CHAPTER

35

Neurodevelopmental Genomics of Autism, Schizophrenia, and Related Disorders

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OUTLINE

35.1 INTRODUCTION AND HISTORICAL OVERVIEW

In 1943, Leo Kanner first described 'infantile autism' as "... children's *inability to relate themselves* in the ordinary way to people and situations from the beginning of life" (page 242, emphasis in original; Kanner, 1943). The modern Diagnostic and Statistical Manual of Mental Disorders, 4th edition text revision (DSM-IV TR; American Psychiatric Association, 2000), categorizes that classical syndrome as autistic disorder, which is thought of as a part of a heterogeneous spectrum of behaviorally defined disorders, the autism spectrum disorders (ASDs). By definition, the ASDs manifest clinically within the first 3 years of life; impair language, communication, and social interaction; and are typified by idiosyncratic interests and repetitive behaviors. In the DSM-IV TR, ASDs also include Asperger disorder, defined as the presence of autism symptoms in the absence of language delay and intellectual disability (ID), and pervasive developmental disorder not otherwise specified, in which autistic features are present but do not meet full criteria for a diagnosis of autistic disorder (see Chapter 34).

Kanner explicitly borrowed his diagnostic term from Eugen Bleuler (1950), who used 'autism' to describe the process of withdrawal into one's own world, which he identified as a hallmark of a heterogeneous set of adult behavioral disorders in his classic book, *Dementia Praecox or the Group of Schizophrenias*. Today, 'schizophrenia' refers to a set of behaviorally defined syndromes, the diagnostic features of which include 'positive symptoms' such as hallucinations, delusions (firmly fixed false beliefs not explained by cultural context), thought disorder, and disorganized or bizarre behavior and 'negative symptoms' such as apathy, anhedonia (inability to feel pleasure), and social withdrawal. Schizophrenia is one of several 'schizophrenia spectrum disorders' (SSDs) that include schizoaffective disorder, in which

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cycles of depression and/or mania occur together with chronic psychosis, and psychotic disorder not otherwise specified, which includes individuals with psychosis who do not meet full criteria for schizophrenia. Family studies also suggest that a nonpsychotic syndrome, called schizotypal personality disorder, is part of the schizophrenia spectrum (Kety et al., 1971, 1994; Tienari et al., 2003). To avoid the misconception that either autism or schizophrenia is a unitary disorder, we will use the terms ASD and SSD throughout this chapter.

35.2 PHENOTYPIC SIMILARITIES AND DIFFERENCES BETWEEN ASD AND SSD

ASD and SSD both produce lifelong disability and, as we have seen from the history of their nosology, share as hallmark manifestations, impaired abilities to function in human social groups. ASD and SSD share many other phenotypic characteristics, but there are also some important differences. ASD and SSD patients share higher rates of ID (Bhaumik et al., 2008; Hemmings, 2006; Matson and Shoemaker, 2009; Morgan et al., 2008), epilepsy (Ep; Gaitatzis et al., 2004), and motor disturbances (Welham et al., 2009) compared with the general population. To make a diagnosis of an ASD according to the criteria of the DSM-IV-TR, behavioral signs of the disorder must be evident by the age of 3 years. In contrast, SSDs are usually first diagnosed during late adolescence or early adulthood. However, cases meeting diagnostic criteria for SSD clearly occur during childhood (Rapoport, 2009) and mounting evidence suggests that neurobehavioral impairments often precede the onset of full-blown SSD, a clinical phenomenon known as the schizophrenia prodrome (Thomas and Woods, 2006). Manifestations of the schizophrenia prodrome include unusual beliefs and patterns of thought, learning disabilities, minor neurological abnormalities, social withdrawal, and problems with peer relationships. Such differences are readily detectable in many cases, such as in a classic study in which raters, unaware of current diagnosis, observed childhood home movies of patients' families and were able reliably to identify the child destined to develop SSD years later (Walker and Lewine, 1990). Thus, as with ASD, neurodevelopmental dysfunction is often evident early in the lives of patients with SSD.

ASDs are approximately fourfold more common in males than females (Control, 2009). In contrast, there appears to be little to no difference in the prevalence of SSD in males versus females (Saha et al., 2005). However, good evidence supports the conclusion that SSD in males tends to be earlier in onset with a less favorable course over the lifespan than in females (Angermeyer et al., 1990; Hafner et al., 1993), so there is some degree of sexual dimorphism in SSD. The range of impairment in psychosocial function across affected individuals is broad for both ASD and SSD, with some patients able to integrate into society and function independently, most exhibiting substantial and lifelong need for help in coping with being part of society, and severely affected individuals exhibiting profound impairment that destroys their abilities to care for themselves or function even minimally in society. From the information just reviewed, it is reasonable to view ASD and SSD as partially distinct sets of neurodevelopmental disorders (NDDs) that share a variety of phenotypic features.

35.3 GENETIC MECHANISMS IN ASD AND SSD

35.3.1 Heritability of Risk for ASD and SSD

ASD and SSD exhibit similar degrees of risk heritability. Family studies show that the recurrence risk for ASD and SSD in siblings of affected individuals is approximately 5–10%, which is substantially greater than the ~1% prevalence of either set of disorders in the general population. Additionally, twin studies show concordance rates in monozygotic twins to be substantially higher than in dizygotic twins for both ASD (up to 90% vs. ~10%) and SSD (up to 80% vs. ~10%), leading to heritability estimates of 0.8–0.9 (Folstein and Rosen-Sheidley, 2001; Losh et al., 2008; Riley and Kendler, 2004).

35.3.2 Overlapping Molecular Genetic Associations in ASD and SSD: Single Genes

In some cases, SSD and ASD appear to share common, or at least substantially overlapping, genetic etiologies. Table 35.1 shows a list of genes in which mono- or biallelic mutations or loss-of-function, single-gene copy number variants (CNVs) have been involved in the etiology of both ASD and SSD. Interestingly, these genes encode synaptic or cell adhesion molecules, which play important roles in neural development and therefore appear to be excellent candidates as key players in the pathophysiology of ASD and SSD (Guilmatre et al., 2009).

At the moment, however, the greatest apparent overlap of genetic factors in ASD and SSD comes from recent discoveries regarding the role of genomic CNV (defined below) in both sets of disorders as well as in other neurodevelopmental conditions including Ep and ID. Although CNVs have thus far been associated with ASD and SSD only in small proportions of patients, the number of CNVs associated with both sets of disorders continues to grow. Even if they account only for a minority

TABLE 35.1 Genes Associated with Both ASD and SSZ Through Loss-of-Function Single-Gene CNVs and/or Functional Mutations

Gene symbol	Chromosomal location	Gene name	OMIM ID	ASD references	SSD references
SHANK3	22q13.3	SH3 and multiple ankyrin repeat domains 3	606230	Durand et al. (2007) and Gauthier et al. (2009)	Gauthier et al. (2010)
CNTNAP2	7q35	Contactin-associated protein-like 2	604569	Strauss et al. (2006) and Zweier et al. (2009)	Friedman et al. (2008)
NRXN1	2p16.3	Neurexin 1	600565	Ching et al. (2010), Wisniowiecka-Kowalnik et al. (2010), and Zweier et al. (2009)	Ikeda et al. (2010) and Rujescu et al. (2009)

of cases, CNV-associated cases of ASDs and SSDs promise to be invaluable for understanding specific relationships between genetic differences and disorder-related phenotypes, by virtue of the clarity with which associations can be established between genetic differences (i.e., presence vs. absence of a CNV) and individual patients. Thus, by understanding similarities and differences among patients carrying a common CNV but diagnosed clinically with an ASD, an SSD, or both, we may be able to elucidate meaningful differences, and commonalities, in developmental and pathophysiological processes leading to one set of disorders or the other.

35.4 CNV IN THE GENOME: KNOWN FOR DECADES, UNDERAPPRECIATED UNTIL RECENTLY

Large-scale variation in the genome, such as chromosomal rearrangements, duplications, and deletions, has been known to cytogeneticists for many decades. However, the recent advent of molecular methods allowing high-resolution examination of the entire genome, such as array comparative hybridization (aCGH; Cowell, 2004) and genome-wide single-nucleotide polymorphism (SNP)-genotyping platforms (Ding and Jin, 2009), has led to a much fuller appreciation of how common and how relevant to complex neurobehavioral disorders such large-scale variation actually is. CNVs comprise a class of genomic variants in which long stretches of DNA, ranging in size from thousands to millions of base pairs (bp), occur in variable numbers of contiguous copies on chromosomes from different individuals (Zhang et al., 2009). While some CNV appears to be 'private,' occurring only within a single individual or family, recurrent CNV can be identified at specific locations in the genome in unrelated individuals.

35.4.1 Genomic Architecture Predisposing to Recurrent CNV

The most frequent overlapping rearrangements are usually recurrent and arise from nonallelic homologous recombination (NAHR), where a segment of unique DNA sequence (50 kb–10 Mb) is lost or duplicated due to the presence of flanking segmental duplications, or low-copy repeats (LCR) – large (>10 kb), highly repetitive (>95% homology), DNA sequences that predispose to genomic instability (Dibbens et al., 2009). When two of these paired segmental duplications are found in the same orientation along the chromosome, they can be improperly aligned during meiosis, leading to the duplication of the intervening sequence in one allele and the deletion of this same region in the other; this is the mechanism behind NAHR. Interestingly, some of the regions in which these recurrent deletions occur also harbor inversion polymorphisms which change the orientation of the paired LCR from inverted, or facing on different directions along the chromosome, to aligned, hence greatly increasing the chance of NAHR occurring. In some instances, the presence of the appropriate inversion allele is necessary for the CNV to occur, as is the case for the 17q21.31 region (Alkan et al., 2009; Sharp et al., 2006).

LCR-mediated NAHR thus repeatedly generates within the population recurrent CNV that is identical or nearly so in size and location. Recognition of recurrent CNV in research and clinical settings has increased tremendously over the past few years, leading to the identification of several previously unknown genomic disorders in which autism and/or schizophrenia is part of the phenotype. As the number of array-based research studies and diagnostic procedures increases, and collaborative pooling of information across research and clinical laboratories grows, more recurrent the CNV that causes or predisposes to NDD.

35.5 RECURRENT CNV ASSOCIATED WITH ASD, SSD, AND OTHER NDDS

The remainder of this chapter will focus on recurrent CNVs and their associations to ASD, SSD, and often other NDDs such as Ep (see Chapter 36) and ID. Emerging evidence implicates a growing list of CNVs that associate with ASD, SSD, and other NDDs. This emerging pattern of common CNVs playing a

presumably causal role in diverse phenotypic outcomes suggests that subgroups of patients with clinically different disorders manifest variable phenotypes arising from common underlying genetic disturbances. It appears likely that at least some of the commonality of risk elevation in ASD, SSD, and other NDDs reflects disruption in fundamental brain developmental processes, some of which might be responsive to specific environmental conditions, epigenetic events, or influences of specific loci distant from the CNV that could influence the trajectory of phenotypic outcome. Identifying and disentangling factors associated with variation in phenotypic outcomes among carriers of specific recurrent CNVs are a major challenge, yet meeting that challenge promises to shed light on the basis for ASD, SSD, and other NDDs. Phenotypic studies of participants specifically ascertained by CNV status will be an important first step toward understanding the phenotypic variability associated with recurrent CNVs. We propose that studies ascertaining participants according to the presence or absence of specific sets of CNVs and focusing on a broad variety of behavioral, cognitive, physiological, metabolic, cellular, and molecular phenotypes are likely to be productive strategies for understanding the relationship of ASDs to SSDs and other NDDs.

In other words, if the goal is to organize developmental and neurobiological analysis of NDDs according to biologically meaningful criteria, then direct ascertainment of cases by CNV status will be superior to doing so by phenomenology. The former approach offers the opportunity to ascertain cases on the basis of likely molecular etiology, while the latter has proved unreliable for classifying cases according to similar mechanisms of clinical risk. Where cost, ethical concerns, and territoriality in scientific funding priorities are not important constraints, CNV would ideally be ascertained in population-based samples of infants at birth, and cases defined by CNV status would be followed prospectively together with demographically matched noncarrier controls. Although in the short-term ascertainment of CNV within large phenotypically identified collections, such as the AGRE resource (Lajonchere, 2010), is the most practical approach to studying CNV and NDD, the ascertainment bias inherent in identifying cases by nonspecific behavioral phenotypes will plague the field until unbiased molecular ascertainment of CNV carriers (some of whom will have only very mild, or absent, clinical phenotypes) becomes a reality in neurodevelopmental epidemiology.

Table 35.2 lists recurrent CNV associated with ASD and SSD, as well as other NDDs (most commonly ID or Ep). Note that most of these pathogenic recurrent CNVs also associate with a large variety of medical and anatomic disorders (the list of such associated disorders probably remains incomplete). Although a detailed discussion of the medical complications of CNV disorders is beyond the scope of this chapter, their presence is very important because it emphasizes the urgent need to begin training clinicians and educators who evaluate ASD, SSD, and other NDDs to include CNV disorders in the differential diagnosis so that appropriate referral for cytogenetic evaluation can be made, and medical as well as behavioral interventions can be instituted. Recently, Miller and colleagues (Miller et al., 2010) suggested that testing for CNV by microarray be made standard of care for evaluation of ASD and ID. No such suggestion has been published for SSD, although in our view, such testing should at least be considered when there is clinical evidence suggesting CNV (e.g., the simultaneous presentation of psychosis and ID). Bassett and Chow (1999)

TABLE 35.2 Recurrent CNVs Identified Across ASD and Schizophrenia

Genomic region	Position (Mb)[a]	Size (Mb)[a]	Number of genes[b]	CNV	References
1q21.1	chr1:144 963 732–145 864 377	0.9	7	del	Brunetti-Pierri et al. (2008) and Consortium (2008)
3q29	chr3:197 244 288–198 830 238	1.6	21	del	Mulle et al. (2010) and Willatt et al. (2005)
15q13.3	chr15:28 698 632–30 234 007	1.5	6	del	Ben-Shachar et al. (2009), Consortium (2008), and Stefansson et al. (2008) (see Chapter 32)
16p11.2	chr16:29 557 553–30 107 434	0.5	25	dup	McCarthy et al. (2009) and Weiss et al. (2008)
16p13.11	chr16:15 421 876–16 200 195	0.8	7	dup	Ingason et al. (2009) and Ullmann et al. (2007)
17q12	chr17:31 893 783–33 277 865	1.4	15	del	Loirat et al. (2010) and Moreno-De-Luca et al. (2010)
22q11.2	chr22:17 412 646–19 797 314	2.4	41	del	Antshel et al. (2007), Consortium (2008), Karayiorgou et al. (1995), Pulver et al. (1994), and Vorstman et al. (2006)

[a] *Size and position are calculated in the hg18 genome assembly and exclude the DNA sequence from flanking segmental duplications.*
[b] *The number of genes in each region is based on RefSeq coding genes.*

have elaborated specific clinical criteria indicating testing by fluorescent *in situ* hybridization (FISH) for 22q11 deletion syndrome (22q11DS) in patients with SSD. Such criteria need reevaluation and expansion as microarrays are rapidly supplanting FISH as the primary molecular–cytogenetic diagnostic procedure (FISH remains essential for confirmation of positive microarray results). The need to consider genome-wide testing for recurrent and rare CNV during the work-up of SSD is, in our view, a critical area for future translational research.

In the following sections, we briefly review current knowledge regarding the relationship of specific recurrent CNV to ASD and SSD. The discussion begins with a review of the 22q11 deletion syndrome (22q11DS) because the molecular basis of 22q11DS has been known for 2 decades, and its associations to NDDs have been most extensively studied. We regard 22q11DS as a prototypic CNV disorder, as it exhibits the phenotypic heterogeneity (i.e., variable expressivity) and variable penetrance that appear to be common to all SSD- and ASD-related CNV disorders thus far described. Following discussion of the 22q11DS, we will review the other disorders listed in Table 35.3 in order of the chromosomes they affect, and then will conclude with remarks on implications and future directions for neurodevelopmental research.

35.5.1 22q11.2 Deletion Syndrome: The Prototypic CNV Disorder

First described in an autopsy series of four infants (Kirkpatrick and DiGeorge, 1968), DiGeorge syndrome (DGS) referred to a constellation of severe immune deficiency and findings suggestive of maldevelopment of the third and fourth pharyngeal arches, including thymic aplasia, parathyroid hypoplasia, and abnormalities of the aortic arch. Additional syndromes, called conotruncal anomaly face (CTAF) syndrome in a case series from Japan (Kinouchi et al., 1976) and velocardiofacial syndrome (VCFS) in another series from the United States (Shprintzen et al., 1978), consisted of velopharyngeal anomalies, cardiac anomalies, typical facial appearance, learning disabilities, and speech and language problems. In 1991, Scambler and colleagues reported that microdeletions at 22q11.2 associated with sporadic and familial DGS, and subsequent studies soon showed the majority of cases of DGS, CTAF, and VCFS were all associated with similar deletions (Burn et al., 1993; Carey et al., 1992; Scambler et al., 1992). Although all the foregoing syndrome designations are still in use, it is clear that the term 22q11DS subsumes almost all of the cases meeting the various phenotype definitions just reviewed and is therefore the most appropriate designation for this common CNV disorder (estimated at 1/4000 live births; Botto et al., 2003).

Behavioral manifestations in 22q11DS vary widely (Ousley et al., 2007) but are common in children and adults. By the mid-1980s, behavioral difficulties in children with VCFS had been described (Golding-Kushner et al., 1985), and psychosis in adolescents with the disorder was reported in 1992 (Shprintzen et al., 1992). Pulver and colleagues confirmed that schizophrenia was common in patients with 22q11DS (Pulver et al., 1994), and Karayiorgou and colleagues found several previously undiagnosed cases of 22q11DS in a series of patients with schizophrenia diagnosed solely on the basis of clinical presentation (Karayiorgou et al., 1995). The latter study was a landmark because it raised the prospect that a small but clinically and epidemiologically significant proportion of the SSD population carried undiagnosed 22q11 deletions. It is now clear that 22q11DS occurs at a low but nontrivial rate (~0.75%, about 30-fold more

TABLE 35.3 Candidate Genes in the 22q11 Deletion Region Plausibly Contributing to Risk for SSD or ASD

Locus	Gene product and function	References
COMT	Catechol-*O*-methyltransferase catalyzes catabolism of neurotransmitters dopamine and norepinephrine	Abdolmaleky et al. (2006), Bassett et al. (2007), Lachman et al. (1996), Munafo et al. (2005), and Shifman et al. (2002)
PRODH	Proline dehydrogenase participates in synthetic pathway for excitatory neurotransmitter, glutamate	Gogos et al. (1999), Jacquet et al. (2002), and Meechan et al. (2009)
ZDHHC8	Zinc finger, DHHC-type containing 8, likely a transmembrane palmitoyl transferase, which posttranslationally modifies proteins involved in intracellular trafficking and synaptic function. Variants associated with abnormal smooth-pursuit eye movements (SPEM) in SSD	Shin et al. (2010)
RANBP1	Variants associated with abnormal SPEM might be due to linkage disequilibrium with *ZDHHC8*	Cheong et al. (2011)
RTN4R	No Go-66 receptor, a key protein in axonal pathfinding during development	Sinibaldi et al. (2004)

frequently than in the population at large; Hoogendoorn et al., 2008) in clinically diagnosed SSD patients. Selecting specific phenotypic characteristics prior to molecular testing (e.g., facial dysmorphology, conotruncal heart defects, high-arched palate or cleft palate, ID) can substantially increase the diagnostic yield for the deletion in cohorts of patients with SSD (Bassett and Chow, 1999).

The most common 22q11 deletion (~80% of cases) is approximately 3 megabases (Mb) long, occurring between two LCRs flanking the deletion (Edelmann et al., 1999a, 1999b). Two additional LCRs lie within the 3 Mb deletion region and account for the majority of remaining deletions (~10% of 1.5 Mb and the rest of varied size). The 3-Mb region encompasses 40 genes, and several of these appear to be compelling candidates as genes contributing to SSD risk. However, none of them has yet been confirmed with sufficient confidence to call them 'schizophrenia genes.' Table 35.3 summarizes candidate genes residing within the 22q11DS region for which there is some evidence (usually mixed positive and negative results) supporting associations to risk for SSD.

It is worth noting that even accepting only the positive evidence supporting associations of individual loci within the 22q11DS region as the truth, the effect sizes of those associations are much smaller than the magnitude of the association of the 22q11 deletion itself with SSD (OR <1.5 for any given locus vs. OR ~20 for 22q11DS). It is thus possible that hemizygosity of multiple genes within the 22q11DS region, each of small individual effect, somehow synergizes to produce a more substantial influence on brain development when risk genes in the region are affected simultaneously. Alternatively, it is possible that deletion of single copies of multiple genes creates numerous opportunities for deleterious effects of risk loci elsewhere in the genome. While speculative, such hypotheses are useful because they suggest specific strategies for examining how 22q11DS elevates risk for SSD, ASD, or other NDDs. For example, a genome-wide analysis of variants in 22q11DS patients affected or unaffected by ASD, SSD, or both could identify specific loci elsewhere in the genome that elevate developmental sensitivity to the effects of hemizygosity of loci at 22q11.

The above summary shows that exciting progress has been made in understanding potential genetic mechanisms in SSD related to 22q11DS. Several genes involved either in neurotransmission, neuronal function, or development may be contributing to risk for SSD. The association of 22q11DS to ASD was described only relatively recently (Antshel et al., 2007; Vorstman et al., 2006), so fewer studies of ASD and individual genes within the deletion region have been published.

However, a recent study comparing symptom profiles among ASD patients with 22q11DS, those with Klinefelter syndrome (KS: karyotype 47 XXY), and ASD patients with no specifically defined genetic syndrome suggested that the ranges of overall ASD symptoms in both 22q11DS and KS were narrower than in the idiopathic group and differed from each other (Bruining et al., 2010). Discriminant function analysis of symptom scores (derived from the Autism Diagnostic Interview, Revised) showed clear distinctions in the profiles of each group. While the study can be criticized for several methodological difficulties (e.g., the patient samples were ascertained separately, thus introducing the possibility of selection bias), it is an important step forward because the results suggest that specific aspects of the broad ASD phenotype may specifically associate with definable genetic differences among patients. If true, such associations could form the basis for dissection of genetically regulated developmental pathways leading to specific 'points' in the 'phenotypic space' of ASD and may also provide a basis for comparing pathways leading to ASD versus SSD.

Finally, 22q11DS may serve as an important prototype for demonstrating the clinical importance of diagnosing specific CNV disorders in patients whose clinical presentation is entirely or predominantly behavioral. From the earliest days, DGS was known to associate with hypocalcemia that in its most severe form could lead to fatal status epilepticus. Hypocalcemia in 22q11DS results from the variable degree of parathyroid hypoplasia that occurs in those afflicted and can vary over an individual patient's lifetime. The condition can usually be corrected by dietary supplementation with vitamin D and calcium, but to establish the diagnosis, clinicians must test ionized serum calcium levels, rather than rely on the total calcium levels available in standard metabolic panels. The failure to test specifically for ionized calcium in patients with 22q11DS can lead to poor clinical outcomes. For example, SSD patients are almost always treated with antipsychotic medications. As a class, those agents tend to lower the seizure threshold. Clozapine is an antipsychotic medication that is among the worst offenders in terms of its effect on seizure threshold but remains a uniquely effective treatment in some patients whose psychotic symptoms do not respond well to other antipsychotic medications (Kane et al., 1988). Patients with SSD, 22q11DS, and untreated hypocalcemia who are given clozapine will be at extremely high risk for seizures owing to the synergistic effects of low calcium and the medication. Clinicians unaware of the patient's 22q11DS diagnosis would almost certainly discontinue clozapine when the patient has a seizure after starting clozapine. In that scenario, prophylactic administration of vitamin D and calcium, rather than discontinuation of clozapine, would have been an unexplored therapeutic alternative. Failure to diagnose 22q11DS in the ~0.75% of SSD patients who carry such deletions can thereby deprive

them of potentially effective treatments. Such cases have been documented, so this matter is of more than theoretical interest (Caluseriu et al., 2007). As we learn more about the large variety of clinical management issues associated with each CNV disorder, moving from phenomenological diagnosis to molecular diagnosis of NDD promises to become increasingly valuable for patient care.

35.5.2 1q21 Deletions

With the advent of cytogenomic array testing, recurrent deletions of 1q21, as well as several other genomic disorders that went previously undetected, have been identified in the last few years. This CNV spans 1.35 Mb and was originally identified in a large cohort of patients with schizophrenia (Stefansson et al., 2008). The 1q21 deletion was detected in 11 out of 4718 cases with schizophrenia (0.23%), compared to 8 of 41 199 controls (0.02%), providing compelling evidence of the association of this CNV and schizophrenia. Almost simultaneously, the identical CNV was identified in patients referred for clinical testing with a wide array of phenotypic features, which include isolated heart defects, cataracts, Müllerian aplasia, and microcephaly (Mefford et al., 2008). It is noteworthy that patients with the reciprocal 1q21 duplication have macrocephaly, pointing toward a dosage-sensitive gene involved in head growth. Additionally, several of these patients had a behavioral phenotype manifesting as ASD (Brunetti-Pierri et al., 2008; Mefford et al., 2008). Differing from other well-known microdeletion syndromes, such as Angelman and Prader-Willi (15q11.q13 deletions), but similar to 22q11DS, deletions in 1q21 lead to wide phenotypic variability and are sometimes found in apparently unaffected parents of affected individuals. However, a thorough phenotypic assessment in these apparently unaffected parents frequently reveals a subclinical neurocognitive or behavioral phenotype (Girirajan and Eichler, 2010).

There are at least seven genes in the 1q21 deleted interval, although the one responsible for the behavioral phenotype of patients with this CNV has not been identified. *GJA5* and *GJA8* are both part of the connexin family of genes and play an important role in membrane junctions. Mutations in *GJA5* are known to cause atrial fibrillation, whereas mutations in *GJA8* give rise to cataracts. Interestingly, GJA8 has been previously associated with schizophrenia (Ni et al., 2007). However, the gene responsible for the neurobehavioral phenotype of these patients remains unknown.

35.5.3 3q29 Deletions

Causing another novel genomic disorder, microdeletions of 3q29 have been associated with a variable array of phenotypes, including mild-to-moderate mental retardation, slightly dysmorphic facial features, gate ataxia, and long tapering fingers (Willatt et al., 2005). Also mediated by segmental duplications, this recurrent deletion is 1.6 Mb in size and contains 21 genes, several of which are interesting candidates for NDD. *DLG1* and *PAK2* are interesting candidates, as they are both autosomal homologs of well-described X-linked ID genes *DLG3* and *PAK3*. *DLG1*, also known as synapse-associated protein 97, also interacts directly with *PTEN* to inhibit axonal stimulation of myelination. This molecular brake is important in maintaining proper myelin thickness and, when removed, produces myelin outfoldings and demyelination. In fact, this brake ceases to function in peripheral neuropathies such as Charcot–Marie–Tooth (Cotter et al., 2010). Additionally, and perhaps most importantly, DLG1 interacts directly with AMPA and NMDA receptors, both key components of the glutamatergic synapse (Howard et al., 2010), in line with recent research showing the role of glutamatergic dysfunction in schizophrenia (Gaspar et al., 2009). *PAK2* also appears as an interesting candidate, as it regulates cytoskeleton dynamics, consequently regulating the morphology of the synapse and glutamate receptor complexes in the process (Kreis and Barnier, 2009).

35.5.4 15q13.2–13.3 Deletions

The proximal region of the long arm of chromosome 15 contains a series of five highly similar LCRs, which predispose this region of the genome to a variety of rearrangements (Mignon-Ravix et al., 2007: see Chapter 32). The most well known of such rearrangements consist of deletions between the two most proximal LCRs, giving rise to the imprinted disorders Prader-Willi syndrome or Angelman syndrome, depending on whether the deletion is paternally or maternally inherited, respectively. More distal deletions on chromosome 15, involving loss of DNA between the third and fifth or fourth and fifth LCRs, give rise to 15q13.2–13.3 deletion syndrome (15q13DS). Such deletions have consistently been identified in genome-wide association study (GWAS) of ASD (Miller et al., 2009; Pagnamenta et al., 2009) and SSD (Consortium, 2008; Stefansson et al., 2008). ID is common in 15q13.2–13.3 DS, as are difficulties with aggressive behavior and rage outbursts (Ben-Shachar et al., 2009; Miller et al., 2009; Sharp et al., 2008). Ep is also common in 15q13DS, with one study estimating this single set of CNVs to account for ~1% of idiopathic cases of Ep (Dibbens et al., 2009).

Among the loci deleted in 15q13DS is *CHRNA7*, encoding the α7 nicotinic acetylcholine receptor (α7nAChR). This observation is of great interest for at least two reasons. First, linkage and association studies have implicated *CHRNA7* as an important genetic modifier of an SSD-related physiological phenotype known as gating of the P50 auditory-evoked potential (P50-AEP). The P50-AEP is a positive deflection on EEG that

occurs ~50 ms after a brief auditory stimulus. Gating of the P50-AEP refers to the phenomenon in which an auditory stimulus shortly before the index stimulus attenuates the P50-AEP. Such gating is often impaired in persons with SSD, as well as in their unaffected relatives. Freedman and colleagues reported linkage between markers on 15q13 and P50-AEP gating in families segregating SSD (Freedman et al., 1997), and subsequent association studies suggested that variation at *CHRNA7* accounts for this linkage (Leonard et al., 1998). Together with the foregoing results, the association of 15q13DS with ASD and SSD suggests *CHRNA7* as a prime candidate gene relevant to altered development and function of the brain in ASD and SSD.

The second reason for specific interest in *CHRNA7* is that the pharmacology of the α7nAChR is well developed, with many compounds available for use in animal models and in some cases humans, which could be used as probes with which to examine the role of the receptor in development and possibly even for therapeutics. We recently described an adult male patient with 15q13DS, SSD, rage outbursts, and Ep, whose aggressive behavior was substantially attenuated by treatment with an acetylcholinesterase-inhibiting positive allosteric regulator of the α7nAChR, galantamine. The case provides at least a single example in which diagnosis of a CNV disorder led directly to altered pharmacotherapy in a clinical situation (Cubells et al., 2011).

35.5.5 16p11.2 Duplications

Weiss and colleagues (Weiss et al., 2008) performed a genome-wide search for recurrent CNV associated with ASD, using data from SNP-genotyping arrays from several large GWAS of ASD. They noted significant associations of *both* deletions and duplications in a ~590-kb region flanked by LCRs, located on chromosome 16p11.2. The finding was even more noteworthy because macrocephaly (enlarged head circumference), an endophenotype observed in a substantial minority of children with ASD, was also associated with the deletion at 16p11.2.

Simultaneously with the report of the Weiss et al. group, two other research teams reported associations between ASD and CNV at 16p11.2 (Kumar et al., 2008; Marshall et al., 2008). Importantly, one of those studies (Kumar et al., 2008) confirmed an association between 16p11.2 deletions and ASD using an independent molecular approach: array comparative hybridization. Although those investigators also found a single case of 16p11.2 duplication in their sample, they observed the duplication in two of their control subjects and therefore did not conclude the duplication associated with ASD. However, other studies have confirmed both the deletion and duplication as clearly associated with ASD (Fernandez et al., 2010; Marshall et al., 2008), despite the variable expressivity highlighted by observations of apparently unaffected individuals occasionally carrying the duplication. Detailed examination of ASD probands carrying CNV at 16p11.2 revealed that the heterogeneous phenotypic spectra associated with these genomic variants include ID and variable facial dysmorphology (Fernandez et al., 2010). That study also found evidence suggesting that 16p11.2 deletions may be more penetrant with regard to ASD than are duplications. Another study confirmed the phenotypic heterogeneity associated with CNV at 16p11.2, adding Ep and motor delay to the manifestations associated with either the deletion or duplication, and attention deficit hyperactivity disorder to those associated with the duplication (Shinawi et al., 2010). Interestingly, that same study found macrocephaly to associate with the deletion and microcephaly (diminished head circumference) with the duplication.

McCarthy and colleagues reported that SSD are also associated with duplications (but not deletions) at 16p11.2 (McCarthy et al., 2009). Interestingly, consistent with earlier results in ASD, this group also observed an association of the 16p11.2 duplication with head circumference in the SSD sample, suggesting this endophenotype may not be specific to ASD but rather associated with the duplication and a broader risk for NDDs. If the 'specificity' of the association between SSD and only the duplication at 16p11.2 withstands more extensive study in additional cohorts of patients, such an observation could help distinguish genes within the CNV region that might more specifically predispose to ASD (when haploinsufficient) rather than SSD (when present in excess). However, more data are necessary before it is clear that only the duplication associates with SSD.

35.5.6 16p13.11 Deletions and Duplications

The short arm of chromosome 16 is particularly rich in LCRs (Martin et al., 2004), with the result that nonhomologous recombination events in the region are common. Thus, another set of recurrent CNVs distal to the 16p11.2 region just discussed occurs on 16p13.11. These CNVs vary somewhat in length, due to the complexity of the region, but most are ~1.4–1.65 Mb in length. Both duplications and deletions were originally described as associated with ASD and ID (Pinto et al., 2010; Ullmann et al., 2007), although apparently unaffected carriers of the duplications were identified in several families with affected members. However, a study that screened a large cohort of patients with ID or multiple congenital anomalies (MCA), as well as two cohorts of European-ancestry adults with no known evidence of NDD (but who were not specifically evaluated) found only the deletions to occur significantly more frequently in patients than in

the control individuals. Those observations led the authors of that study to suggest that duplications at 16p13.1–13.2 might be nonpathogenic variants. A more recent study, of >4300 patients with SSD and >35 000 controls ascertained in several European countries and evaluated using SNP-genotyping arrays, found an overall association between duplications at 16p13.1 and SSD, with approximately a threefold excess observed in the patient group. When the investigators classified the duplications according to their positions across three subregions of 16p13.1, they found a stronger association with duplications residing in the proximal two subregions (with respective odds ratios increasing from 3.27 to 7.27). The authors of the latter study, while acknowledging the difficulty of declaring duplications at 16p13.1 to be pathogenic, given heterogeneity in duplication size and the prior inconclusive results with regard to ID and MCA, argue that additional factors add to evidence that such duplications are pathogenic. They point out that the subregion analysis just summarized, in addition to strengthening the statistical association also identifies a strong candidate locus, *NDE1*. That gene encodes a protein that interacts with *DISC1*, which itself is the product of a strongly supported 'schizophrenia gene.' Another binding partner of *NDE1* is the gene product of *LIS1*, which is strongly associated with the severe NDD, lissencephaly.

35.5.7 17q12 Deletions

Deletions in 17q12 were until recently believed to be one of the few recurrent genomic disorders that spared the central nervous system. This 1.4-Mb recurrent deletion harbors the *HNF1B* gene, which is responsible for the renal cysts and diabetes (RCAD, MIM ID #137920) syndrome. Generally, affected patients have various degrees of renal compromise, including renal cysts and hyperechogenic kidneys that might progress to renal failure (Sovik et al., 2002). Additionally, maturity-onset diabetes of the young type 5 is usually seen by early adulthood. Affected females may have uterine malformations such as bicornuate uterus and Müllerian aplasia (Bellanne-Chantelot et al., 2004). This clinical presentation is often accompanied by a characteristic facial gestalt that includes macrocephaly and prominent forehead, downslanting palpebral fissures, depressed nasal bridge, and protruding maxilla in adulthood (Moreno-De-Luca et al., 2010). However, patients with a milder phenotype, even without these core clinical features and hence without a diagnosis of RCAD, are not infrequent (Moreno-De-Luca et al., 2010).

As alluded to previously, until recently, there was no evidence that a central nervous system phenotype is associated with 17q12 deletion syndrome. However, recent studies have shown that ID, ranging from mild to moderate, is common in patients with 17q12DS. More interestingly, behavioral anomalies have been identified in small cohorts of these patients, particularly involving problems in social interactions reminiscent of ASD. A recent report (Moreno-De-Luca et al., 2010) found that six of nine patients with 17q12DS met DSM-IV TR criteria for ASD. This finding was then confirmed in larger cohorts of patients with ASD (Moreno-De-Luca et al., 2010). Additionally, given the clinical and genetic overlap between ASD and SSD, large cohorts of patients with schizophrenia were investigated to assess the frequency of the deletion. A strong association was identified between 17q12DS and SSD. This CNV was absent from a very large sample of control individuals (52 448), which could be interpreted as a strong impact of this CNV over the phenotype of affected individuals, albeit with variable expressivity (Moreno-De-Luca et al., 2010).

Interestingly, the 17q12 region overlaps with a replicated linkage and association peak found in families with ASD (IMGSAC, 2001; McCauley et al., 2005; Stone et al., 2004, 2007; Yonan et al., 2003). It is tempting to hypothesize that one of the genes within this region is responsible for that linkage signal. However, the frequency of the deletion across different populations is 1 in 900 on average, and the frequency of yet-undiscovered mutations in one of the genes, which would account for a similar phenotype, is very likely rare as well and might not fully explain the linkage signal.

The 17q12DS region harbors 15 genes, and haploinsufficiency in one or more of these likely accounts for the neurocognitive phenotypes observed in these patients. *HNF1B* is responsible for the core features of RCAD (Bellanne-Chantelot et al., 2004); however, patients with point mutations or single-gene deletions do not appear to have a behavioral phenotype, which would mean that one of the other genes within the region might be responsible for the central nervous system findings. *LHX1* is a transcription factor involved in brain development and axonal guidance (Avraham et al., 2009) and appears as an interesting candidate. Knockout mice lack proper patterning of the midbrain–hindbrain barrier (Shawlot and Behringer, 1995). Nevertheless, no mutations in humans have been documented, so the pathogenic role of haploinsufficiency cannot be clearly established. More studies are needed to clarify this issue.

35.6 CONCLUSIONS AND FUTURE DIRECTIONS

The information just summarized illustrates exciting progress in understanding genomic mechanisms contributing to ASD, SSD, and other NDDs. While our current, very incomplete, knowledge of the roles of CNV in ASD and SSD suggests common pathways of risk for

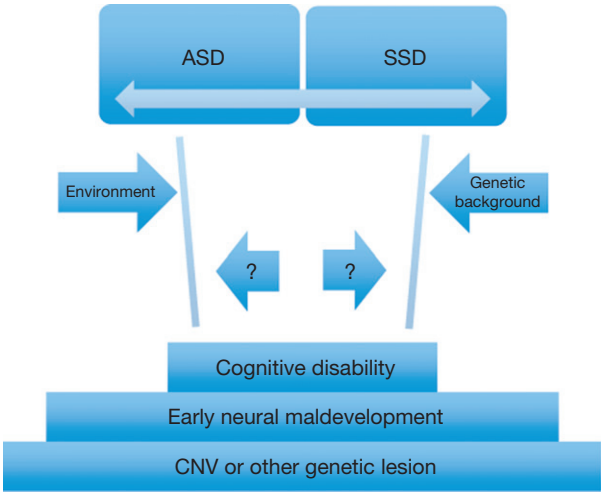

FIGURE 35.1 A heuristic model relating CNV to risk for ASD and SSD. The model is based on the premises that (i) genes within CNV participate in gene networks regulating neural development; (ii) specific factors, including environmental events, epigenetic factors, and stochastic processes can alter developmental trajectories, thereby influencing phenotypic outcomes; and (iii) timing of such events may be critical, especially relative to key developmental epochs such as the prenatal, early childhood, and adolescent periods. Note that the model posits ID as an outcome that precedes ASD or SSD. That component of the model reflects the virtual universal association of some form or degree of ID (or at least learning disorders) with CNV. Thus, we hypothesize that impaired abilities to engage in social learning, probably beginning at birth or possibly earlier, contribute cumulatively to the development of ASD and SSD. Fundamentally, however, such learning difficulties arise from suboptimal function at the cellular and molecular levels.

these two sets of disorders, a major challenge is to understand how similar or identical CNV results in widely different clinical outcomes in different individuals. In Figure 35.1, we summarize a heuristic model for generating testable hypotheses regarding the developmental impact of CNV on risk for ASD, SSD, and other NDDs (although for simplicity, we include only ASD and SSD in the diagram). The model incorporates the following three hypotheses:

1. CNV predisposing to ASD, SSD, and other NDDs do so by altering the function of gene-regulatory networks in which loci at or near the particular CNV participate. Note that a variety of mechanisms could alter such networks, including under- or overexpression of the products of dosage-sensitive genes within a CNV region; unmasking (in the case of deletion) or enhancement (in duplications) of expression of recessive deleterious alleles within the CNV region; effects of CNV on chromatin structure, leading to 'spreading' effects on regulation of genes in *cis* near the CNV or altered *trans* regulation via mechanisms such as chromatin looping (Miele and Dekker, 2009); or the presence of risk alleles at loci elsewhere in the genome but involved in the same regulatory networks as those within the CNV.
2. Specific environmental factors might interact with CNV-associated gene-regulatory networks to alter developmental trajectories. A well-known (and therapeutically modifiable) environmental factor affecting neural development, for example, is maternal intake of folic acid during pregnancy, which strongly impacts the risk of open neural tube defects in offspring (Berry and Li, 2002; see Chapter 27). Understanding how such factors interact with genetic networks at the cellular level during development of the brain could lead to effective preventive or ameliorative strategies in patients with CNV disorders.
3. Variability in the timing or magnitude of specific environmental exposures in the context of specific CNVs might alter developmental trajectories. As noted above, ASD and SSD differ in their typical timing of clinical presentation. However, the typical epochs of presentation (early childhood for ASD, or during or just after puberty for SSD) are periods of profound developmental changes in brain structure or function. It is possible that specific CNVs set up carriers for vulnerability to specific risk factors occurring during these critical periods.

Future research is needed at all levels on CNVs and their association to risk for NDD. To date, patients with CNV have been ascertained almost entirely within clinical contexts or in case–control studies where cases have been selected based on phenomenology. 'Unaffected' (or more likely, mildly enough affected to escape clinical notice) carriers have generally been discovered upon family testing once a proband has been identified, or in the context of case–control studies where 'controls' may not represent the general population, but rather are ascertained for absence of a particular set of syndromes. Current literature, while extremely valuable, is therefore almost certainly laden with biased ascertainment and other difficulties that preclude rigorous epidemiological delineation of the role of CNV in public health. The availability of relatively low-cost methods for scanning the genome for CNV (e.g., aCGH) should support the development of sampling strategies in which molecular rather than phenomenological criteria drive case and control ascertainment. Such studies would be particularly valuable for clarifying factors that distinguish clinical subtypes of specific CNV disorders from each other. As alluded to in examples from 22q11DS and 15q13.3 DS, the clear fact that subsets of patients diagnosed according to phenomenological schema such as the DSM-IVTR are at elevated risk for carrying specific CNV has potentially profound implications for diagnosis and treatment of behavioral disorders.

Another exciting direction enabled by expanding knowledge of CNV-associated behavioral disorders is that credible animal models for fundamentally human disorders become possible. Thus, while nobody will ever be able to guess what constitutes psychosis or autism in a mouse, experiments on rodents carrying engineered syntenic CNVs are shedding light on specific neural and developmental mechanisms likely to be relevant to behavioral deficits in SSD and ASD (Meechan et al., 2009; Sigurdsson et al., 2010). Animal models of neurodevelopmentally important CNV promise to introduce novel strategies for understanding pathological neural development as well as new platforms for testing therapeutic drugs.

While political and economic barriers, such as insurance discrimination against behavioral disorders and (at least in the United States) inadequate or absent health coverage for large proportions of the population, will continue to impede progress in the diagnosis and treatment of behavioral disorders, the emerging literature on CNV as causative factors in mental illness adds to overwhelming evidence that NDDs are every bit as 'biological' and therefore medically 'real' as other complex disorders. Hopefully, the mountain of evidence supporting such a proposition will eventually get large enough that even the American Congress will be unable to continue ignoring it, thus leading to the elimination of barriers to healthcare access that currently severely impact patients with ASD and SSD. In this regard, the ongoing explosion of knowledge on CNV disorders will benefit patients with NDD whether or not they carry associated CNV.

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