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Social Phenotypes in Neurogenetic Syndromes

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A major factor in the quest to define behavioral phenotypes has been the identification of a substantial and growing number of specific gene deletion or mutation syndromes that result in genetic neurodevelopmental disorders (GNDDs). These GNDDs are characterized by distinctive patterns of cognitive and behavioral features and congenital medical sequelae. Specific genotypes, defined by the biologically validated presence of known mutated or deleted genes, seem to result in distinctive behavioral phenotypes. In this article we focus on the distinctive social traits of several GNDDs. We begin by summarizing some of the trends and controversies in research to date. This step is necessary to explain why, for several disorders, social features were not mentioned in the earlier versions of some of the behavioral phenotypes and only recently have been studied in a systematic fashion.

Phenotype and behavioral phenotype: definitions

In this article, we rely on the general definition of a phenotype provided by Gottesman and Gould [1] as: "observable characteristics of an organism, which are the joint product of both genotypic and environmental influences." Although there are a handful of known, highly invariant genotype-to-behavioral phenotypic trait linkages, we rely on the definition of a behavioral phenotype provided by Dykens and Cassidy [2]: "The heightened probability or likelihood that people with a given syndrome will exhibit certain behavioral and developmental sequelae relative to those without the syndrome," in recognition of the behavioral heterogeneity generally present in all GNDDs. The clinical neuroscience research approach that has focused

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on the developmental unfolding of behavioral phenotype in neurogenetic syndromes has been termed "behavioral neurogenetics" [3,4]. This approach is predicated on the concept that in individuals with a defined, biologically validated gene disorder, it is possible to follow the ontogeny of the resulting brain–cognitive-behavioral phenotype over the course of development from earliest childhood to adulthood.

Distinctions between "psychiatric phenotypes" and "behavioral phenotypes"

The major impetus driving research in the behavioral phenotypic expression of GNDDs followed from the distinctive behavioral features described in children with these disorders soon after their genetic etiology was confirmed [5]. In the first generation of reporting discoveries in behavioral phenotypes, clinically oriented researchers created a detailed narrative account of the characteristic behavioral traits for a given GNDD based on direct observation and clinical experience [5]. In many cases, this account was followed by a second generation of research that entailed widely used and standardized "off the shelf" structured and semi-structured research diagnostic interviews that used Diagnostic and Statistical Manual (DSM) and World Health Organization diagnostic criteria and behavioral checklists eliciting standardized behavior symptom data for well-accepted dimensions of psychopathology. The findings from this research approach generated prevalence rates for the various established DSM/World Health Organization psychiatric disorders in the various GNDDs. In some cases in which these data were the main source of behavioral information regarding a given syndrome, the resulting patterns might more accurately have been called "psychiatric phenotypes" to distinguish them from true behavioral phenotypes, because there is more to behavior than psychiatric symptoms.

There are major problems with this second-generation "psychiatric phenotype" approach. Most importantly, psychiatry's diagnostic classification system describes disorders increasingly acknowledged to be heterogeneous, lacking biologic validation, and having multifactorial, polygenic origins [1]. In contrast, the GNDDs, although influenced phenotypically by environmental factors, have a biologically validated, far better understood genotypic origin and phenotypic specificity than the less-validated DSM psychiatric disorders from which they are reported to suffer. There is a conceptual mismatch between the specificity and biologic validity of the GNDD disorders and the heterogeneity and lack of biologic validity of the DSM disorders that have been superimposed as the "psychiatric phenotype" on these GNDDs. An additional mismatch arises from the fact that several of the GNDDs meet criteria for multiple DSM disorders, whereas different GNNDs may have applied to them the same "psychiatric phenotype" (eg, attention deficit hyperactivity disorder, anxiety disorder, autistic disorder).

Another problem with applying DSM-based psychiatric phenotypes to GNDDs is that many of the most significant and distinctive behaviors found for some of the neurodevelopmental disorders have no representation in the DSM. Consequently, behaviors that uniquely distinguish the behavioral phenotypes of the GNDDs are not accounted for in a DSM-based psychiatric phenotyping approach. As seen in the discussion of specific GNDDs, there are situations in which there seems to be a cleavage within specific GNDDs—even in the presence of a behavioral phenotype—between individuals who have a major psychiatric disorder (eg, schizophrenia, autism) and individuals who do not.

Social trait aspects of behavioral phenotypes

Distinctive social phenotypes have only gradually become recognized for most of the GNDDs, with two significant exceptions: fragile X syndrome and Williams syndrome. For these two conditions, the social abnormalities were so prominent that the early clinical observations leading to the initial formulation of their behavioral phenotypes highlighted them. Study of these two syndromes has led the way in the exploration of neurogenetic influences on social cognition and social behavior.

Advances in the understanding of the social phenotype in other GNDDs were likely delayed by several interrelated issues: The failure of most standardized psychiatric phenotyping studies to ascertain symptoms for autistic spectrum disorders (the diagnostic category in which most attention is paid to social impairment), controversies interpreting the presence of autistic (social deficit) symptoms when they are found, the frequent omission of measures of adaptive behavior in defining behavioral phenotypes, and controversies as to whether all significant social deficits must be based on a comorbid diagnosis of an autistic spectrum disorder.

Diagnostic overshadowing: attributing social deficits solely to cognitive deficiency

Diagnostic overshadowing [6,7] also remains an unfortunate tendency to attribute the cause of behavior problems and social deficits in GNDDs solely to cognitive deficiencies rather than to social influences, co-occurring psychiatric disorders, or independent genetic influences on social cognition. Deficits in social functioning found in individuals with lower-than-average IQ are particularly likely to be attributed uncritically to cognitive deficits, even if they are distinctive features of a GNDD. It is not easy, however, to decide whether a pattern of poor social skills for any given GNDD is part of a particular behavioral phenotype—a common downstream effect of psychosocial disadvantage and stigmatization—or is secondary to reduced cognitive capacity.

Distinctions between commonly occurring social impairments and autistic spectrum symptoms

Many cognitively normal children who do not have a GNDD or autism spectrum disorder still have social impairments [8]. Over decades, sociometric studies repeatedly have confirmed that approximately 15% of all children are considered unpopular, have problematic social skills, and are avoided by their peers [8]. Cognitively normal children with psychiatric disorders (eg, attention deficit hyperactivity disorder) repeatedly have been shown to have poor social functioning that may not respond to standard treatment for that disorder [9]. When social deficits are present in the GNDDs, it is not entirely clear whether they are caused by the genotypic abnormality or simply reflect the range of social competence found in all groups of children.

Paucity of adaptive behavior data regarding social functioning

It is not clear why adaptive behavior scales were used so rarely in studies of behavioral phenotypes. Possibly they were viewed by researchers as nonspecific, downstream indicators of cognitive deficiency rather than as sources of information about behavior pertinent to distinctive behavioral phenotypes. As a result, social adaptive information for some of the GNDDs has been lacking, such as could have been provided by the Vineland Adaptive Behavior Scale [10]. The failure to use adaptive behavior measures was also unfortunate because abundant normative social functioning data were available for developmentally disabled children with which the findings of any specific disability group could have been compared.

Distinctions between endophenotypic traits and formal psychiatric diagnoses

A further conceptual issue complicates deciding whether a behavior phenotypic trait found in a GNDD is interpretable as a part of a psychiatric diagnosis. This issue concerns the concept of the endophenotype in psychiatry, which was given little attention until the last few years. Endophenotypes refer to measurable traits associated with underlying susceptibility genes. These traits are associated with illness, are heritable and state independent (present even when the illness is not active), and co-segregate within families of probands. Endophenotypes for heritable disorders occur more frequently in nonaffected family members of probands than in the general population [1]. Specifically, these endophenotypic traits, although they may bear resemblance to symptom criteria for the illness being studied, may not meet criteria for that illness. For the scientific understanding of behavioral phenotypes in GNDDs it may be more heuristic to view these phenotypes as endophenotypes rather than as psychiatric disorders.

The concept of an endophenotype has been particularly relevant to studying the behavioral phenotype in 22q11 deletion syndrome, in which a critical issue has been determining which 30% of children with this condition will develop a schizophrenic disorder by young adulthood [11–14]. In research directed at finding the vulnerable 30%, it could be stated that the cognitive-behavioral phenotype in children with velocardiofacial syndrome (VCFS) is an endophenotype for prodromal schizophrenia.

The concept of endophenotype was used more recently in elucidating possible familial mechanisms to explain the puzzling fact that approximately 7% to 10% of children who have Down syndrome—typically a syndrome associated with high sociability—are autistic [15]. Recent reports of high rates of autistic spectrum disorder symptoms (and attention deficit hyperactivity disorder) in premutation carriers for fragile X [16] suggested that such traits might constitute an autism susceptibility endophenotype associated with fragile X premutation carriers.

Fragile X syndrome

Fragile X syndrome is the most common genetic cause of mental retardation and developmental delay. It occurs in approximately 1 in every 4000 boys and 1 in every 6000 to 8000 girls and is caused by an expansion mutation of the FMR1 gene of the X chromosome [17]. Symptoms are typically more severe in boys than girls, because girls retain one X chromosome, whereas boys who have fragile X syndrome have none. The behavioral phenotype of fragile X syndrome includes several cognitive deficits and behavioral anomalies, such as attention deficits, gaze aversion, hand flapping, and hand biting [18–20].

The social phenotype of fragile X syndrome, especially in boys, is characterized by social withdrawal, anxiety, high emotionality, poor eye contact, and atypical speech [21]. Although girls usually suffer from milder impairments, social anxiety and withdrawal are still relatively common, even in individuals with IQs in the normal range, which implies that their social dysfunction is not merely a consequence of general cognitive disability but also involves specific problems in social cognition [22–24]. Girls with normal IQs and full mutations have impairments in social interaction, organization difficulties, impulsivity, shyness, and moodiness [25,26]. Children who have fragile X syndrome also have theory of mind impairments that are qualitatively different from groups with other learning abilities [27].

Social gaze is strikingly impaired in boys with fragile X syndrome. Greeting behavior is characterized by distinct avoidance of eye contact, even when initiating a handshake or offering a salutation [28]. In tasks such as determining gaze direction of people in photos, boys with fragile X syndrome fare poorly compared with matched controls. Neuroimaging, electrophysiologic, and neuroendocrine studies have demonstrated neuronal dysfunction involving the fusiform gyrus plus clear evidence that direct gaze is processed

abnormally. Studies also have shown that face-to-face gaze and eye contact are associated with hyperarousal and a high level of stress [29–32].

A substantial percentage of children, especially boys, who have fragile X syndrome meet DSM criteria for autism. Numerous studies document a rate of autism in fragile X syndrome between 25% and 47%, using various diagnostic methods [33–38]. Some investigators found that the severity of autistic symptoms declines with age [39]; however, other studies indicated high rates of autism at all ages [40]. Recently, behavioral phenotyping studies of carriers of the premutation for fragile X syndrome have been associated with an increased rate of autistic symptoms [16,41].

There has been much debate as to whether "autism" found in fragile X syndrome is truly the same as that seen in idiopathic autism [42]. The key point is that fragile X syndrome is a biologically validated, extensively studied condition with a highly specific behavioral phenotype (in boys), whereas autism is a somewhat more phenotypically heterogeneous disorder that seems to involve many genes [43]. Currently, it is difficult to say more than that the mutation responsible for the autistic-like behaviors in fragile X syndrome is probably one of many genetic configurations that can lead to the DSM categorical diagnosis of autism. In this sense, fragile X syndrome presents one behavioral genetic model of how autism can occur. If it differs in some ways from the autism phenotype seen in "idiopathic" autism, it is likely that as other gene mechanisms are discovered, numerous slightly different biologically validated phenotypic varieties of autism will be identified.

Down syndrome

Down syndrome is caused by trisomy of all or a critical portion of chromosome 21 [44]. It is the most common chromosomal cause of mental retardation and occurs in 1 in 1000 live births, with the incidence increasing with maternal age. Down syndrome is associated with distinctive facial features, congenital heart disease, duodenal stenosis, and mental retardation [44–46].

In most cases, children who have Down syndrome tend to be engaging and affectionate [47]. Compared with adults with learning disabilities matched on age and developmental quotient, a group of adults who have Down syndrome had lower prevalence of aggression, antisocial behavior, property destruction, disturbing others at night, attention seeking, untruthfulness, excessive activity, and excessive noise [48]. Despite language impairments, social communication and relationships seem to be comparable to normally developing controls [49]. Some social processing deficits have been found in recognizing facial expression overall, particularly surprise and fear.

In an investigation of the verbal communication, play, and language skills of children who have Down syndrome, Sigman and colleagues [50] found that the children "engaged in more functional and symbolic play than normal children of equal mental and language age." The children also requested objects

and help with objects more frequently than the control group. Similarly, in study of task-related social behavior, Kasari and Freeman [51] found that children who have Down syndrome "looked to an adult and requested help more frequently" than normally developing children and children with idiopathic mental retardation.

In contrast to the more prevalent phenotype of strong sociability observed in Down syndrome is the repeated finding that 7% to 10% of people who have Down syndrome have autistic traits that meet diagnostic criteria for DSM autism [52–58]. This finding indicates that something about Down syndrome confers approximately a tenfold increased risk for autism. Ghaziuddin [15] studied first-degree relatives of individuals who have autistic Down syndrome and compared them with first-degree relatives of individuals who have Down syndrome who had no autistic traits. The author found that the relatives of the individuals who have autistic Down syndrome had a significantly higher rate of traits of the broader autism phenotype. This finding suggested that either Down syndrome is a potent risk factor for autism when other risk genes for autism are present or that something about the chromosomal abnormality predisposes toward autistic traits.

Prader-Willi syndrome

Prader-Willi syndrome is a genetic disorder that usually involves a deletion or uniparental disomy in chromosome 15. Prader-Willi syndrome affects approximately 1 in 10,000 to 15,000 births and is characterized by hyperphagia, hypotonia, hypogonadism, diminished fetal activity, obesity, muscular hypotonia, mental retardation, short stature, hypogonadotropic hypogonadism, small hands and feet, developmental delays, and distinct facial features [59].

Although many studies have considered the behavioral phenotype of Prader-Willi syndrome, few have focused exclusively on the social deficits associated with the syndrome. A study by Dykens and Cassidy [2] found higher frequencies of stubbornness, tantrums, disobedience, and talking too much in children who have Prader-Willi syndrome. Thirty-four percent of tantrums that were reported involved a physical attack of others. Other antisocial behaviors noted in Prader-Willi syndrome include lying, stealing, and hiding, often to obtain or hoard food [60,61]. Research also shows that patients who have Prader-Willi syndrome frequently suffer from compulsive and impulsive-aggressive behaviors [62]. High rates of specific obsessive-compulsive behaviors not related to food—mainly compulsions concerning a need to tell or ask (ie, repeated questioning)—have been identified [63,64].

A survey by Greenswag [65] described solitary behavior, social withdrawal, and poor peer relations in Prader-Willi Syndrome personalities. A later study estimated that most patients preferred being alone, observing that many patients displayed argumentative, verbally abusive, and aggressive behavior toward others [66]. Keonig and colleagues [67] described the

performance of patients who have Prader-Willi syndrome on an experimental task, the Social Attribution Task, which measures a specific ability necessary for interpreting social information. The poor performance of the individuals who have Prader-Willi syndrome compared to a cognitively matched group suggested that individuals who have Prader-Willi syndrome have difficulty recognizing social cues and interpreting social situations. In semi-structured interviews of 28 individuals who have Prader-Willi syndrome, many mentioned the importance of friendship; however, most of the participants had few actual friendships and few of them referred to a "best friend." It is important to note that hyperphagia and obesity often restrict the lives of patients who have Prader-Willi syndrome to secluded environments, which leaves them fewer opportunities and more limited social contexts in which to develop and interact [68].

Smith-Magenis syndrome

Smith-Magenis syndrome is a genetic disorder associated with a deletion of band 17p11.2. The typical phenotype of an individual who has Smith-Magenis syndrome includes brachycephaly, midface hypoplasia, prognathism, hoarse voice, speech delay with or without hearing loss, psychomotor and growth retardation, and behavior problems [69]. The prevalence of Smith-Magenis syndrome is estimated to be as high as 1 in every 25,000 births [70].

In a study on maladaptive behaviors of children and adolescents who have Smith-Magenis syndrome, Dykens and Smith [71] reported affective lability, property destruction, impulsivity, nervousness, physical aggression, and argumentative behavior in most participants. The study also revealed a stronger demand for one-on-one attention among patients who have Smith-Magenis syndrome compared to individuals who have Prader-Willi syndrome and mixed intellectual ability. In an article based on interviews with teachers and caregivers of children who have Smith-Magenis syndrome, Barbara Haas-Givler [72] described the following:

> "Children with Smith-Magenis syndrome are very adult-oriented, with a sometimes insatiable need for individualized attention from the teacher (and other adults); when this is denied, aggression toward others, behavioral outbursts, tantrums, and self-injurious behavior frequently result. Individuals with Smith-Magenis syndrome have engaging and endearing personalities (impish smile, selfhugging, good eye contact), are eager to please, and often have a well-developed sense of humor. They enjoy and thrive on adult attention. In the classroom, they are able to learn, remember and recall all the names of fellow teachers and other students."

In our direct clinical experience, the intense attention-seeking behavior directed at adults by individuals who have Smith-Magenis syndrome—with the attendant rage outbursts when the individualized attention is not forthcoming or is withdrawn—is also a manifestation of intense egocentrism and an inability to see the perspective or subjective needs of the other. Although an as-yet untested hypothesis, this pattern suggests deficits in theory of mind.

Turner syndrome

Turner syndrome is a genetic disorder associated with partial or complete absence of one of the two X chromosomes in a phenotypic girl [73]. It occurs in approximately 1 in 2000 live female births. The physical phenotype includes short stature and abnormal pubertal development and a webbed neck, renal dysgenesis, and cardiac malformation [74]. Women who have Turner syndrome are also at high risk of premature ovarian failure [75].

Several studies have pinpointed distinct psychosocial difficulties associated with Turner syndrome, particularly in the areas of social maturity, social cognition, social relationships, and self-esteem [76,77]. According to parental report, girls who have Turner syndrome have lower self-esteem and fewer friends and generally engage in fewer social activities than age-matched controls [76]. The question of whether these social deficits are the result of other aspects of the Turner syndrome phenotype also has been addressed by several studies. Downey and colleagues [78] found that women who have Turner syndrome have more impairment in social functioning than women with constitutional short stature. A study by Schmidt and colleagues [79] compared women with premature ovarian failure, women who have Turner syndrome, and normal controls on scales of shyness, social anxiety and self-esteem. They found that women with premature ovarian failure and women who have Turner syndrome had significantly lower scores on all three scales. They did not, however, find a significant difference between the Turner syndrome group and the premature ovarian failure group. In a study that compared girls who have Turner syndrome to their sisters, the affected girls had more social, thought, and attention problems and poor adaptive socialization skills compared to their own sisters [77]. Reports also have found that girls who have Turner syndrome who undergo hormone treatment typically experience an increase in self-concept though the course of adolescence [80].

An investigation by Lawrence and colleagues [81] into gaze processing in Turner syndrome uncovered other impairments associated with social functioning. Although women who have Turner syndrome performed normally on facial recognition tasks, they showed significant impairment in classification of expression from the upper face, particularly for expressions of "fear" from the eyes. Researchers hypothesized that this impairment is the result of overresponsiveness of the amygdala (because of its enlarged size) to direct gaze or fear in faces [81,82].

Williams syndrome

Williams syndrome is a rare genetic disorder caused by a microdeletion on chromosome 7q11.23 [83–85]. It is characterized by infantile

hypercalcemia, hyperacusis, distinctive facial features, and abnormalities of the heart, muscles, and kidneys, usually accompanied by mild to moderate mental retardation [86]. The brain morphology of Williams syndrome has distinctive alterations, some of which can be correlated with distinctive neurocognitive deficits in visual-spatial processing [85].

Hypersociability is a hallmark of the social phenotype of Williams syndrome. Despite initial delays in vocabulary acquisition, grammar use, and gesturing, individuals who have Williams syndrome exhibit a strong interest in social interaction throughout their lives. As infants they are unusually interested in faces, sometimes staring and smiling at the experimenters or administrators of psychological evaluations rather than completing the assigned task [87,88]. As children they are commonly described as "overly friendly." Children who have Williams syndrome often approach strangers and attempt to engage them in conversation, which concerns parents [89,90]. Studies have shown that individuals who have Williams syndrome consistently rate unfamiliar faces more approachable compared with normal and mentally disabled controls, regardless of facial expression [91].

A study by Doyle and colleagues [92] that compared the social behavior of children who have Williams syndrome to typically developing children and children who have Down syndrome concluded that the sociability characteristic of Williams syndrome cannot be attributed to the cognitive impairments associated with the disorder. Individuals who have Williams syndrome consistently scored higher than individuals who have Down syndrome who are also cognitively impaired and normally developing individuals on nearly every aspect of sociability measured, which implied that it is not merely a "lack of understanding of the social conventions governing contact with others."

Despite their highly sociable nature, individuals who have Williams syndrome are generally more socially anxious, and by adulthood, many of them experience failure to develop and maintain friendships and suffer from social isolation and maladaptive and unsatisfying peer interactions [93–96]. It seems that individuals who have Williams syndrome rely primarily on superficial signals but fail to recognize more subtle social cues in their interactions with others [97]. Impairments in theory of mind and limitations in the capacity to interpret more complex facial emotional expressions are the rule [87,95,98,99]. Individuals who have Williams syndrome generally have fewer friends and have difficulty establishing and maintaining friendships with peers. Other studies reported generalized and anticipatory anxiety in most patients who have Williams syndrome, with 96% showing specific phobias [93].

The pattern of strengths and deficits that comprise the social phenotype in Williams syndrome illustrates that social functioning has several dimensions that can be disassociated from each other, including affiliativeness (which is a strength in Williams syndrome), empathy and intersubjective awareness (also a relative strength), and higher order theory of mind involving

perspective taking and the incorporation of social contextual cues (a pronounced deficit in Williams syndrome) [95]. In the words of these authors: "...the behavioral and personality profile of people with WBS has produced a complex picture, suggesting a paradoxical combination of high sociability and empathy but poor social relationships and difficulties in social functioning."

Velocardiofacial syndrome

VCFS is associated with a microdeletion at the chromosome region 22q11.2 [100]. The prevalence of VCFS is approximately 1 in 4000, with most cases being de novo mutations [101,102]. Symptoms include cleft palate, velopharyngeal insufficiency, cardiac defects, and distinctive facial features [103–105]. Individuals who have VCFS are likely to have somewhat reduced intelligence, with a mean IQ of approximately 70, and a dramatic delay in early language development. They have receptive and higher order language deficits, abstract reasoning deficits, and visual-spatial deficits [106,107]. The behavioral phenotype for younger children who have VCFS is characterized by mood lability, social withdrawal, awkwardness and shyness, attentional problems, overactive and disinhibited behaviors, and many anxiety symptoms [12,101,108,109].

Approximately 30% of individuals who have VCFS develop psychosis—generally schizophrenia or schizo-affective disorder—by adolescence or young adulthood, which accounts for approximately 2% of all cases of schizophrenia [13,110–113]. VCFS has been referred to as a neurodevelopmental model for schizophrenia, because childhood prodromal cognitive and behavioral features (eg, attentional problems, language problems, social deficits, and learning disabilities) that are characteristic of VCFS have been found consistently in studies of children and adolescents at high risk for schizophrenia [11,114].

The social skills difficulties found in individuals who have VCFS have been widely reported and include communication difficulties, withdrawn and shy behavior, difficulties initiating interactions, and decreased repertoire of facial expressions [115–117]. This finding has led some researchers to consider whether children with this social and communication phenotype have autistic spectrum disorder. Fine and colleagues [115] approached this problem with the premise that applying standard research interviews, such as the Autism Diagnostic Interview-Revised, could clarify the question of autism as a feature of VCFS. This approach raised interesting questions. Social and communication deficits are shared features of autism spectrum disorders and schizophrenia (including premorbid schizotypal states).

Currently, there is no clarity as to how social and communication deficit traits seen in these different neurodevelopmental disorders (autism and schizophrenia) might be the same or different or what the implications might be. It is also not known what the findings would be if assessment

instruments for autism were to be applied to a highly vulnerable or prodromal preschizophrenic or schizophrenic population. Some prodromal schizophrenic individuals possibly would exceed the threshold for the diagnosis of autism on the tests. What would that finding mean, however? In our view, parsimony dictates that if an individual meets criteria for schizophrenia or develops schizophrenia within a reasonable time period after autism testing, then a positive finding for autism should be considered a false-positive result. This methodologic quandary is ultimately less interesting than a finding that the social communications deficits seen in these two disorders—autism and schizophrenia—are, in some cases, indistinguishable from each other.

Summary

A review of the social phenotypes seen in GNDDs indicates many subtle variations and complex features that distinguish the conditions from each other. The net effect is to remind us that social functioning is not a monolithic trait but a complex set of interacting operations. A wide variety of social functioning profiles that result from selective central nervous system social substrate "hits" (secondary to the specific gene–brain features of any given GNDD) seems to be emerging from the science of behavioral neurogenetics, which may serve to illuminate the mechanisms of sociability in nonimpaired humans.

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