AUTISM AND 15Q11-Q13 DISORDERS: BEHAVIORAL, GENETIC, AND PATHOPHYSIOLOGICAL ISSUES

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New insights into biological factors that underlie autism may be gained by comparing autism to other neurodevelopmental disorders that have autistic features and relatively well-delineated genetic etiologies or neurobiological findings. This review moves beyond global diagnoses of autism and instead uses an endophenotypic approach to compare specific clusters of autistic symptomatology to features of chromosome 15q11-q13 disorders. Paternally or maternally derived deficiencies of 15q11-q13 result in Prader-Willi or Angelman syndromes, and we first use a global approach to review potential autism susceptibility genes in the 15q11-q13 region. We then use a more trait-based approach to suggest possible ties between specific phenotypic characteristics of autism and Prader-Willi syndrome, namely savant-like skills. We conclude with insights from pathophysiological studies that implicate altered development of specific neuron types and circuits in the cerebral cortex as part of the pathophysiological processes associated with autism and mental retardation.   © 2004 Wiley-Liss, Inc.
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Despite advances in understanding the behavioral, genetic, and neurobiological features of autism, it remains a clinically diagnosed disorder with heterogeneous etiologies [Lord and Volkmar, 2002]. In light of this heterogeneity, some researchers are using neurodevelopmental disorders with known genetic etiologies as possible contrasting conditions to autism. Some of these neurodevelopmental disorders are associated with full-blown autism, while others feature autistic-like behaviors; examples include fragile X syndrome, Rett syndrome, and Tuberous Sclerosis (see Piven, in press). Thus, greater insight into converging biological factors that cause autism is gained by comparing autism to disorders with autistic features and relatively well-delineated genetic etiologies or neurobiological findings. Conversely, neurodevelopmental disorders with relatively few behavioral symptoms of autism might provide novel clues regarding possible protective factors.

As researchers make comparisons between autism and other neurodevelopmental disorders, they can adopt one of several approaches. Specifically, they can (1) use autism as a single, categorical diagnosis; (2) examine symptoms or phenotypic subsets of autism; or (3) identify etiological mechanisms underlying specific autistic symptoms. Although we briefly describe the first approach, most of this review focuses on comparing phenotypic domains in autism to other disorders and examining genetic and pathophysiological correlates that may underlie common symptomatology. Such newer approaches hold particular promise for identifying mechanisms associated with autism.

In the first, global approach, persons who meet current diagnostic criteria for autism are compared to other groups. This seemingly straightforward approach is complicated by multiple issues. First, the diagnostic criteria for autism have evolved over the years, resulting in temporal shifts in the stringency of diagnoses. The more narrowly defined disorder described by Leo Kanner in 1943 (Kanner, 1943) has evolved into a broader autism spectrum diagnosis, as seen in changes to DSM criteria [Volkmar et al., 1997].

Consider the connections of fragile X syndrome and autism. Comparisons of persons with fragile X syndrome who did or did not meet criteria for autism were characteristic of more than 100 studies conducted in the 1980s and 1990s [Dykens et al., 1994]. Researchers either screened samples with autism for the fragile X marker *or* they applied diagnostic criteria for autism to those with genetically confirmed fragile X syndrome. Wildly discrepant prevalence rates resulted, ranging from 0 to 60%. Such divergent rates were due to differences in samples sizes, diagnostic criteria, and the shift from cytogenetic testing to

molecular assays of fragile X–related triplet repeat expansions in the 1990s.

A second concern is that matching persons with autism to others is challenging, and many studies have not used appropriate matching procedures. Complexities related to matching persons with autism to other groups were recently highlighted in a special issue of the *Journal of Autism and Developmental Disorders* (Burack, 2004). Multiple issues were raised about the types of scores used to match persons (raw, age-equivalent, or standard scores); types of tasks used to match persons (nonverbal language, IQ, visual–spatial, adaptive); advantages and disadvantages of using multiple comparison groups who vary in genetic susceptibility to disorders; and the feasibility of within-group research designs that use no comparison groups.

Researchers also need to be particularly careful about the composition of contrast groups, as many commonly used comparison groups have their own distinctive profile of behavioral strengths or weaknesses that confound findings. Down syndrome, for example, is a frequent contrast group. Children with Down syndrome show increased sociability, looking to others, and smiles [e.g., Kasari and Freeman, 2001]; these are all areas of pronounced impairment in autism. Down syndrome–autism comparisons have also been used in studies of family stress and coping, yet such comparisons have not taken into account the so-called "Down syndrome advantage." Compared to others with developmental delay, families of children with Down syndrome often fare quite well, placing those families who have a child with autism at an increased disadvantage [Seltzer et al., 2004]. Further, siblings of children with a nonsporadic, genetically influenced disorder such as autism are at increased risk to express symptoms of the disorder (e.g., language delay); such risk to siblings may not be evident with other disorders of a sporadic or nongenetic etiology.

For these reasons, many researchers are moving beyond global, categorical comparisons to instead compare specific trait-based subsets or "endophenotypes" associated with autism. Endophenotypes are smaller clusters of behavioral symptoms that hypothetically represent a subset of genetic and/or pathophysiological mechanisms involved in the overall phenotype [e.g., Szatmari et al., 2004]. Thus, studies might focus on social deficits in autism; cognitive/language impairments; psychiatric symptoms such as repetitive/compulsive behaviors or anxiety; or specific features such as stereotypies, restricted interests, or savant skills. A neurodevelopmental disorder with a known etiology can then be selected for study that shares one of more of these autistic traits. Qualitative or quantitative similarities and differences in endophenotypes across groups can be examined, with an eye toward future studies on genetic or pathophysiological mechanisms that underlie these shared endophenotypes.

For the remainder of this review, we provide an in-depth example of the endophenotypic approach by reviewing research-to-date on autism and chromosome 15q11-q13. (A more comprehensive review of links between autism and other neurodevelopmental disorders is beyond the scope of this review and may be found in Piven (in press). Paternally or maternally derived deficiencies of 15q11-q13 result in Prader–Willi or Angelman syndromes, and we first use a global approach and review potential autism susceptibility genes in the 15q11-q13 region. Using more trait-based approaches, the review then describes possible ties between specific phenotypic characteristics of autism and Prader–Willi syndrome (PWS), namely savant and savant-like skills. We then review insights from pathophysiological studies that implicate altered development of specific neuron types and circuits in the cerebral cortex as part of the pathophysiological processes associated with autism and mental retardation.

AUTISM SUSCEPTIBILITY AND 15Q11-Q13

Chromosomal alterations, and hypothetical genetic variation, affecting 15q11-q13 are the focus of three phenotypes with areas of clinical overlap: Prader–Willi and Angelman syndromes (PWS: MIM# 176270 and AS: MIM# 108350) and autism (*AUTS4*; MIM# 209850). While sharing certain pair-wise phenotypic commonalties, these disorders and their connection with this region are associated with different chromosomal abnormalities.

PWS and AS [reviewed in Jiang et al. 1998; Nicholls and Knepper, 2001] are caused most frequently by paternal- or maternal-specific deletions, respectively, of a common, ~5 Mb (megabase) 15q11-q13 interval (see Fig. 1). These deletions are mediated by mispairing of chromosomal homologs via large sequence duplications, or so-called duplicons, flanking the deletion interval [Amos-Landgraf et al., 1999; Christian et al., 1999]. Chromosome 15 generally, and 15q11-q14 in particular, have many copies of similar highly homologous sequence duplicates that can span hundreds of kilobases (kb) and mediate a variety of intra- or interchromosomal rearrangements [Amos-Landgraf et al., 1999; Christian et al., 1999; Ji et al., 2000; Ungaro et al., 2001; Pujana et al., 2002].

Contrasting deletions resulting in parental-specific hemizygosity, in PWS and AS, are two forms of chromosomal duplication observed in some individuals with autism- spectrum phenotypes. Finally, interstitial (i.e., within the chromosome) triplications of this region have also been identified in a few cases. Autism-related duplication (hereafter dup(15) autism) occurs in only a small percentage (1–3%) of persons diagnosed with, or screened for, autism-spectrum phenotypes.

Comparison of duplicated content in dup(15) autism to deletions in PWS/AS reveals that one form of the dup(15) autism is interstitial and represents the reciprocal meiotic product to that seen in PWS/AS deletions. Interstitial or tandem duplications are mediated by the same duplicons mediating deletion in PWS and AS, and affected individuals will have three copies of genes in the corresponding interval. The more frequent second class of duplication represents the occurrence of a supernumerary marker chromosome 15 with an inverted, duplicated isodicentric structure (so called idic(15) markers, in which two centromeres are present, however, only one is functional). Two classes of such marker chromosomes 15 have been identified and are differentiated by their inclusion or exclusion of the PWS/AS deletion interval. So-called "small" markers have two copies of the region extending from the centromere to the proximal PWS/AS deletion breakpoints; these 15 markers are generally associated with a normal phenotype [Huang et al., 1997]. By contrast, the larger classes of idic(15) markers utilize one of several duplicons distal to the PWS/AS interval (e.g., BP4, BP5; [Ji et al., 2000; Pujana et al., 2001, 2002; Ungaro et al., 2001]). Individuals with these markers carry two normal homologs and two additional copies of the PWS/AS region plus DNA extending several Mb distal to the PWS/AS deletion interval. The phenotype in these cases is generally pronounced, with symptoms of autism that are on the more severe end of the spectrum in terms of cognitive functioning and comorbid clinical findings [Clayton-Smith et al., 1993; Robinson et al., 1993; Schinzel et al., 1994; Flejter et al., 1996; Cook et al.,
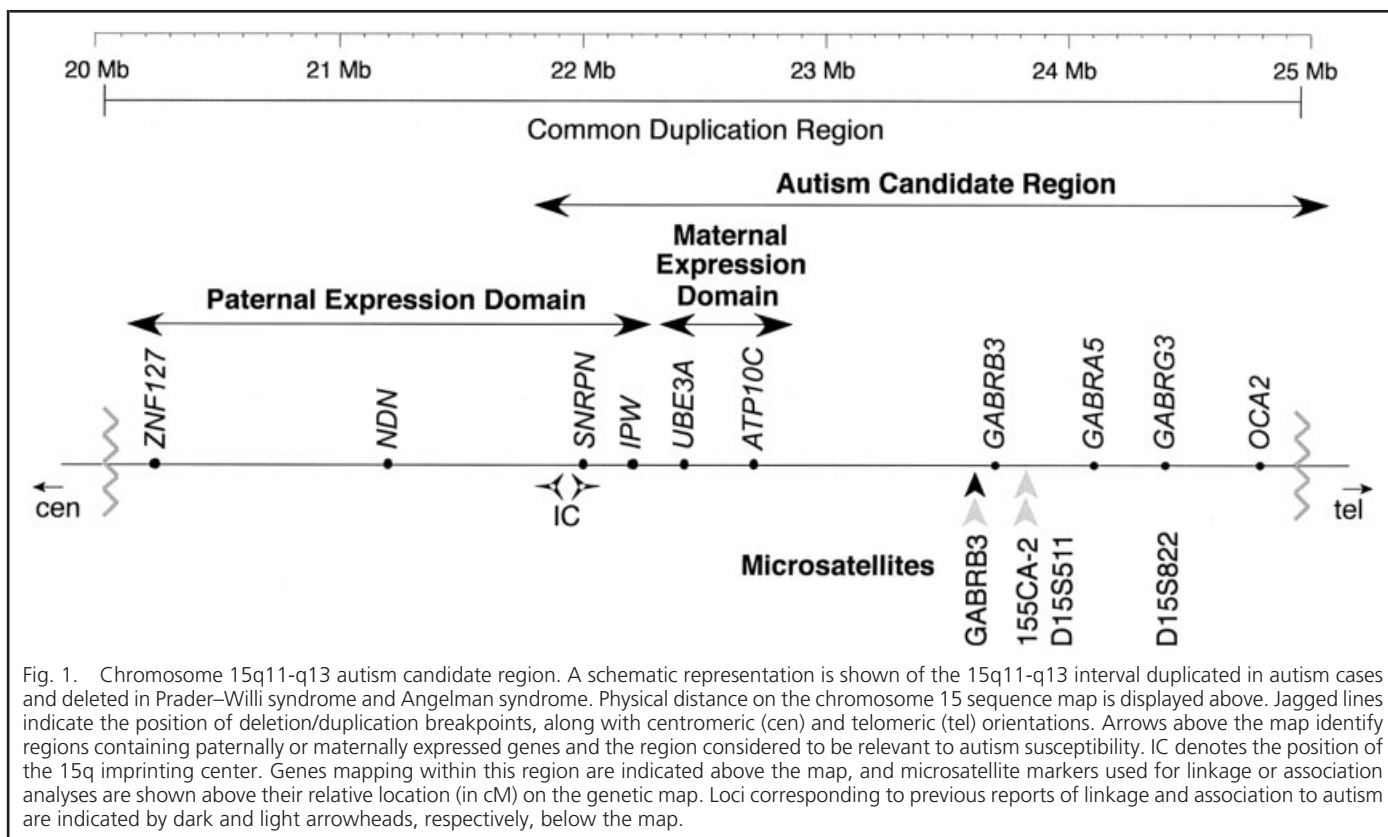
Fig. 1. Chromosome 15q11-q13 autism candidate region. A schematic representation is shown of the 15q11-q13 interval duplicated in autism cases and deleted in Prader–Willi syndrome and Angelman syndrome. Physical distance on the chromosome 15 sequence map is displayed above. Jagged lines indicate the position of deletion/duplication breakpoints, along with centromeric (cen) and telomeric (tel) orientations. Arrows above the map identify regions containing paternally or maternally expressed genes and the region considered to be relevant to autism susceptibility. IC denotes the position of the 15q imprinting center. Genes mapping within this region are indicated above the map, and microsatellite markers used for linkage or association analyses are shown above their relative location (in cM) on the genetic map. Loci corresponding to previous reports of linkage and association to autism are indicated by dark and light arrowheads, respectively, below the map.

1997; Bolton et al., 2001; Roberts et al., 2002].

Phenotypes caused by such chromosomal abnormalities are termed genomic disorders. PWS paternal-specific deficiencies can also be caused by maternal uniparental disomy (UPD) in ~25% of cases. In ~5–7% of cases there are defects in the imprinting process, also resulting in a loss of paternal-specific gene expression; these defects are typically mediated by small (e.g., 10–100 kb) deletions in a region defining the 15q imprinting center (IC) that regulates the switch in the chromosomal "imprint" during gametogenesis. While a number of imprinted, paternally expressed genes and noncoding transcripts have been identified, gene–phenotype relationships remain unclear. Maternal deficiencies in AS can also be caused by a comparatively infrequent (~2%) paternal UPD or by imprinting defects such as described for PWS (~5–7%). A fourth class of cases exhibiting none of these abnormalities led to the identification of the E6-AP ubiquitin protein ligase (UBE3A) as the Angelman gene upon findings of maternally inherited or de novo null mutations [Kishino et al. 1997; Matsuura et al. 1997]. Therefore, maternal-specific deficiency of UBE3A is necessary and sufficient to cause AS. Even so, a lack of molecular confirmation exists in about

15% of cases with a clear clinical diagnosis but with an absence of the other four types of defects.

The Role of Imprinting

PWS and AS are clinically quite distinct and are disorders that exhibit opposite patterns of genomic imprinting. Dup(15)-associated autism is also subject to a significant imprinting bias, and phenotypic severity varies as a function of gene copy number. Interstitial duplication of the 15q11-q13 interval does not, per se, cause autism, but is a substantial risk factor for developing autism, with a maternally derived interstitial duplication resulting in much greater risk than a paternally derived duplication [Cook et al. 1997; Bolton et al., 2001; Roberts et al. 2002]. One of the more comprehensive studies of a number of such cases showed that 7 of 10 instances of maternal interstitial dup(15) result in an autism diagnosis [Browne et al. 1997; Bolton et al. 2001]. Idic(15) marker chromosomes are almost always of maternal origin and are generally associated with a comparatively more severe phenotype. This increased severity results either from tetrasomy for additional genes or from having three copies of maternal 15q11-q13 and its corresponding genes [Clayton-Smith et al., 1993; Robinson et al., 1993; Schinzel et al., 1994; Flejter et al., 1996; Cook et

al., 1997; Bolton et al., 2001; Roberts et al., 2002].

The maternal bias of dup(15) with autism spectrum phenotypes has led some to speculate that, if this region was involved in idiopathic autism, then the most likely candidates are the maternally expressed AS gene UBE3A or potentially its similarly imprinted neighbor ATP10A (previously ATP10C). However, paternal dup(15) can lead to autism and largely anecdotal comparisons of del(15) PWS to UPD-PWS reveals only weak support for an increase in "autistic behaviors" in PWS-UPD compared to PWS- deletion cases [Veltman et al., 2004]. This supports the hypothesis that dup(15) autism is a contiguous gene duplication syndrome [Sutcliffe et al., 2003], influenced by degree of maternal-specific expression of UBE3A and/or ATP10A.

Trait–Based Approaches

While some of the numerous genome-wide linkage studies have implicated proximal 15q in autism [CLSA et al., 1999; Philippe et al., 1999; Shao et al., 2002], this has not been a universal finding and it is not uncommon for disorders of complex genetic etiology. A major problem in dissecting the genetics of a disorder of complex genetic architecture is that locus heterogeneity, particularly in the case of autism [Pickles et

al., 1995; Risch et al., 1999], lessens statistical power to detect susceptibility genes and corresponding alleles. Thus, more recent studies utilizing trait-based subsets of autism, identified through factor analyses of variables in the Autism Diagnostic Interview [ADI; Cuccaro et al., 2003; Tadevosyan-Leyfer et al., 2003], has lead to a number of such putative phenotypic subsets we hypothesize represent a smaller number of underlying susceptibility alleles [Nurmi et al., 2001; Shao et al., 2003; Tadevosyan-Leyfer et al., 2003]. One such study from our group led to the finding that families in which affected individuals exhibiting savant skills (relative to overall cognitive functioning) had significantly increased evidence for linkage to markers between *GABRB3* and *GABRA5* [Nurmi et al. 2003], two genes encoding γ-amino butyric acid (GABA) neurotransmitter receptor-type A subunits. Another report found increased evidence for linkage in this same region, utilizing an ADI-derived factor termed "insistence on sameness" [Shao et al.2003].

These "traits" are of particular interest in light of the increasingly well-described PWS phenotype. Many individuals with deletion-PWS have increased skills in assembling jigsaw puzzles compared to PWS-UPD cases and non-PWS groups with or without mental retardation [Dykens, 2002]. The PWS behavioral phenotype also includes needs for sameness in daily routine and environmental stimuli [Dykens et al., 1996]; behaviors that are similar to the "maintenance of sameness" first observed by Kanner in his description of autism [Kanner, 1943]. Ordering, arranging, concerns with symmetry, and self-injury are seen in both disorders as well. These observations support the hypothesis that a commonality in genetic contribution may be responsible for the similarities and overlap in phenotype. The fact that deletion PWS cases have better jigsaw puzzle skills (a hypothetical correlate to the savant skills effect in autism) might suggest a partial loss-of-function effect in the $GABA_A$ receptor subunit cluster (particularly *GABRB3* or *GABRA5*), a unifying genetic mechanism for these aspects of the phenotype. Supporting this idea are recent imaging studies in PWS deletion subjects [Lucignani et al. 2004] and autism [Blatt et al. 2001] that show reduced $GABA_A$ receptors in several cortical regions and hippocampus. These studies are promising as they implicate GABAergic neurons in the phenotypes of PWS and autism and as we suggest below. We have hypothesized that the

disruption of interneuron function also is likely to be involved in many other neurodevelopmental disorders as well [Levitt et al., 2004].

INTERNEURON PATHOGENESIS: A POINT OF CONVERGENCE IN AUTISM AND OTHER NEURODEVELOPMENTAL DISORDERS

The endophenotypic characteristics of neurodevelopmental disorders provide insight for identifying common clinical features that may have dissimilar underlying etiologies. These common features have the potential to serve another important purpose— to identify the specific aspects of brain circuitry that may have shared disturbances in their development and maturation in specific disorders.

There is currently a sufficient body of knowledge from basic science to begin to address possible links amongst disorders, beyond the identification of macrocircuitry (e.g., frontal and temporal lobes, amygdala), to the circuits and neuronal populations whose development is disrupted. However, the time of onset, the developmental trajectory, and the specific domains of cognitive and emotional disturbances all speak to the difficulty in identifying the underlying pathogenetic processes that may overlap among disorders.

It also has been difficult to identify the molecular constituents responsible for disrupted brain development, because, at the biological level, individual molecules that are candidates for causing developmental errors are generally pleiotropic (multi- functional) in nature, and we know that many molecules combine in complex pathways to regulate specific developmental events, such as cell migration, neuronal differentiation, synapse formation, and myelination. Furthermore, while more widely acknowledged in the psychology and education fields than in the past, it is essential to embrace the now well-documented fact that both genes and environment are acting on the same target—the brain—to guide biological processes during development.

The alteration of complex information processing reflects the likely involvement of cortical circuits in autism, Prader–Willi, Angelman, Down, fragile X, and Williams syndromes, but there are clearly distinctive features of each that likely reflect overlapping involvement of cortical circuits. What do they all have in common at the pathophysiological level? In a relatively large fraction of the population in neurodevelopmental disorders,
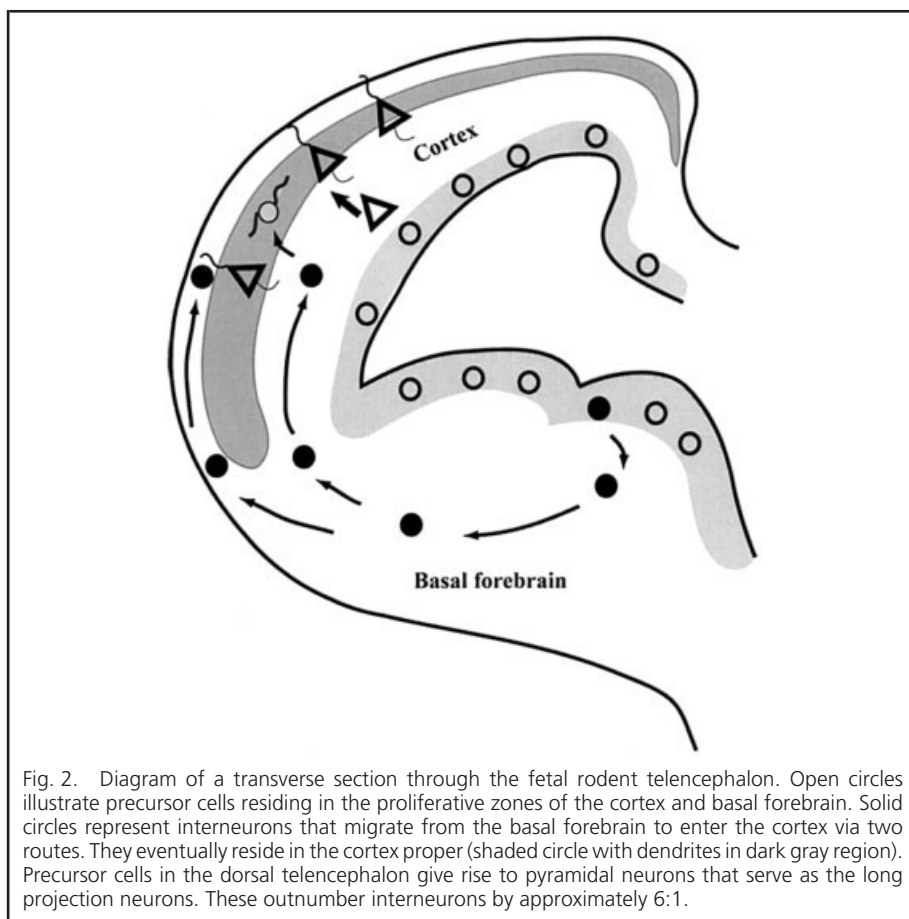
disturbances in the balance of excitation and inhibition are commonly identified [Rennie and Boylan, 2003], including seizures and subclinical spike wave activity, perturbations in arousal mechanisms, and broadly defined disruption of homeostatic processes, such as sleep–wake cycle. For example, compared to the typical population, frank epilepsy or infantile spasms has a far greater incidence in neurodevelopmental disorders (3- to 30-fold greater risk) such as autism, fragile X, or Angelman syndromes [Thirumalai et al., 2002; Tuchman and Rapin, 2002; Rennie and Boylan, 2003]. The temporal onset of seizures may vary with regard to syndrome, reflecting potentially different mechanisms that create susceptibility of interneuronal circuitry. Likewise, although cognitive and social–emotional problems are common features of these disorders, they are sufficiently distinct in nature to suggest that different aspects of information processing, and even perhaps different circuitry, is the target of pathogenic processes of brain development and maturation.

The Central Role of GABAergic Interneurons

There are several reasons why we suggest that cortical and subcortical GABAergic interneurons serve as prime candidates for the study of pathogenic processes in many neurodevelopmental disorders. First, interneurons regulate the degree of excitation in the neocortex, the fine tuning of sensory maps, and the quality of information processing between cortical regions whose principal responsibility is to integrate information from various modalities [Mountcastle, 1997]. Second, there are well-known genetic and environmental influences, defined by experiments performed by basic neurobiologists, which direct the development of interneurons [Marin and Rubenstein, 2003]. Thus, interneuron development can be disrupted by a combination of distinct gene mutations and environmental pathologies. Given the complex and distinct etiologies that are likely to underlie different neurodevelopmental disorders, disturbances in interneuron development could serve as a common feature that would yield overlapping, yet distinctive endophenotypes.

During pre- and postnatal development, the number and specific phenotypic properties of interneurons are established. These same time periods serve as the most vulnerable times for disturbing the balance of cortical excitatory neurons:interneurons. Multiple steps are involved in the development of interneurons; thus, there are po-

Fig. 2. Diagram of a transverse section through the fetal rodent telencephalon. Open circles illustrate precursor cells residing in the proliferative zones of the cortex and basal forebrain. Solid circles represent interneurons that migrate from the basal forebrain to enter the cortex via two routes. They eventually reside in the cortex proper (shaded circle with dendrites in dark gray region). Precursor cells in the dorsal telencephalon give rise to pyramidal neurons that serve as the long projection neurons. These outnumber interneurons by approximately 6:1.

tentially many discrete points of susceptibility to disturb neurodevelopmental processes [Levitt et al., 2004]. For example, almost all forebrain interneurons originate in lower mammals from a region of the basal forebrain, the ganglionic eminence, that also gives rise to neurons of the basal ganglia and amygdala [Anderson et al., 1997; Marin and Rubenstein, 2003]. In humans, almost 50% of interneurons originate from this location, which is distant from their final destination in the overlying cerebral cortex [Letinic and Rakic, 2001]. This creates unique problems for the developing interneuron, as it must exit the proliferative zone that gives rise to noncortical neurons, begin the process of differentiation into a GABA-producing neuron, and migrate long distances to the overlying cortex. Moreover, these neurons must intercalate into the developing cortex at the same time that glutamateric projection neurons reach their final positions in deep (subcortically projecting) and superficial (cortico-cortical) layers. Together, these neurons begin the extended pre- and postnatal process of synapse formation and modification that is highly dependent upon experience derived from the child's world [Levitt, 2003].

A number of chromosomal loci implicated in neurodevelopmental disorders house genes that encode proteins involved in interneuron development (e.g., *Dlx* genes on chromosomes 2 and 7; Rubenstein and Merzenich, 2003] or control the ability of interneurons to signal. In the 15q11-q13 region highlighted in this review, for example, genetic studies of families with idiopathic autism provide an increasingly compelling case that the genetic risk factor(s) lie not with the maternally expressed genes, but with a cluster of GABA$_A$ receptor subunit-encoding genes (*GABRB3, GABRA5,* and *GABRG3*) located distal to the PWS and AS imprinted genes. Reports of association in 15q11-q13 most consistently identify *GABRB3*. Three groups, including a metaanalysis, have reported association at microsatellite markers in this gene [Cook et al., 1998; Martin et al., 2000; Buxbaum et al., 2002], and preliminary studies by Cook and colleagues show association at two single nucleotide polymorphisms (SNPs) in *GABRB3* [Weiss et al., 2002]. Recently, we undertook the first detailed study of the 1-Mb 15q12 GABA$_A$ subunit-encoding cluster for the presence of a common susceptibility allele for autism [McCauley et al., 2004] and found nominally significant evidence for association within a few haplotype blocks, predominantly in *GABRB3*, and one in *GABRA5*. These results raise

the specter of allelic heterogeneity; one of the truly confounding factors in dissecting a complex genetic disorder, as it represents a departure from the traditional "common disease–common allele" hypothesis. This is a persistent concept in genetic epidemiological circles, but not borne out by lessons from studies of Mendelian genetic disorders.

The combinatorial nature (genes and experience) of interneuron development thus raises the possibility that there is a sequential nature to the pathogenesis of neurodevelopmental disorders, with specific gene mutations causing fundamental problems in interneuron development or signaling, resulting in altered developing circuits whose further maturation is perturbed by abnormal processing of information during sensitive periods of postnatal development.

Whatever the complexity of interneuron development, it is remarkable that, in all mammalian species examined, the ratio of glutamateric:GABAergic neurons is approximately 6:1 across cortical regions (see Fig. 2). This reflects a highly conserved developmental mechanism to ensure proper balance of excitation and inhibition. Yet, the subtypes of GABAergic interneurons are far more complex than projection neurons, exhibiting dramatically different neurochemistry, morphology, and even synaptology within the cortex. It is not clear how this diversity is regulated, but we now have a few examples from the study of genetic mutations in animal models in which disruption of interneuron development results in long-term seizure activity, altered social–emotional states, and disrupted cognitive function [Powell et al., 2001, 2003]. In a sense, then, the outcome of initial abnormal development of the circuitry during pre- and early postnatal development would establish the framework for a "self-fulfilling" prophecy, in which experience-expectant features of circuit maturation and refinement would be atypically driven, without appropriate intervention, to yield a complex pathophysiology and disturbed function.

Beyond the obvious contribution to pathological brain states, such as epilepsy, how important is proper interneuron development for cognitive and social–emotional processes? Interneurons are critical for regulating the qualitative and quantitative features of projection neuron function. For example, the temporal correlation of pyramidal cell output is regulated by the bursting activity of interneuron networks [Blatow et al., 2003; Klausberger et al., 2003]; the bursting electrical activity that is essential for

controlling pyramidal (excitatory) neuron output can be measured in the theta range of electrophysiological rhythms that are discerned by EEG. Theta rhythms are evident at multiple levels of cortical circuitry. For example, theta oscillations represent coordinated activation of neuronal populations, within and across cortical regions that are correlated with specific encoding features of cognitive functions, such as working memory. The extent of coupling between cortical regions, such as occurs between frontal, parietal, and temporal cortices, reflects the ability of the brain to retrieve and utilize information that is essential for performing complex cognitive tasks.

Interneurons also are responsible for controlling the temporal resolution of the inputs on the pyramidal projection neurons [Pouille and Scanziani, 2001]. For example, each excitatory projection neuron may receive thousands of bits of information within a specific time window (a few to hundreds of milliseconds), through their afferent synaptic connections. None of the inputs individually can activate the neuron. Thus, each neuron has the difficult task of utilizing the incoming information and, somehow, activating in concert with other neurons of like-function to enable the most important information to be passed downstream to other parts of the circuit. The time window is set by interneurons. A narrow window, in which only a small fraction of the inputs may arrive, would have a different impact on physiological activation and information processing compared to a broad window, in which a much greater diversity of information may arrive and require deciphering. There is ample experimental evidence demonstrating that synapses become validated functionally by a process of physiological activation. Those neurons that fire together generally retain strong connections [Katz and Shatz, 1996]. Those that fail eventually are removed as part of the normal deconstruction process that occurs during postnatal brain development. The interneuron appears to be a key component of cortical circuitry that controls this developmental process. For example, recent experiments reveal that proper interneuron function is essential during the critical period for the development of binocular vision [Fagliolini et al., 2004; Hensch and Stryker, 2004]

Interneuron Pathogenesis as a Marker of Neurodevelopmental Disruption

One can quickly imagine the difficulties in information processing if inter-neuron development was disrupted. More rapid inhibitory neuron maturation could result in a narrowing of the time window too soon, disrupting the normal maturation of important cross-modal processing of information. Perhaps the circuit functions well, even better, with limited input, but under conditions of a need for complex information processing, a pathophysiological state is reached. Might this underlie certain features of autism? Disruption of interneuron maturation would result in altered organization of the principal processing unit of the cerebral cortex, the minicolumn [Mountcastle, 1997; Buxhoeveden and Casanova, 2002], and the possibility of more poorly tuned projection neurons. Casanova and colleagues, have, in fact, reported altered structure of minicolumns in autism, dyslexia, and PDD-NOS, [Buxhoeveden and Casanova, 2002; Casanova et al., 2002]. Furthermore, postmortem studies reveal decreased expression of markers of GABAergic circuitry in the hippocampus [Blatt et al., 2001]. We know, however, that there is both gray and white matter neuropathology in autism [for reviews, see Cody et al., 2002; Acosta and Pearl, 2003]. Can interneurons modulate the development of cellular elements in both regions? We have noted the central role that interneurons play in the formation of gray matter maps in the neocortex. A recent study suggests that GABAergic neurons can even influence the behavior of oligodendrocyte progenitors during development [Lin and Bergles, 2004]. While a direct link has not been established between the altered growth of subcortical white matter, reported recently in autism and language delay disorder [Herbert et al., 2004], and disrupted interneuron development, this unexpected relationship between interneurons and oligodendrocytes is intriguing and deserves additional attention. It also highlights the pleiotropic nature of the molecular signals that control neural development; growth factor and neurotransmitter signaling typically modulates multiple neurodevelopmental events.

In relation to the syndrome-unique features of a variety of neurodevelopmental disorders, such as autism, the pathogenesis of interneurons in different cortical regions could provide the basis for selective neuropathology in specific brain regions, as well as skills highly developed in one cognitive domain, yet severely impaired in other cognitive functions [Casanova et al, 2001; Herbert et al, 2004]. Finally, we know little about how these fundamental processes of the tuning of interneuron–projection neu-

ron networks work in the control of social–emotional states. The organization of interneurons in subcortical brain regions is distinct from that described in the cortex, but they are no less complex. These cells form networks that appear to be more modifiable, but equally important in the fine tuning of circuits involved in anxiety, aggression, and other mental health domains that are commonly disturbed in many neurodevelopmental disorders [Freund et al., 2003].

NEXT STEPS

We are left with several tasks at hand that require the collective activity (and wisdom) of basic and clinical researchers in neurodevelopmental disorders: (1) to identify the genetic and environmental mechanisms that regulate complex features of interneurons and the formation and plasticity of specific circuits; (2) to utilize information of the unique and overlapping endophenotypes of neurodevelopmental disorders to focus on specific neurobiological domains to help define in far more detail the cellular and brain regional pathophysiology of each disorder; (3) to apply experience-based interventions that activate brain mechanisms that can be harnessed to modify, in a positive way, neurodevelopment. Each disorder will likely have some overlapping and some unique features of disrupted development. Although these features are well-characterized in more common conditions (e.g., autism, fragile X, Prader–Willi, Williams, and Down syndromes), most of the more than 1,200 known genetic conditions associated with mental retardation have yet to receive a single behavioral study that could guide intervention. Such work is clearly needed as interventions that tap into the signature patterns of disturbed neurodevelopment for each disorder are the most likely to be effective. ■

REFERENCES

Acosta MT, Pearl PL. 2003. The neurobiology of autism: New pieces of the puzzle. Curr Neurol Neurosci Rep 3:149–156.

Amos-Landgraf JM, Ji YG, Gottlieb W, et al. 1999. Chromosome breakage in the Prader– Willi and Angelman syndromes involves recombination between large, transcribed repeats at proximal and distal breakpoints. *Am J Hum Genet* 65:370–386.

Anderson SA, et al. 1997. Interneuron migration from basal forebrain to neocortex: Dependence on Dlx genes. *Science* 278:474–476.

Blatow M, Caputi A, Burnashev N, Monyer H, Rozov A. 2003. Ca$_2$+ buffer saturation underlies paired pulse facilitation in calbindin-D28k-containing terminals. *Neuron* 10:79–88.

Blatt GJ, Fitzgerald CM, Guptill JT, et al. 2001. Density and distribution of hippocampal neurotransmitter receptors in autism: An autoradiographic study. *J Autism Dev Disord* 31:537–543.

Bolton PF, Dennis NR, Browne CE, et al. 2001. The phenotypic manifestations of interstitial duplications of proximal 15q with special reference to the autistic spectrum disorders. *Am J Med Genet 105:*675−685.

Browne CE, Dennis NR, Maher E, et al. 1997. Inherited interstitial duplications of proximal 15q-genotype−phenotype correlations. *Am J Hum Genet 61:*1342− 1352.

Burack J. 2004. Editoral preface to special issue: Research methodology-matching. *J Autism Dev Disord 34:*3−4.

Buxbaum JD, Silverman JM, Smith CJ, et al. 2002. Association between a GABRB3 polymorphism and autism. *Mol Psychiatry 7:*311−316.

Buxhoeveden DP, Casanova MF. 2002. The minicolumn hypothesis in neuroscience. *Brain* 125:935−951.

Casanova MF, et al. 2002. Minicolumnar pathology in autism. *Neurology 58:*428− 432.

Christian SL, Fantes JA, Mewborn SK, et al. 1999. Large genomic duplicons map to sites of instability in the Prader−Willi/Angelman syndrome chromosome region (15q11−q13). *Hum Mol Genet 8:*1025−1037.

Clayton-Smith J, Webb T, Cheng XJ, et al. 1993. Duplication of chromosome 15 in the region 15q11−13 in a patient with developmental delay and ataxia with similarities to Angelman syndrome. *J Med Genet 30:*529−531.

CLSA, Barrett S, Beck JC, et al. 1999. An autosomal genomic screen for autism: Collaborative linkage study of autism. *Am J Med Genet 88:* 609−615.

Cody H, Pelphrey K, Piven J. 2002. Structural and functional magnetic resonance imaging of autism. Int. J. Dev. Neurosci. 20:421−438.

Cook EH, Courchesne RY, Cox NJ, et al. 1998. Linkage-disequilibrium mapping of autistic disorder, with 15q11−13 markers. *Am J Hum Genet 62:*1077−1083.

Cook EH Jr, Lindgren V, Leventhal BL, et al. 1997. Autism or atypical autism in maternally but not paternally derived proximal 15q duplication. *Am J Hum Genet 60:*928−934.

Cuccaro, ML, Shoa Y, Grubberm J, et al. 2003. Factor analysis of restricted and repetitive behaviors in autism using the Autism Diagnostic Interview-R. *Child Psychiatry and Human Development, 34,* 3−17.

Dykens EM. 2002. Are jigsaw puzzles skills "spared" in persons with Prader−Willi syndrome? *J Child Psychol Psychiatry, 43:*343−352.

Dykens EM, Hodapp RM, Leckman JF. 1994. *Behavior and Development in Fragile X Syndrome.* Thousand Oaks, CA: Sage Publications.

Dykens EM, Leckman JF, Cassidy SB. 1996. Obsessions and compulsions in Prader−Willi syndrome. *J Child Psychol Psychiatry, 27:*11−23.

Fagliolini M, Fritschy JM, Low K, et al. 2004. Specific GABAA circuits for visual cortex plasticity. *Science 303:*1681−1683.

Flejter WL, Bennett-Baker PE, Ghaziuddin M, et al. 1996. Cytogenetic and molecular analysis of inv dup(15) chromosomes observed in two patients with autistic disorder and mental retardation. *Am J Med Genet 61:*182−187.

Freund TF, et al. 2003. Interneuron diversity series: Rhythm and mood in perisomatic inhibition. *Trends Neurosci 26:*489−495.

Hench TK, Stryker MP. 2004. Columnar architecture sculpted by GABA circuits in developing cat visual cortex. Science 303:1678−1681.

Herbert MR, Ziegler DA, Makris N, et al. 2004. Localization of white matter volume increase in autism and developmental language disorder. *Ann Neurol 55:*530−540.

Hodapp RM, Ly T, Fiddler DJ, Ricci L. 2001. Less stress, more rewarding: Parenting children with Down syndrome. *Parenting: Sci Pract 1:* 317−337.

Huang B, Crolla JA, Christian SL, et al. 1997. Refined molecular characterization of the breakpoints in small inv dup(15) chromosomes. *Hum Genet 99:*11−17.

Ji Y, Eichler EE, Schwartz S, et al. 2000. Structure of chromosomal duplicons and their role in mediating human genomic disorders. *Genome Res 10:*597−610.

Jiang YH, Tsai TF, Bressler J, et al. 1998. Imprinting in Angelman and Prader−Willi syndromes. *Curr Opin Genet Dev 8:*334−342.

Kanner L. 1943. Autistic disturbance of affective contact. *Nervous Child 2:*217−250.

Kasari, C., Freeman, S.F.N. (2001). Task-related social behavior in children with Down syndrome. *Am J Mental Retard 106,* 253−264.

Katz LC, Shatz CJ (1996). Synaptic activity and construction of cortical circuits. *Science 274:* 1133−1138.

Kishino T, Lalande M, Wagstaff J. 1997. UBE3A/ E6-AP mutations cause Angelman syndrome. *Nat Genet 15:*70−73.

Klausberger, T., Magill, P.J., Marton, L.F., et al. (2003). Brain-state-and cell-type-specific firing of hippocampal interneurons in vivo. *Nature 20,* 797−799.

Letinic, K., Rakic, P. (2001) Telencephalic origin of human thalamic GABAergic neurons. *Nat Neurosci 4,*931−936.

Levitt, P (2003) Structural and functional maturation of the developing primate brain. *J Pediatrics 143,* 835−845.

Levitt, P., Eagleson, K.L., Powell, E.M. (2004) Regulation of neocortical interneuron development and the implications for neurodevelopmental disorders. *Trends Neurosci, 27,* 400−406.

Lin S-C, Bergles DE (2004) Synaptic signaling between GABAergic interneurons and oligodendrocyte precursors in the hippocampus. *Nat Neurosci 7:*24−32.

Lord, C., Volkmar, F. (2002). Genetics of childhood disorders: XLII. Autism, Part I: Diagnosis and assessment in autistic spectrum disorders. *J Am Acad Child Adolesc Psychiatry, 41,* 1134−1136.

Lucignani G, Panzacchi A, Bosio L, et al. 2004. GABAA receptor abnormalities in Prader−Willi syndrome assessed with positron emission tomography and [11C]flumazenil. *Neuroimage 22:*22−28.

Marin, O., Rubenstein, J.L. (2003) Cell migration in the forebrain. *Annu Rev Neurosci 26,* 441−483.

Martin ER, Menold MM, Wolpert CM, et al. 2000. Analysis of linkage disequilibrium in gamma-aminobutyric acid receptor subunit genes in autistic disorder. *Am J Med Genet 96:*43−48.

Matsuura T, Sutcliffe JS, Fang P, et al. 1997. De novo truncating mutations in E6-AP ubiquitin-protein ligase gene (UBE3A) in Angelman syndrome. *Nat Genet 15:*74−77.

McCauley JL, Olson IM, Delahanty R, et al. 2004. A linkage disequilibrium map of the 1- Mb 15q12 GABAA receptor subunit cluster and association to autism. *Am J Med Genet* 131: 51−59.

Mountcastle, V.B. (1997) The columnar organization of the neocortex. *Brain 120,* 701−722.

Nicholls RD, Knepper JL. 2001. Genome organization, function, and imprinting in Prader−Willi and Angelman syndromes. *Annu Rev Genom Hum Genet 2:*153−175.

Nurmi EL, Bradford Y, Chen Y, et al. 2001. Linkage disequilibrium at the Angelman syndrome gene UBE3A in autism families. *Genomics 77:* 105−113.

Nurmi EL, Dowd M, Tadevosyan-Leyfer O, et al. 2003. Exploratory subsetting of autism families based on savant skills improves evidence of genetic linkage to 15q11- q13. *J Am Acad Child Adolesc Psychiatry 42:*856−863.

Philippe A, Martinez M, Guilloud-Bataille M, et al. 1999. Genome-wide scan for autism susceptibility genes. *Hum Mol Genet 8:*805−812.

Pickles A, Bolton P, Macdonald H, et al. 1995. Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: A twin and family history study of autism. *Am J Hum Genet 57:*717−726.

Piven, J. The pathophysiological basis of neurodevelopmental disorders: The example of autism and autistic behaviors. Chapter in Tusman A, Jerald K, and Lierbman J. (2003) *Psychiatry,* 2nd edition.

Pouille, F., Scanziani, M. (2001). Enforcement of temporal fidelity in pyramidal cells by somatic feedforward inhibition. *Science* 293: 1159−1163.

Powell, E.M., et al. (2001). Hepatocyte growth factor/scatter factor is a motogen for interneurons migrating from the ventral to dorsal telencephalon. *Neuron 30,* 79−80.

Powell, E.M., et al. (2003). Genetic disruption of cortical interneuron development causes region- and GABA cell type-specific deficits, epilepsy, and behavioral dysfunction. *J Neurosci 23,* 622−631.

Pujana MA, Nadal M, Gratacos M, et al. 2001. Additional complexity on human chromosome 15q: Identification of a set of newly recognized duplicons (LCR15) on 15q13, 15q24, and 15q26. *Genome Res 11:*98−111.

Pujana MA, Nadal M, Guitart M, et al. 2002. Human chromosome 15q11−q14 regions of rearrangements contain clusters of LCR15 duplicons. *Eur J Hum Genet 10:*26− 35.

Rennie, J.M., Boylan, G.B. (2003) Neonatal seizures and their treatment. *Curr Opin Neurol* 16, 177−181.

Risch N, Spiker D, Lotspeich L, et al. 1999. A genomic screen of autism: Evidence for a multilocus etiology. *Am J Hum Genet 65:* 493−507.

Roberts SE, Dennis NR, Browne CE, et al. 2002. Characterisation of interstitial duplications and triplications of chromosome 15q11−q13. *Hum Genet 110:*227−234.

Robinson WP, Binkert F, Gine R, et al. 1993. Clinical and molecular analysis of five inv dup(15) patients. *Eur J Hum Genet 1:*37−50.

Rubenstein, J.L., Merzenich, M.M. (2003) Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav* 2, 255−267.

Schinzel AA, Brecevic L, Bernasconi F, et al. 1994. Intrachromosomal triplication of 15q11−q13. *J Med Genet 31:*798−803.

Seltzer, M.M., Abbeduto, L., Krauss, M.W., et al. (2004). Comparison groups in autism family research: Down syndrome, fragile X syndrome, and schizophrenia. *J Autism Dev Disord 34,* 41−48.

Shao Y, Cuccaro ML, Hauser ER, et al. 2003. Fine mapping of autistic disorder to chromosome 15q11−q13 by use of phenotypic subtypes. *Am J Hum Genet 72:*539−548.

Shao Y, Wolpert CM, Raiford KL, et al. 2002. Genomic screen and follow-up analysis for autistic disorder. *Am J Med Genet 114:*99−105.

Sutcliffe JS, Nurmi EL, Lombroso PJ. 2003. Genetics of childhood disorders: XLVII. Autism, Part VI: Duplication and inherited susceptibility of chromosome 15q11–q13 genes in autism. J *Am Acad Child Adolesc Psychiatry 42*:253–256.

Szatmari, P., Zwaigenbaum, L., Bryson, S. (2004). Conducting genetic epidemiology studies of autism spectrum disorders: Issues in matching. *J Autism Dev Disord 34,* 49–57.

Tadevosyan-Leyfer O, Dowd M, Mankoski R, et al. 2003. A principal components analysis of the Autism Diagnostic Interview–Revised. *J Am Acad Child Adolesc Psychiatry 42*:864–872.

Thirumalai, S.S., et al. (2002) Rapid eye movement sleep behavior disorder in children with autism. *J Child Neurol* 17, 173–178.

Tuchman, R., Rapin, I. (2002) Epilepsy in autism. *Lancet Neurol* 1, 352–358

Ungaro P, Christian SL, Fantes JA, et al. 2001. Molecular characterisation of four cases of intrachromosomal triplication of chromosome 15q11–q14. *J Med Genet 38*:26–34.

Veltman MW, Thompson RJ, Roberts SE, et al. 2004. Prader–Willi syndrome: A study comparing deletion and uniparental disomy cases with reference to autism spectrum disorders. *Eur Child Adolesc Psychiatry 13*:42–50.

Volkmar FR, Klin A, Cohen DJ. 1997. Diagnosis and classification of autism and related conditions: Consensus and issues. In: Cohen DJ, Volkmar FR, editors. *Handbook of autism and pervasive developmental disorders-second edition.* New York: Wiley. p 5–40.

Weiss LA, Gonen D, Kim SJ, et al. 2002. Association of variation between GABRB3 exon 3 and 155CA-2 with autistic disorder. *Am J Hum Genet 71*:A448.