy & Skuse, 2008]. Questionnaire, interview, and direct observation data all point to the presence of a range of OCB in ASD that, to some extent, are dependent on the individual’s mental age (Table I). While there are a few overlapping items such as ordering/arranging, collecting, and need for things to be “just right,” it is also clear that the range of repetitive behaviors includes some seen in typically developing children that may persist in individuals with ASD and OCD [Esbensen, Seltzer, Lam, & Bodfish, 2009].

From the ASD perspective, information collected during formal evaluations using the Autism Diagnostic Inventory—Revised (ADI-R), [Lord, Rutter, & Le Couteur, 1994] provides a sense of what behaviors are typical of some individuals with ASD. For example, Frazier et al. [Frazier, Youngstrom, Kubu, Sinclair, & Rezai, 2008] recently reported the

results of both exploratory and confirmatory factor analysis of the ADI-R and confirmed the existence of a Stereotyped behavior and Restricted interests factor that includes each of the ratings on the Repetitive behavior domain (R1: circumscribed interests; R2: compulsive routines; R3: stereotyped motor mannerisms; and R4 preoccupation with objects) (Table I). A number of other questionnaires and direct observation measures contain similar constructs [Berument, Rutter, Lord, Pickles, & Bailey, 1999; Bodfish et al., 2000; Wetherby, Watt, Morgan, & Shumway, 2007]. At present, the most detailed of these scales is the Repetitive Behavior Scale—Revised that includes 43 items divided into five domains (Table I). Of interest, scores in each of these domains are sensitive to both chronological and mental age. The scores for each domain decrease with advancing chronological age and are higher in the presence of intellectual disability [Esbensen et al., 2009]. The slope of the decline with chronological age was steepest for the stereotyped repetitive behaviors and the ritualistic/sameness repetitive behaviors domains.

However, typically developing young children beginning around the second year of life develop a variety of rituals, habits, routines, and preferences, some of which resemble the behaviors associated with ASD and OCD [Evans et al., 1997; Zohar & Felz, 2001]. The idea that compulsive ritualistic behaviors may be normative in young children is not new. Gesell et al. [Gesell, 1928; Gesell & Llg, 1943] were among the first to recognize that young children—particularly those around the age of two and a half—begin to establish rigid routines that Gesell termed the “ritualisms of the ritualist.” Rather than addressing emotional needs, Gesell believed children engage in rituals to master the tasks of a specific developmental epoch, for instance, matters of feeding, toileting, and dressing. More than 80% of parents report the presence of a bedtime ritual for children by the age of 3 years. Less well known is that for most children a regular sequence exists in which a need to arrange things “just right” or in a symmetrical pattern appears next, followed by the child’s being very concerned with dirt and germs, and finally, the need to collect and store objects. With the exception of hoarding, each of these behaviors peaks at the age of 3 years [Evans et al., 1997]. Hoarding, in contrast, shows a monotonic increase, at least until the age of 6 years, when more than 60% of normal children display this trait [Evans et al., 1997; Zohar & Felz, 2001]. The earlier the age at which these concerns appear, the more advanced is the child’s developmental level. It is also striking that children with severe intellectual disabilities, including many children with ASD whose mental age remains in the low range, show a persistence of many of these OCB [Evans & Gray, 2000; Greaves, Prince, Evans, & Charman, 2006]. From this perspective, one could ask whether the repetitive behaviors seen in some ASD children are little more than the persistence or increase in severity or frequency of these “normal” repetitive behaviors.

The complex clinical presentation of OCD can be summarized using a few consistent and temporally stable symptom dimensions [Mataix-Cols, Rosario-Campos, & Leckman, 2005]. These can be understood as a spectrum of potentially overlapping features that are likely to be continuous with “normal” worries and extend beyond the traditional nosological boundaries of OCD. Although the understanding of the dimensional structure of obsessive-compulsive (OC) symptoms is still imperfect, recent large-scale meta-analysis of data from more than 5,000 individuals provides the clearest picture of data of the inter-relationship of these symptom dimensions [Bloch, Landeros-Weisenberger, Rosario, Pittenger, & Leckman, 2008a]. The four factors that are well supported by this systematic analysis were—(Factor I) Forbidden thoughts—Aggression, sexual, religious, and somatic obsessions and checking compulsions; (Factor II) Symmetry—Symmetry obsessions and repeating, ordering and counting compulsions; (Factor III) Cleaning—Cleaning and contamination and (Factor IV) Hoarding—Hoarding obsessions and compulsions. While any of these may be present in individuals with ASD, Factor II is particularly common. This symptom dimension is also one where various sensory phenomena are commonplace. These sensory elements often

occur prior to the repetitive movement and include localized tactile and muscle-skeletal sensations that are associated with an urge to perform certain repetitive behaviors; “just-right” perceptions associated with sensory stimuli such as visual, tactile, or auditory; as well as a feeling of incompleteness which refers to an inner sense of discomfort that can only be relieved by performing the repetitive behaviors [Prado et al., 2008].

Efforts to use the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) in assessing the OCB in ASD began with the work of McDougle [McDougle et al., 1995]. They recruited 50 ASD subjects (with or without significant intellectual disability) and compared them to 50 age- and sex-matched individuals with OCD. They reported that compared to the OCD group, the ASD patients were significantly less likely to experience thoughts with aggressive, contamination, sexual, religious, or somatic content. With regard to compulsions, cleaning behaviors were less common in the ASD group; however, other compulsions including repetitive ordering, hoarding, touching, tapping, or rubbing, and self-damaging or self-mutilating behavior occurred significantly more frequently in the ASD patients. Self-injurious behaviors are a subset of stereotypic behaviors that can be negatively correlated with intellectual functioning (reviewed in [Minshawi, 2008]). When compared to age, sex, and IQ-matched controls, children with autism engaged in more severe self-injury. It has been found to be associated with deficits in adaptive and communicative skills in children with autism and has been described in a range of neurodevelopmental disorders [Symons, Sperry, Dropik, & Bodfish, 2005].

More recently, Russell et al. [Russell, Mataix-Cols, Anson, & Murphy, 2005] studied 40 individuals with high-functioning ASD and compared them to a matched group of individuals with OCD. Although the OCD group had higher OC symptom severity ratings, up to 50% of the ASD group reported at least moderate levels of interference from their OC symptoms. Some of the most frequent OC symptoms reported from the Y-BOCS symptom checklist in the high-functioning ASD group included: obsessions of contamination (60%), symmetry (55%), aggressive content (50%), and hoarding (43%); as well as compulsions of checking (60%), cleaning (55%), and repeating (43%). In addition, Cath et al. also used the Y-BOCS to compare a group of high-functioning ASD cases with either comorbid OCD or comorbid social anxiety disorder (SAD) with individuals with either OCD or SAD alone as well as with a group of normal controls [Cath et al., 2008]. Twelve subjects were in each of the four groups. The factor scores for the four OC symptom dimensions were then compared across the four groups. Although few significant differences were observed, in each case the mean values for the OC symptom dimensions were higher in the OCD group and in the ASD comorbid group compared to the SAD and the normal control groups. This study is in need of replication with a larger number of subjects in each group and with the addition of a pure ASD contrast group. That said, these findings are of interest and bring to mind a recent report by Pine et al. [Pine, Guyer, Goldwin, Towbin, & Leibenluft, 2008] that found that pediatric patients with mood disorders exhibit higher scores on ASD symptom scales than healthy children or children with non-OCD anxiety disorders.

There has also been an effort to adjust the available OCD severity rating scales such as the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS) for use in children with ASD [Scahill et al., 2006]. This has led to the creation of CY-BOCS modified for pervasive developmental disorders (CY-BOCS-PDD, Table I). Scores on the CYBOCS-PDD only modestly correlated with the Repetitive behavior domain of the ADI-R and they also failed to discriminate between measures of repetitive behavior and maladaptive behavior. This suggests that these two scales may be measuring partially distinctive traits. Another approach would be to use the Dimensional Yale-Brown Obsessive Compulsive Scale (DY-BOCS), [Rosario-Campos et al., 2006]. The DY-BOCS separately assesses the clinical severity associated with each OC symptom dimension. The use of this scale in family-

genetic, twin, linkage and association studies would allow investigators to better characterize the nature of the OC traits seen in the relatives of ASD probands.

Neuropsychological Endophenotypes

Yet another approach is to identify potentially informative endophenotypes based on neuropsychological test performance or on brain imaging findings. Ideally, traits identified in this manner would be evident in unaffected family members as well as the probands. One example of this approach is reported by Delorme et al. [Delorme et al., 2007]. They administered five tests assessing executive functions (Tower of London, verbal fluency, design fluency, trail making, and association fluency) to 58 unaffected first-degree relatives (parents and siblings) of probands with ASD and 64 unaffected first-degree relatives of OCD patients. Only the Tower of London results showed similarities between the ASD relatives and the relatives of OCD patients, suggesting shared executive dysfunction in this domain. There are several endophenotypes of this sort that have recently emerged in OCD. For example, Chamberlain et al. [Chamberlain et al., 2008] identified reduced activation of several cortical regions, including the lateral orbitofrontal cortex in both OCD patients and a matched group of unaffected first-degree relatives, during a reversal learning task. It would be useful to know if a similar result would be seen in the first-degree relatives of ASD probands.

Recently, Bloch et al. [2008] discovered that as many as half of pediatric onset OCD cases have a marked verbal–performance IQ discrepancy. This association of verbal–performance IQ discrepancy and OCD was still significant after adjusting for full-scale IQ, age and gender and excluding OCD subjects with comorbid ADHD or a tic disorder. This finding is of potential interest given that [Williams, Goldstein, Kojkowski, & Minshew, 2008] also found a similar profile of lower performance IQ scores relative to verbal IQ scores in 18–32% of children with high-functioning ASD.

Evidence for a Familial Relationship Between ASDs and OCB

Twin and Family Studies

There are a range of genetic and environmental factors that interact over the course of brain development that lead to the emergence of autistic disorder and related OCB phenotypes (see Figure 1). The finding of Folstein and Rutter [Folstein & Rutter, 1977] that many of the nonautistic co-twins in their ASD twin study, while not meeting the criteria for autism showed ASD traits, sparked a renewed interest in identifying heritable “lesser variants.” This finding led, in part, to the initiation of two large studies done more or less in parallel [Bolton et al., 1994; Piven et al., 1997]. The results taken together indicate that the first-degree relatives of individuals with ASD have an increased tendency to show social reticence and communication difficulties as well as an insistence on sameness (IS).

Subsequently, there have been at least three family-genetic studies that have indicated that OCD itself may be part of the “broader ASD phenotype.” There are data to suggest that the association with OCD may be strongest in families of individuals on the more severe end of the ASD (i.e. those with autistic disorder), especially those with prominent repetitive behaviors [Bolton et al., 1998; Hollander, King, Delaney, Smith, & Silverman, 2003; Wilcox, Tsuang, Schnurr, & Baida-Fragoso, 2003]. Specifically, Bolton et al. [Bolton et al., 1998] studied the pattern of familial aggregation of psychiatric disorders in relatives of 99 autistic and 36 Down syndrome probands and found that motor tics, OCD, and affective disorders were significantly more common in relatives of autistic probands. Those relatives with OCD were also more likely to exhibit autistic-like social and communication impairments. Subsequently, [Wilcox et al., 2003] interviewed 300 family members of

autistic probands (120 first-degree, 150 second-degree, and 30 third-degree relatives). In addition, they interviewed 290 family members of probands with more broadly defined pervasive developmental disorders (PDD, 121 first-degree, 139 second-degree, and 30 third-degree relatives) and 310 family members of a healthy control group (123 first-degree, 149 second-degree, and 38 third-degree relatives). They found a significant concentration of psychiatric disorders, primarily OCD and other anxiety disorders, in just the relatives of the autistic probands. The degree of mental illness in the families of autistic probands was more than five times higher than in either the PDD contrast group ($\chi^2 = 8.45$, $P < 0.001$) or the healthy control group ($\chi^2 = 9.58$, $P < 0.001$).

The finding that OCD was largely seen just in the families of probands with autistic disorder is striking and requires replication, particularly in light of the findings reported by Hollander et al. [Hollander et al., 2003]. They evaluated just the parents of autism disorder probands with high vs. low rates of repetitive behaviors as measured by high scores on R1 and R2 subscales of the ADI-R (Table I). They found that children who had high total scores on the repetitive behavior domain of the ADI-R were significantly more likely, by a factor greater than 3, to have one or both parents with OC traits or OCD compared with children who had low total scores on this domain ($\chi^2 = 4.70$, $P = 0.03$). This was especially true of the fathers, 27% of whom met criteria for OCD as opposed to just 7% of the mothers. In future studies, it will be of interest to examine the OC symptom dimensions that are the most prominent in these fathers. Our prediction is that OC symptoms associated with ordering, symmetry, counting, doing and re-doing, and the need for things to be “just-right” would be particularly common. It will also be important to determine if this association was more common among the fathers of autistic children compared to the fathers of nonautistic developmental disordered probands.

Quantitative Genetics

Quantitative genetic studies are designed to evaluate the relative strength of genetic and environmental influences on variations of particular traits within a population. In human research, this is most commonly studied using twin and adoptee designs. They are highly dependent on the assumptions underlying the models being used to evaluate the available data and as such cannot “prove” that a particular model is true. The most that can be said is that a particular model is “consistent with the available data.” Another challenge for quantitative genetic studies in autism is that analytic methods for evaluating multiple genes of small effect size, as found in autism, are still in their early stages of development.

In relation to ASD, several quantitative genetic studies have sought to estimate the heritability of ASD-related OCB. Using items from the ADI-R, in a large sample ($N=457$) of individuals within 212 multiply affected sibships, Silverman et al. [Silverman et al., 2002] found evidence that the severity of an autistic person’s ASD-related OCB were largely unrelated to their level of social-communication impairment. This finding was supported by a subsequent study from the same group [Klevzon et al., 2004], which compared intrafamilial to interfamilial trait variability to estimate familiarity. In a sample of 15 pairs of identical twins and one set of quadruplets, they found no evidence supporting the view that ASD-related OCB were related to their level of social-communication impairment.

Subsequently, investigators [Ronald et al., 2006a; Ronald, Happe, & Plomin, 2005] completed two twin studies that yielded a similar conclusion. First, they gave a questionnaire to parents and teachers of over 3,000 twins, who were part of the Twins Early Development Study, a cohort of twins born in the UK between 1994 and 1996. This questionnaire had ten items designed to measure possible “social impairments” (social and communication deficits typical of ASD) and six items addressing “nonsocial behaviors

relevant to autism.” Only modest correlations between these two scales were found using either the parent data or the teacher data ($n=3,090$). In the formal twin analyses looking at additive genetic variance vs. shared and unshared environmental factors, they reported that both traits were highly heritable (62–76%), but that the genetic correlation between social impairments and nonsocial behaviors relevant to autism was quite low. This led the authors to predict that “over half of the genes found to be associated with quantitative variation in social behaviors will not be found to be associated with nonsocial behaviors associated with autism”. In sum, the available quantitative genetic literature is consistent with the view that the OCB associated with ASD are partially genetically independent of those associated with the social disabilities of ASD.

Linkage Analyses

Although there is considerable evidence for a strong genetic component to the intergenerational vulnerability to develop ASD, several genome-wide screens for susceptibility genes have been carried out with limited success in consistently identifying specific loci. This is likely to reflect the presence of a multiplicity of genes of modest effect as well as phenotypic, genetic, and population diversity. Among the available genome-wide studies, Alarcon et al. [2002] were the first to explore the OCB subphenotype [Alarcon et al., 2002]. In addition to finding strong quantitative trait locus evidence for age-of-first word on chromosome 7q, they also reported a smaller broad peak on 7q for restrictive–repetitive behavior phenotype that is considered a distinct locus.

Subsequently, Buxbaum et al. [Buxbaum et al., 2004] systematically assessed the value of severe OCB in defining a more homogenous subset of families. OCB were assessed using the ADI-R (Table I). In the sample with more severe OCB, the strongest evidence for linkage was at the marker D1S1656 (Chromosome 1: 245.1 cM) where the multipoint NPL score was just above 3.00. The authors concluded that their data supported the presence of an ASD susceptibility gene associated with OCB on chromosome 1 and provided modest support for the presence of OCB-related ASD susceptibility genes on chromosomes 6 and 19.

Another study that explicitly sought to identify genetic loci associated with the OCB of ASD was reported by Shao et al. [Shao et al., 2003]. They limited their focus to a specific region on chromosome 15q11–13 and utilized a novel technique called ordered subset analysis to ensure a greater measure of sample homogeneity with regard to the OCB associated with ASD (“IS”). Individual scores were computed by summing a subset of the ADI-R items designed to measure the OCB associated with ASD. Their analysis of families sharing high scores on the IS factor increased the probability for linkage evidence in the 15q11–q13 region from a LOD score of 1.45 to a LOD score of 4.71. While their results support the hypothesis that the analysis of phenotypic homogeneous subtypes may be a powerful tool for the mapping of disease-susceptibility genes in complex traits, it is notable that this chromosomal region was not one of the chromosomal regions identified in the Buxbaum et al. [2004] study. This is probably explained because Buxbaum’s group used very severe OCB to define a homogeneous subset of families; and Shao focused on subjects with IS to create homogeneity.

Several autism linkage studies have pointed to the 17q region near the serotonin transporter gene (*SERT*) [Stone et al., 2004; Sutcliffe et al., 2005]. The highest logarithm of the odds score for a linkage peak in the 17q11.2 region (where *SERT* is located) was found when all male affected sibling pairs were considered [Stone et al., 2004], but no similar peak in this region was present when sibling pairs had at least one affected female [Sutcliffe et al., 2005]. This suggests that sex differences also need to be considered in studying genetic risk

for OCB-related subphenotype given that fathers share OC traits more frequently with their ASD children [Hollander et al., 2003].

Candidate Gene Studies

Serotonin Genes

Serotonergic pathways have been consistently implicated in the pathobiology of both ASD and OCD [Goddard, Shekhar, Whiteman, & McDougle, 2008; Pardo & Eberhart, 2007]. Several serotonergic genes have been evaluated as candidate genes in both ASD and OCD including *SERT* (*SLC6A4*), tryptophan hydroxylase (*TH2*) and *SLC6A4*, and *5-HT(2B)* receptor gene.

SERT, SLC6A4—The *SERT* gene is located on 17q11.1–q12 and is called *SLC6A4* because it belongs to the monoamine transporter family. *SERT* has 13–14 exons with alternate splicing of exon 1B. It also has a well-characterized functional polymorphism upstream of the coding sequence. The promoter region of *SERT* contains a polymorphism with “short” and “long” repeats that leads to variation levels of gene transcription [Lesch et al., 1994, 1996]. The long (L) allele consists of 16 copies of a 20–23 base pair repeat unit and the short (S) allele contains 14 copies. In addition to these length variants, there is a single nucleotide polymorphism (SNP) (rs25531, A→G) that changes the functional status of the L allele [Hu, Frank, Heine, Lee, & Quackenbush, 2006]. Another SNP (rs25532, C→T) also relates to gene expression suggesting further categorization of functional variants [Wendland et al., 2008]. Unrecognized SNP variability related to functional expression may explain some of the contradictory results with combined subgroups when examining disorder association.

Initially, OCD studies reported a family-based association with the L allele in European-American families [McDougle, Epperson, Price, & Gelernter, 1998] and that OCD probands were more likely to carry two copies of the long allele or L/L (48 vs. 32%), [Bengel et al., 1999]. However, L allele associations were not found with OCD patients of Afrikaner, Mexican, Jewish, German, French, or other descent [Bloch et al., 2008b; Camarena et al., 2001; Chabane et al., 2004; Di Bella, Erzegovesi, Cavallini, & Bellodi, 2002; Frisch et al., 2000; Walitza et al., 2004]. There was no overall association in a Korean sample, but there was a very low percentage of L/L genotypes and the L/L group combined with the S/L group had higher scores for religious/somatic-related symptoms on the Y-BOCS [Kim, Lee, & Kim, 2005]. Population differences of polymorphism frequencies, SNP variability, how polymorphisms are grouped or combined, and sample ascertainment or phenotype variability all contribute to the complexity of the possible association of *SERT* polymorphisms and OCD.

SERT polymorphism studies in ASD have also yielded complex and mixed results that are likely due to phenotypic and ethnic heterogeneity. There have been reports of increased occurrence of the S allele variant in an American ASD sample [Cook et al., 1997] and the tendency for the L variant in a German sample [Klauck, Poustka, Benner, Lesch, & Poustka, 1997]. Although there is some population-specific replications [Devlin et al., 2005], the range of mixed results reported in the literature likely reflects methodological and sample differences.

A few studies have focused on subphenotypes of ASD that include OCB. For example, a Dutch group found that the 12/12 long allele genotype of Intron 2 VNTR had the highest severity of OCB [Mulder et al., 2005]. They did not find significant differences between L or S *SERT* polymorphisms. In an independent American sample [Brune et al., 2006], there were no significant subphenotype relationships with the Intron 2 VNTR genotypes but there

was a L/L genotype association with the stereotyped and repetitive motor mannerisms sub-domain of the ADI-R. Sutcliffe et al. reported that the presence of novel *SERT* variants, including Gly56Ala, Ile425Leu, and Leu550Val, was correlated with high scores on OCB items of the ADI-R scale [Sutcliffe et al., 2005]. This study illustrates the importance of looking for rare vs. common variants. *SERT* Ileu425Leu was reported in male sibling pairs, both of whom had ASD [Sutcliffe et al., 2005]. Because it was also present in their unaffected mother and three sisters but not their unaffected brother, Sutcliffe et al. suggested that this might be due to a male-biased genetic risk for ASD. This group also reported 19 other *SERT* variants (4 coding, and 15 in 50 and intronic regions) and examined their association with rigid–compulsive traits in their ASD sample [Sutcliffe et al., 2005].

Indeed, it has been suggested that rare gene variants associated with OCD phenotypes may be found in up to 2% of OCD cases [Wendland et al., 2008] and as many as 10% of cases of ASD [Freitag, 2007]. Examining rare variants is an alternative method to the broader scale genome-wide evaluations seeking common variants accounting for common diseases. Both in ASD and OCD, it seems possible that uncommon, relatively highly penetrant functional variants may more directly contribute to these relatively common diseases.

For example, the *SERT* Ileu425Val was originally found in six individuals with OCD (two of whom also had Asperger disorder) within two unrelated families among 112 OCD probands [Ozaki et al., 2003; Wendland et al., 2008]. The total frequency of *SERT* Ileu425Val in all populations that have been genotyped (3155 individuals) is 0.61%. It is a hypermorphic mutation, which produces a gain of *SERT* function [Prasad et al., 2005]. Wendland et al. summarized that Ileu425Val has been identified in 15 clinically evaluated individuals, including 9 with OCD and 1 obsessive–compulsive personality disorder from 5 families out of a total OCD sample of 530 probands/families [Wendland et al., 2008]. Of the 14 cases where *SERT* was also genotyped, it is important to note that Ileu425Val occurred together with the L allele or LL (or L_AL_A) genotype. Looking over all diagnoses in this rare variant sample, social dysfunction disorders such as ASD and social phobia were present in 5/8 men but only 1/6 women, suggesting sex differences of clinical phenotype.

Tryptophan hydroxylase (TPH2)—The *TPH2* gene has been studied in ASD and OCD because it is the rate-limiting enzyme responsible for 5-HT synthesis in the brain. Coon et al. reported a possible association between the *TPH2* gene and two SNP variants (rs4341581 in intron 1 and rs11179000 in intron 4) in ASD, especially in patients reported to have more severe repetitive and stereotyped behaviors [Coon et al., 2005]. Similarly, Mössner et al. studied *TPH2* and found two common SNPs in a different region of the gene (rs4570625 and rs4565946 in intron 2) to be associated with childhood onset OCD in a family-based sample of 71 trios [Mossner et al., 2006]. More recent studies have failed to replicate these initial studies of *TPH2* and OCD association. When rs4341581, rs11179000, and a different set of eight SNPs were selected to cover the 95 kb region of the *TPH2* gene and tested in a large cohort of 352 families with ASD, no significant associations in the overall group or in any clinically dened subsets of families with either severe OCB or self-stimulatory behaviors were found [Ramos et al., 2006]. On a larger sample of Italian and American probands with ASD, *TPH2* alleles and haplotypes were not significantly associated with research diagnostic criteria for ASD, with presence or absence of repetitive and stereotyped behaviors, or with endophenotypic analyses for 5-HT blood levels, cranial circumference, and urinary peptide excretion rates [Sacco et al., 2007].

5-HT(2B) receptor gene—Given that atypical antipsychotics are sometimes successful in augmenting OCD treatment with SSRIs, the 5HT(2B) receptor is a potential candidate for involvement in the neurobiology of OCD. *5HT(2B)* is located on chromosome 2q36–37.1 and the 2q region was implicated in a genome scan with 56 individuals from seven families

with multiplex pediatric probands [Hanna et al., 2002]. DNA from probands from these seven families, along with ten unrelated control subjects and ten unrelated ASD probands, were studied but no evidence for a functional mutation was found.

Glutamate Genes

The glutamatergic system has been implicated in the neurobiology of both ASD and OCD [Bhattacharyya & Chakraborty, 2007; Pardo & Eberhart, 2007; Pittenger, Kelmendi, Wasylink, Bloch, & Coric, 2008]. A majority of the studies have examined the role of a high-affinity glutamate transporter and several of the glutamate receptors.

SLC1A1—The *SLC1A1* gene is located on chromosome 9p24 and belongs to the monoamine transporter family as a neuronal glutamate transporter expressed in the brain (EAAC1/EAAT3). Animal studies have shown that *Slc1a1* deficient (−/−) mice have decreased neuronal glutathione levels and develop brain atrophy and behavioral changes with aging [Aoyama et al., 2006]. Similar to *SERT*, the glutamate transporter is important for the excitatory actions of glutamate and for maintaining extracellular concentrations within a normal range. The chromosomal region of *SLC1A1* showed suggestive linkage in a genome-wide scan of seven, large extended pedigrees of probands with early onset OCD [Hanna et al., 2002] and linkage in 42 pedigrees with early onset OCD [Willour et al., 2004]. In addition, three studies have reported an association between markers at *SLC1A1* and independent OCD samples [Arnold, Sicard, Burroughs, Richter, & Kennedy, 2006; Dickel et al., 2007; Stewart et al., 2007]. In a collaborative autism genome-wide linkage project, *SLC1A1* was identified as a candidate gene because it fell close to the linkage peak at 9p24.1 that occurred in families with female probands with ASD [Szatmari et al., 2007]. Brune et al. tested three SNPS (rs301430, rs301979, rs301434) previously associated with OCD and looked for haplotype associations in 86 strictly defined trios with ASD [Brune et al., 2006]. In males only, Family-Based Association Tests showed nominally significant associations between ASD and rs301979 as well as the rs301430–rs301979 haplotype under a recessive model.

Glutamate Receptor Genes

Glutamate receptor 6 gene (*GRIK2* or *GLUR6*) plays a role in synaptic transmission related to learning a memory. It became a candidate gene after studies indicated chromosome 6q21 as a region linked to ASD [Jamain et al., 2002; Philippe et al., 1999]. *GRIK2* is a member of the ionotropic kainate receptor family that is expressed during brain development. Although some studies have reported that markers within *GRIK2* are associated with ASD [Jamain et al., 2002; Kim, Kim, Park, Cho, & Yoo, 2007; Shuang et al., 2004], these same markers do not replicate in all ethnic populations [Dutta et al., 2007]. In a study of *GRIK2* with 156 OCD probands of European descent, the I867 allele on exon 16 was less transmitted than expected [Delorme et al., 2004]. Future research needs to examine subgroups of ASD with more severe OCB as well as to examine the genetics of other genes within the glutamatergic pathway. For example, mRNA levels of several genes in the glutamate system (including *SLC1A3*, glutamate receptor *AMPA1*, and glutamate receptor binding proteins) were abnormal when brain samples of 10 individuals with ASD were compared with 23 matched controls [Purcell, Jeon, Zimmerman, Blue, & Pevsner, 2001].

GABA Receptor Genes

GABA is the main inhibitory neurotransmitter in the human brain and it binds to two distinct receptor types: the ionotropic GABA_A and GABA_C receptors with Cl[−] channels and fast synaptic transmission, or the metabotropic GABA type B (GABA_B) G-coupled protein for prolonged inhibitory signals. Three GABA_A receptor genes (*GABRB3*, *GABRA5*, and

GABRG3) are located in the 15q11–q13 chromosomal region. Several studies have shown linkage to markers near or within *GABRB3* to be associated ASD [Buxbaum et al., 2002; Cook et al., 1997; Curran et al., 2005; Kim et al., 2007; Martin et al., 2000; McCauley et al., 2004; Philippe et al., 1999; Shao et al., 2003], although other studies have failed to replicate this association [Maestrini et al., 1999; Salmon et al., 1999; Tochigi et al., 2007]. Recently, Kim et al. examined SNPs within the 15q11–q13 for association with specific restrictive–repetitive behavior phenotypes measured on the ADI-R and ADOS [Kim et al., 2008a]. Among 93 SNPs, 5 SNPs showed nominally significant association, 3 of 5 were close in proximity to *GABA_A* and 2 of the 5 near *GABA_A* showed genotype-phenotype interactions with an ADI-R subdomain related to inflexible language behavior. Only one study has examined *GABA_A* receptor genes in individuals with OCD [Zai et al., 2005]. They reported nominally significant trends toward biased transmission of the –7265A allele and associations with elevated Y-BOCS severity.

Structural Variant Disorders Associated With Both ASD and OCB

Prevalence of chromosomal abnormalities in individuals with ASD is estimated between 5 and 10% [Zhao et al., 2007a]. Here we focus on known single or multigene alterations that have been associated with the presence of OCB.

Fragile X and Other X-Linked Syndromes

The most prevalent chromosomal abnormality associated with ASD is Fragile X syndrome (FXS). Molecular testing for the *FMR1* gene is recommended in individuals diagnosed with ASD and probands identified with FXS are excluded from most genetics studies of ASD. The behavioral phenotype of FXS includes OC behaviors as well as stereotypic behavior, gaze aversion, inattention, impulsivity, hyperactivity, hyperarousal, social anxiety, withdrawal, social decits with peers, abnormalities in communication, and unusual responses to sensory stimuli. The full mutation is described as having more than 200 CGG repeats in the 5' untranslated region of the *FMR1* located at Xq27.3 and typically involves an altered pattern of methylation. There is transcriptional silencing of the *FMR1* gene and lack of the *FMR1* protein called FMRP. Recent studies suggest that some males with the premutation also have social, emotional, and cognitive decits, although sample sizes are small or clinically referred [Aziz et al., 2003; Dorn, Mazzocco, & Hagerman, 1994; Goodlin-Jones, Tassone, Gane, & Hagerman, 2004; Hagerman & Hagerman, 2002; Moore et al., 2004; Tassone, Hagerman, Chamberlain, & Hagerman, 2000].

A study of men and women with the permutation, but without age-related fragile X-associated tremor/ataxia syndrome (FXTAS), reported higher levels of OC symptoms on the Symptom Checklist-90-R [Hessl et al., 2005]. In men only, elevated *FMR1* mRNA, rather than CGG repeat size or percent of FMRP expression (peripheral lymphocyte immunocytochemistry), was significantly associated with increased OC symptoms and psychotic episodes with and without FXTAS symptoms. They did report an association with elevated *FMR1* mRNA and anxiety in women, but only in women with skewed X activation ratio toward active premutation alleles. Previous studies have shown elevated levels of anxiety and OCB in some females with FXS [Lachiewicz, 1992].

In a recent cytogenetic analysis of 26 patients with OCD, 21% of the peripheral cells of one male patient with OCD were found to have fragile site at Xq27–q28 [Wang & Kuo, 2003]. This was determined to be in the region of FRAXE mutation, a hyperexpansion of the CCG repeat in the 5' untranslated region of the *FMR2* gene [Wang & Kuo, 2003]. Typically FRAXE is associated with mild or borderline mental retardation (50<IQ<85) [Gecz, 2000]. In this patient's family, expansion of FRAXE CCG repeats and methylation co-segregated

with OCD in the proband and a speech impairment in a maternal uncle. Unfortunately, the specific OC symptom presentation in this individual was not reported.

Hendriksen and Vles [2008] also recently reported on the results of a questionnaire study of 351 males with Duchenne muscular dystrophy (DMD). DMD is characterized by progressive proximal muscular dystrophy and is the result of mutations in a very large gene that encodes dystrophin and is located at Xp21.2. In this study, 11 of the subjects were reported to have ASD and of this number 3 (27%) also had OCD [Hendriksen & Vles, 2008]. Unfortunately, no details were provided concerning either the nature of the ASD or OCD symptomatology.

Finally, several other studies involving individuals with other X-chromosome abnormalities have suggested a link between ASD and OCB. For example, El Abd, Patton, Turk, Hoey, and Howlin [1999] identified five women with deteriorating social skills as well as attentional problems, impulsive and aggressive behaviors, and prominent OCB. All of these women had a subphenotype of Turner's syndrome with a small, active, early replicating, ring X chromosome and inactive specific transcript locus confirmed by fluorescent in situ hybridization. There have been at least eight other cases with similar karyotypes and behavioral–cognitive phenotypes that included intellectual disabilities and developmental delays [El Abd et al., 1999]. In another case report, a patient with Asperger syndrome, OCD and major depression was discovered to have 45X/46XY mosaicism [Fontenelle, Mendlowicz, Bezerra de Menezes, dos Santos Martins, & Versiani, 2004]. An earlier study [Telvi, Lebbar, Del Pino, Barbet, & Chaussain, 1999] reported that 2 (7%) patients were diagnosed with ASD in a sample of 27 patients with 45X/46XY mosaicism, but the nature and severity of OCB were not assessed.

Prader–Willi Syndrome and Other Disorders Associated With Chromosomal Alterations in the 15q11–q13 Region

Duplications and deletions of genes within this chromosomal region have been associated with both ASD and OCB. Inherited duplications of 15q11–q13 (mostly maternal) have been observed in 1–3% of cases of ASD, either as interstitial duplications or supernumerary isodicentric marker chromosomes containing one or two extra copies of this region [Zhao, Pak, Smrt, & Jin, 2007b]. If the paternal copy of this region is deleted, Prader–Willi syndrome (PWS) occurs. In contrast, the loss of the maternal copy of this region is associated with Angelman's syndrome. PWS is of interest because the clinical presentation of these individuals frequently includes mild to moderate intellectual disability and social deficits as well as OCB. The OCB include: hoarding of nonfood items, ordering/arranging things, requiring symmetry and exactness, preference for daily routines, verbal perseveration or talking too much, the need to know, ask, tell or re-write, and repeating rituals with grooming, toileting or showering [Dykens & Cohen, 1996; Dykens & Roof, 2008]. The majority of individuals with PWS have a paternally derived interstitial deletion of 15q11–13, but 25% have maternal uniparental disomy 15 (UPD) and 2–5% have imprinting defects [Dykens & Roof, 2008]. Recent studies suggest that those with maternal UPD are at greater risk for ASD symptomatology than those with paternal deletions of 15q11–q13 [Dimitropoulos & Schultz, 2007; Milner et al., 2005]. Although Milner et al. [2005] found no clear differences in OC symptom severity comparing PWS cases due to paternal deletions vs. maternal UPD, Zarcone et al. recently reported that PWS individuals with the long type TI deletion had more compulsions regarding personal cleanliness (i.e. excessive bathing/grooming) while those with the short type TII deletion were more likely to have OC symptoms in the symmetry and ordering domain [Zarcone et al., 2007].

Smith–Magenis Syndrome and Alterations in the Region of 17p11.2

Behavioral issues with patients with duplications of 17(p11.2p11.2) are notable for variable symptoms including expressive language delay, attention problems, hyperactivity, and intellectual disability. A subset of these patients also displays OCB [Nakamine et al., 2008; Potocki et al., 2000]. For example, Nakamine et al. described an individual who inherited a 17p(11.2p11.2) duplication de novo on a paternal chromosome and whose clinical presentation included an expressive language delay, ASD, and OCB [Nakamine et al., 2008], whereas another patient inherited the duplication on a maternal chromosome and presented with hyperactivity and OCB [Potocki et al., 2000].

OCBs and Animal Models

One approach to examining specific consequences of genetic, neuroanatomical, developmental, environmental, and pharmacological manipulations is to utilize animal models of OCB. Animal studies allow scientist to investigate how specific gene(s) influence behavior or relate to pathophysiological mechanism. Given the heterogeneity of diagnostic categories like ASD and OCD, current approaches focus on modeling specific subcomponents rather than the complex human syndromic phenotypes. Although obsessive thoughts or intrusive ruminations are difficult to model in OCD, repetitive motor behaviors such as atypical grooming or excessive stereotypic behaviors in animals have served as spontaneous OCB models. The Sapap3 knock-out mice, lacked a scaffolding protein at excitatory synapses, groomed to excess and even to the point of injury or during sleep [Welch et al., 2007]. Associations with human OCD have been made because (1) chronically treating these mice with SSRIs reduces the frequency of grooming and (2) cortico-striatal pathways implicated in human imaging research are affected by defects in their glutamatergic synapses. Based on this animal model, recent human genetic work has reported 2.1% of a samples with OCD or trichotillomania had rare non-synonymous variants in *SAPAP3* compared to 0.56% in their control sample [Zuchner et al., 2009]. OCB animal models suggesting fronto-subcortical dysfunction and pathway connections to OCD include the Sapap3 knockout mouse, as well as DCIT-7, DATKD, and deer mice that are reviewed in detail elsewhere [Wang, Simpson, & Dulawa, 2009b].

Given the multiple symptom domains of autism, animal models often focus on a single symptom domain such as communication measured by behaviors like ultrasonic vocalizations [Moy & Nadler, 2008]. Within the restrictive, repetitive domain, OCB animal models have attempted to capture the range of behaviors in ASD by studying stereotyped motor movements, repeated manipulations, repetitions leading to self-injury, to models of cognitive rigidity related to rituals and inflexible or circumscribed behaviors [Lewis, Tanimura, Lee, & Bodfish, 2007]. Behavioral genetic approaches related to ASD have examined manipulations on a range of candidate genes [Moy & Nadler, 2008] and have methods to study “IS” or change in habit through reversal learning tasks [Crawley, 2007]. Carefully designed behavioral tasks for Assessing a broader range of repetitive behaviors in ASD have been utilized to test existing inbred strains of mice that may translate to ASD findings [Moy et al., 2008]. Recently, it was reported that *FKBP12* mutant mice exhibited perseverative or repetitive behavior in the marble burying task, water maze, Y-maze reversal task, and the novel object recognition and could be a model for ASD or OCD [Hoeffler et al., 2008]. There is treatment or therapeutic potential because FKBP12 binds the immunosuppressant drugs FK506 and rapamycin as well as regulating several signaling pathways, including mammalian target of rapamycin (mTOR) signaling that is disrupted in Tuberous Sclerosis.

Future Directions for OCB and the Broader Phenotype of ASD

In this final section, we point to the need for greater specification of component ASD and OCB phenotypes over the course of development, and then briefly consider a few of the emerging areas of research including the expanded use of genome-wide association studies and copy number variation.

Clinical Studies of Relevant Phenotypes Over the Course of Development

Currently available data suggest that, with rare exceptions, ASD is typically a multidimensional, polygenic disorder in which the effects of individual genes are much smaller than previously thought. It is likely that certain genes will differentially influence the emergence of specific domains of ASD-related behaviors. At the moment, a number of scales have been developed to measure restricted repetitive and stereotyped patterns of behavior. One additional scale, the DY-BOCS, has been developed for use in studies of individuals with OCD. The value of this scale for ASD has not been evaluated. Rating the severity of each of the OC or symptom categories, including the symmetry dimension, in ASD family-genetic, twin, linkage and association studies would allow investigators to determine whether or not this set of OC symptoms predominates in ASD probands and their relatives.

In any case, additional research is needed to sort out which of the available scales provides the best coverage and how these behaviors correlate, or not, with (1) the social and communicative deficits seen in ASD; (2) with repetitive behaviors seen in other disorders such as OCD as well as with the repetitive behaviors that are normally seen in typically developing children; and (3) to what extent these phenotypes change with advancing chronological age and are influenced by the individual's mental age. When examining subgroupings of OCB in ASD, it has recently been reported that circumscribed interests or IS may have a stronger familial relationship whereas stereotypies/repetitive motor behaviors may be related to severity or intellectual disability [Lam, Bodfish, & Piven, 2008]. It is important to note that there were no significant differences in OCB overall and in subgroupings except for repetitive sensory behaviors when 33 pairs of sex, IQ, and age-matched children with Aspergers or high-functioning autism were compared [Cuccaro et al., 2007]. In addition to questionnaire and interview data, future studies need to collect data acquired by direct observation. Performance on standardized neuropsychological tasks (and perhaps on the associated patterns of brain activation) may also provide valuable endophenotypes for future studies, but this will require testing unaffected (or less affected) family members [Chamberlain et al., 2008].

Gene Array Studies

Given the sequencing of the human genome, it is now possible to monitor expression levels of thousands of genes simultaneously using DNA microarrays.

Work using DNA microarrays in ASD is underway, but in the future it will permit investigators to consider hundreds, or perhaps thousands of genes to assess an individual's genetic vulnerability and to use these sets of genes in research that explores developmental change and continuity, co-morbidity with other disorders, as well as gene-gene and gene-environment interactions. With this technology and large numbers through combined autism samples, novel common SNP variants are being detected near neuronal cell-adhesion molecules genes (between *CDH10* and *CDH9*) on 5p14.1 [Wang et al., 2009a] and near genes encoding axonal guidance proteins (*SEMA5A*) on 5p15 [Weiss, Arking, Daly, & Chakravarti, 2009]. Current genome-wide studies are underway for OCD and may be interesting when compared to ASD studies, especially those with well-characterized OCB

phenotypes. We also anticipate that the use of gene expression data will increase, and that gene expression information will be better integrated with a greater specification of the relevant phenotypes including OCB associated with ASD.

Copy Number Variation Studies

Genomic microduplications and microdeletions, also known as copy number variants (CNVs), refer to differences in the number of copies of a particular region of DNA within the genome of an individual. Recent reports have suggested the possibility that CNVs play a role in the development of complex disorders including ASD and schizophrenia [Sebat et al., 2007]. Genomic structural variation is not entirely new to the field of ASD genetics, as chromosomal disorders were among the earliest identified genetic abnormalities associated with ASD phenotypes. The increased resolution of array-based approaches suggests that the proportion of cases attributable to structural variants will be considerably higher than the 6–7% identified by standard cytogenetic techniques. CNVs with a potentially large impact on ASD susceptibility include maternal duplication (15)q11–q13, deletion (22)q13-*SHANK3*, deletion(16) p.11.2, deletion(X)p22-NLGN4, deletion(X)q13-*NLGN3*, homodeletion(4)q28.3, *PCDH10*, and there are more than a dozen CNVs with moderate or mild effects that probably require other genetic (or nongenetic) factors to take the phenotype across the ASD threshold [Cook & Scherer, 2008]. CNV findings [Marshall et al., 2008] highlight post synaptic density genes (*SHANK3-NLGN4-NRXN1*) and synaptic complex genes (*DPP6-DPP10-PCDH9*). Recently, new susceptibility genes for cell-adhesion molecules, such as *NLGN1* and *ASTN2*, were enriched with CNVs in ASD cases vs. controls [Glessner et al., 2009]. Furthermore, CNVs within or near ubiquitin pathway genes, such as *UBE3A*, *PARK2*, *RFWD2*, and *FBXO40*, were observed in ASD and not controls. We are again in anticipation of genome-wide CNV studies that are underway for OCD sample collaborations. When comparing these results, it will be critical for investigators to consider the relevant ASD sub-phenotypes within OCBs as they analyze and interpret these formidable data sets.

Molecular Developmental Studies

Discoveries with far-reaching implications for future genetic research include epigenetic modifications and the study of noncoding RNAs like microRNAs (miRNAs). Studies suggest that tissue-specific miRNAs may function at multiple hierarchical stages within gene regulatory networks, from targeting hundreds of effector genes to controlling the levels of key transcription factors [Makeyev & Maniatis, 2008]. In addition, epigenetic modulations during development, mediated in part by DNA methylation, RNA-associated silencing, and histone modification, can transform dynamic environmental experiences into altered genomic function and the emergence of stable alterations in phenotypic outcome. Behavioral analyses of rare imprinted disorders, such as Rett syndrome, FXS, PWS, and Angelman syndrome, will continue to provide insight regarding the phenotypic impact of imprinted genes in the brain, and can be used to guide the study of normal behavior as well as more common, but genetically complex, disorders such as ASD [Goos & Ragsdale, 2008; Zhao et al., 2007b]. In the future, we will have the capacity to induce pluripotent “stem” cells by reprogramming somatic cells from patients with ASD. This will permit investigators to recapitulate neuronal development in vitro by differentiating neuronal progenitors of various CNS lineages and compare patterns of expression in ASD cell lines vs. those seen in typically developing individuals as well as OCD patients [Gurdon & Melton, 2008].

Conclusion

The last three decades of research have demonstrated that ASD is more genetically heterogeneous than initially thought. Important progress toward the understanding of genetic

influences in ASD has been made by the combination of family and twin studies, segregation analyses, parametric and nonparametric linkage analyses and association studies, as well as the study of rare genetic variants. The currently available data suggest that, with few exceptions, ASD is typically a multidimensional, polygenic disorder in which the effects of individual genes are much smaller than previously thought. This implies that in a majority of cases, ASD vulnerability is determined by a multiplicity of genes interacting with specific environmental risk factors over the course of development. One of the relevant phenotypes within the broader ASD phenotype is OCB. Like ASD itself, the etiologies of OCB are likely to prove to be multidimensional and polygenic and significant progress is being made in assessing the relevant symptom domains (and neuropsychological endophenotypes) and their inter-relationship with the family of vulnerability genes that underlie OCD and related disorders.

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Figure 1.

Developmental and genetic variables and their interaction influence the emergence of obsessive-compulsive behaviors in individuals with Autism Spectrum Disorders. Both genes and events affecting the course of brain development can influence the emergence of autism spectrum disorders (ASD) and Obsessive-compulsive behaviors (OCB). Some genes may also influence an individual's exposure to risk (and protective) environments. There is also a growing body of evidence on the importance of gene-environment interactions ($G \times E$) in relation to ASD and obsessive-compulsive disorder such that even adverse experiences might have a negligible effect in the absence of relevant susceptibility genes and yet have a very large effect in the presence of such genes.

Table I

Overlapping Phenotypes and Assessment Tools

Class	Description	Measurement
DSM-IV-TR criteria #3 for autistic disorder	<p>Restricted repetitive & stereotyped patterns of behavior, interests, and activities</p> <p>At least one of the following:</p> <ul style="list-style-type: none"> • Encompassing preoccupation with 1+ stereotyped and restricted patterns of interest that is abnormal either in intensity or focus • Apparently inflexible adherence to specific, nonfunctional routines or rituals • Stereotyped and repetitive motor manners (e.g. hand or finger flapping or twisting, or complex whole-body movements) • Persistent preoccupation with parts of objects 	<p><i>Autism Diagnostic Interview-Revised</i> [Lord et al., 1994]:</p> <p>R1: Encompassing preoccupation or circumscribed pattern of interest</p> <p>R2: Apparently compulsive adherences to nonfunctional routines or rituals (e.g. verbal or nonverbal compulsions/rituals)</p> <p>R3: Stereotyped and repetitive motor mannerisms including hand and finger mannerisms or other complex mannerisms</p> <p>R4: Preoccupations with part-objects or nonfunctional elements of materials (e.g. repetitive use of objects & unusual sensory interests)</p> <p><i>Autism Screening Questionnaire</i> [Berument et al., 1999]: Eight items loaded on a single factor: Repetitive used objects; Unusual sensory interests; Compulsions and rituals; Unusual preoccupations; Use of other's body to communicate; Complex body mannerisms; Unusual attachment to objects; and Circumscribed interests</p> <p><i>Repetitive and Stereotyped Movement (RSM) Scales</i> [Wetherby & Morgan, 2007]: Direct observation:</p> <p>RSM with body: Flaps; Rubs Body; Pats Body; and/or Stiffens body parts and postures;</p> <p>RSM with Objects: Restricted preoccupation in intensity or focus with restricted interest; Swipes; Rubs/Squeezes; Rolls/Knocks Over; Rocks/Flips; Wobbles; insists on sameness or difficulty with change in activity; Collects; Moves/Places; Lines up/Stacks and/or Clutches</p> <p><i>Repetitive Behavior Scale—Revised</i> [RBS-R, Bodfish et al., 2000]: Questionnaire completed by parent, teacher or caregiver, five empirical derived subscales:</p> <p>Stereotyped behavior; Self-injurious behavior; Compulsive “just-right” behavior; Ritualistic/ sameness; and Restricted interests</p>
Obsessive–compulsive behaviors within pervasive developmental disorders	<ul style="list-style-type: none"> • From an obsessive–compulsive disorder symptom instrument, investigators adapted the “compulsions” portion of the Y-BOCS symptom checklist • Symptoms that most closely resemble the repetitive behaviors seen in ASD include: ordering and arranging, counting, doing and redoing often prompted by sensory phenomena urges, and rituals associated with sleep-wake transitions, separation from attachment figures, as well as habits associated with dressing and grooming; ordering and arranging; and collecting 	<p><i>Children's Yale-Brown Obsessive Compulsive Scale for Pervasive Developmental Disorders</i> [CY-BOCS-PDD, Scahill et al., 2006]:</p> <p>The same nine categories of compulsions are present in both the CY-BOCS & CY-BOCS-PDD symptom checklist: Washing/cleaning; Checking; Repeating rituals; Counting compulsions; Ordering/arranging; Hoarding/saving compulsions; Excessive games/superstitious behaviors; Rituals involving other persons; and miscellaneous compulsions</p> <p>The content of only two of the CY-BOCS categories were modified for this scale: repeating rituals for the CY-BOCS-PDD includes: “touching in patterns; rocking; spinning, twirling, pacing; spinning objects; and echolalia”</p> <p>Likewise the Miscellaneous Compulsions category for the CY-BOCS-PDD includes: “Repetitive sexual behavior (Masturbation, grabbing at crotch)”</p>
Classic obsessive–compulsive disorder behaviors	<ul style="list-style-type: none"> • Obsessive–compulsive disorder is clinically heterogeneous • There are a variety of obsessive–compulsive dimensions that are usually prompted by anxious intrusive thoughts or images or sensory phenomena 	<p><i>Children's Yale-Brown Obsessive Compulsive Scale</i> [CYBOCS, Scahill et al., 1997]:</p> <p>This scale is modeled on the original Yale-Brown Obsessive Compulsive Scale [Y-BOCS, Goodman et al., 1989a,b] with nine categories of compulsions (see above)</p> <p>It also includes eight categories of obsessions: Contamination obsessions; Aggressive obsessions; Sexual obsessions; Hoarding/saving obsessions; Magical thoughts/superstitious obsessions; Somatic obsessions; Religious obsessions; and Miscellaneous obsessions</p> <p><i>Dimensional Yale-Brown Obsessive Compulsive Scale</i> [DY-BOCS, Rosario-Campos et al., 2006]:</p> <p>This scale specifically rates the severity of obsessive–compulsive (OC) symptoms within multiple</p>

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		<p>symptom dimensions</p> <p>Recent large-scale meta-analysis of data from more than 5,000 individuals provides the clearest picture of data of the inter-relationship of these symptom dimensions [Bloch et al., 2008a]</p> <p>The four factors validated by this meta-analysis are included in the DY-BOCS:</p> <p>(Factor I) FORBIDDEN THOUGHTS—Aggressive, sexual, religious, and somatic obsessions and checking compulsions;</p> <p>(Factor II) SYMMETRY—Symmetry obsessions and repeating, ordering and counting compulsions;</p> <p>(Factor III) CLEANING—Cleaning and contamination;</p> <p>(Factor IV) HOARDING—Hoarding obsessions and compulsions. The Miscellaneous obsessions and compulsions were not included in these analyses</p>
Normative repetitive behaviors	<ul style="list-style-type: none"> • Mental age dependent multidimensional rituals associated with: sleep-wake transitions, separation from attachment figures, as well as habits associated with dressing and grooming; ordering and arranging; and collecting • The content of many of these items resembles the symptom dimensions that are commonplace in pediatric-onset as well as adult onset OCD: worries about harm and separation; ordering and arranging; contamination worries and collecting 	<p><i>Childhood Routine Inventory</i>: [CRI, Evans et al., 1997]: 19 items, parental report:</p> <p>Prefer to have things done in a particular order or in a certain way (i.e. is he/she a “perfectionist?”); Very attached to one favorite object? Very concerned with dirt, cleanliness or nearness? Arrange objects, or perform certain behaviors until they seem “just right” to him/her? Have persistent habits? Line up objects in straight lines or symmetrical patterns? Prefer the same household schedule or routine every day? Act out the same thing over and over in pretend play? Insist on having certain belongings around the house “in their place”? Repeat certain actions over and over? Have strong preferences for certain foods? Like to eat food in a particular way? Seem very aware of, or sensitive to how certain clothes feel? Has a strong preference for wearing (or not wearing) certain articles of clothing? Collect or store objects? Seem very aware of certain details at home (such as flecks of dirt on the floor, imperfections in toys and clothes)? Strongly prefer to stick to one game or activity rather than change to a new one? Make requests or excuses that would enable him/her to postpone going to bed? Prepare for bedtime by engaging in a special activity or routine, or by doing or saying things in a certain order or certain way?</p>