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Insights on Social Behavior From Studying Williams Syndrome

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ABSTRACT—Central to the developmental psychopathology perspective is the claim that studying normal and atypical development are related. In this article, we argue that studying a naturally occurring genetic condition—Williams syndrome—provides insight into social behavior in typically developing children. Toward this end, we describe the social phenotype of Williams syndrome, then offer three insights regarding biological and environmental factors that account for variability in social behavior in individuals who are developing typically and individuals with the syndrome. In so doing, we illuminate genetic, neural, and environmental processes that likely influence typical social development as informed by Williams syndrome.

KEYWORDS—social behavior; development; Williams syndrome; $G \times E$

Central to the developmental psychopathology perspective is the claim that studying typical and atypical development have much to teach each other (1, 2), especially regarding the interplay between levels of analysis. In this article, we argue that studying a naturally occurring genetic condition—Williams syndrome, a rare neurodevelopmental disorder with a distinctive socioemotional phenotype—provides insight into many determinants of social behavior. Toward this end, we describe the Williams syndrome social phenotype and highlight three insights regarding biological and environmental factors that account for variability in social behavior in individuals with Williams syndrome and in typically developing individuals. First, we touch on a genetic insight involving variation within and outside the critical region for Williams syndrome, then we discuss a neurological insight involving brain networks underlying social behavior. Finally, we examine a Gene \times Environment insight involving interactions that account for variability in social behavior. In this way, we illuminate genetic, neural, and environmental processes that may influence typical social development as informed by Williams syndrome.

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WILLIAMS SYNDROME

Williams syndrome is a disorder caused by a deletion on the long arm of chromosome 7q11.23, occurring approximately once in 7,500 births (3). It is known for its distinctive pattern of physical (e.g., facial dysmorphic characteristics), medical (e.g., cardiovascular problems), cognitive (e.g., moderate mental delay), and socioemotional features (4). Much of the initial interest in Williams syndrome was stimulated by its dissociative cognitive architecture; indeed, the syndrome was originally regarded as a paradigmatic case of innate cognitive modularity, in which

expressive language and face processing remained intact while number and visuospatial processing was impaired (4). However, this view was challenged by evidence of atypical developmental trajectories and impairments in several cognitive domains originally believed to be functionally intact (2).

Some of the most striking social aspects of Williams syndrome are indiscriminate social behavior, loquaciousness, enhanced empathy, and greater preference for social over nonsocial stimuli. Collectively, these aspects led scientists to characterize individuals with Williams syndrome as hypersociable (5), reflecting their overly friendly and socially disinhibited personality. The fact that 8-month-olds with Williams syndrome gaze more intently at strangers' faces than do children matched for age (6) indicates that hypersociability in individuals with the syndrome emerges early in development. Relatedly, compared with toddlers matched for mental age, toddlers with Williams syndrome are more socially engaged with experimenters on taking turns and establishing eye contact after being tickled (7). Children and adults with Williams syndrome also pay disproportionate attention to social over nonsocial stimuli. In a study that tracked participants' eye movements while looking at pictures of social scenes or scrambled images of faces (8, 9), individuals with Williams syndrome looked at faces and eyes longer than did typically developing individuals and individuals with autism. Such interest in social stimuli, in particular, human faces, may affect the social behavior and interactions of individuals with Williams syndrome (8, 9).

Further evidence of the sociability of children with Williams syndrome—in the cognitive realm—comes from research on using language for social purposes (4, 10). In contrast to typically developing children, children with Williams syndrome use more references to affective states, exaggerated affective expressions, and vocal affective prosody, apparently to attract attention (10). Not only are these phenotypical attributes of Williams syndrome evident across cultures as well as throughout life, they also distinguish individuals with the syndrome from those with other genetically based disorders (e.g., Prader–Willi syndrome; 11). Even as children with Williams syndrome are characterized as hypersociable, other research indicates substantial variability in their social profile, with some even described as withdrawn (12–14). Personality traits (e.g., level of impulsiveness), inhibitory control, and familial factors (e.g., level of parental supervision) apparently account for such variability (14). Next, we propose three insights from the study of Williams syndrome that can inform the development of typical children.

Genetic Insight: Williams Syndrome Candidate Genes in Studying Social Behavior

Research on the genetics of Williams syndrome may illuminate genetically based variation in the social functioning of typically developing individuals. The Williams syndrome genotype is characterized by a deletion on the long arm of chromosome 7q11.23, which includes approximately 26–28 genes. Although

the absence of some of these genes has been linked to particular features of Williams syndrome (e.g., cardiovascular features and haploinsufficiency of the elastin gene), we know less about whether and how genes in the critical region of the syndrome relate to hypersociability. Nevertheless, some research on individuals with partial deletions within the critical region of Williams syndrome suggests that when the deletions do not include some genes of the syndrome (e.g., *GFF2i*, *GTF2IRD1*, *CYCL2*), these individuals with partial deletions are less social than would otherwise be expected. However, parsing the effects of specific genes on the social behavior of people with Williams syndrome has been hindered by the few case reports and limited behavioral data (15, 16).

Further evidence on the genetics of Williams syndrome comes from research on nonhuman animals. Researchers have used genetically modified models of animals to investigate the role of individual genes in this region. Indeed, several such models have been developed to illuminate the genetic etiology of the physiology and phenotype of Williams syndrome. Using them, researchers have identified the *Stx1*, *Gtf2ird1*, *Limk-1*, *Cyln2*, and *Fzd9* as potentially important candidate genes, given their expression within the central nervous system and their hypothesized association with social behavior characteristic of individuals with Williams syndrome.

Knockout animals (i.e., animals that are genetically modified to inactivate a specific gene) for the *Stx1a* gene have impaired selective attention, as well as abnormal social behavior involving more social interaction with unfamiliar conspecifics than wild animals (17). Furthermore, compared to wild animals, knockout mice for the *Gtf2ird1* gene display decreased anxiety, reduced aggression toward unfamiliar conspecifics, impaired fear conditioning, and more social interaction with unfamiliar mice (18). Overall, this genetic evidence suggests that disruption in *Stx1a* and *Gtf2ird1* contributes to reduced behavioral inhibition, more interest in social interactions, and readiness to approach strangers, all of which can be seen in individuals with Williams syndrome. Furthermore, hemizyosity—a genetic condition in which there is only one copy of a gene—for the *Limk-1*, *Cyln2*, and *Fzd9* genes is associated with a decreased ability to implement cognitive strategies to process and regulate emotions, and to focus and shift attention, all characteristics of Williams syndrome (5).

In genetic studies of typically developing individuals, researchers have documented associations between specific polymorphisms on chromosome 7, as well as within the critical region of Williams syndrome. Variation in chromosome 7 is associated with variation in externalizing behavior, behavior that has been linked to more sociability. Such findings raise the possibility that this chromosome regulates social (dis)inhibition in some way, since both hypersociability and externalizing problems reflect failure to inhibit behavior (19). Further support for this view comes from evidence that duplication of the Williams syndrome critical region is associated with separation anxiety

and hyposocial behavior (20). Furthermore, the GTF2I gene has been implicated in social communication and social anxiety in individuals with and without Williams syndrome. Specifically, variation in GTF2I genotypes for rs4717907 and rs13227433 SNPs is associated with less social anxiety in typically developing individuals (21). Genetic variation in the GTF2I gene is also related to other disorders characterized by abnormal social behavior, including autism and schizophrenia (22).

Considered together, this evidence suggests that genetic variation within and outside the critical region for Williams syndrome may be relevant for understanding social behavior in typical and atypical development. However, this work linking genotype with phenotype does not illuminate the neural processes that underlie social behavior, which we now address.

Neurological Insight: Brain Networks Underlying Social Behavior

Social behavior is subserved by a network of interconnected brain structures, including, among others, the amygdala, prefrontal cortex, cingulate cortex, insula, hypothalamus and brain stem, temporal lobe structures, superior temporal sulcus (23), and cerebellum (24). The structure and function of these brain regions in modulating social behavior have been documented in both typically developing individuals and individuals with Williams syndrome (25–28). In particular, abnormal structures characterize the brains of individuals with Williams syndrome: the hippocampus, amygdala, and medial prefrontal cortex are enlarged disproportionately (28–30).

Of particular interest, altered hippocampal function and abnormal connections between the amygdala and the prefrontal cortex are considered by some to be the neural basis for social approach behavior in individuals with Williams syndrome (25). This may be due to abnormal frontostriatal circuitry that results in altered response inhibition (31), and is consistent with abnormal connectivity between brain regions such as the amygdala and the orbitofrontal cortex (25). Individual differences in social approach toward strangers predict the response of the left amygdala to fearful compared to neutral facial expressions: In individuals with Williams syndrome, a greater tendency to approach strangers is associated with less response in the left amygdala to fearful facial expressions relative to neutral ones (32).

Brain regions other than the amygdala and prefrontal cortex also influence social behavior in individuals developing typically and atypically (for a review, see 23). Specifically, the insula plays an important role in social, emotional, and behavioral regulation, and the atypical anatomy of the insula structure is regarded by some as a neural risk factor for hyperaffiliative social behavior (26). In addition, the cerebellum is associated with social, cognitive, and emotional processing (24); a cluster of executive, visuospatial, and linguistic impairments has been observed in patients with cerebellar lesions, as have heightened anxiety and hyperspontaneous, disinhibited behavior (for a

review, see 24), a profile that also resembles the Williams syndrome phenotype (27).

This evidence that the structure and functioning of many brain regions underlie social cognition in children with Williams syndrome and typically developing children takes on special meaning in light of earlier observations about genetics. In fact, alterations in some of the genes of the critical region of Williams syndrome have been associated with altered brain structure and function of these highlighted brain regions (e.g., altered morphology of the amygdala, dendritic spines, and increased cellular packing densities in the hippocampal formation; 33). In addition, genetic variation within the critical region of Williams syndrome in typically developing individuals is associated with altered neural function of the prefrontal cortex and amygdala, as well as with more sociability (34, 35). Specifically, the GTF2I rs13227433 AA genotype predicts decreased amygdala reactivity to fearful and angry facial expressions (34), and the GTD2I rs2527367 SNP is associated with reactivity of the right dorsolateral prefrontal cortex in response to aversive social stimuli, mediated by propensity for anxiety (35). In summary, both genes and neural function associated with social behavior are related to each other.

Gene × Environment Insight: Genetic and Environmental Interactions in Accounting for Variability in Social Behavior

The aforementioned molecular/genetic and neuroanatomic/neurofunctional studies support our claim that research on Williams syndrome can illuminate the genetic and neural correlates of a hypersocial phenotype in clinical and general populations. Despite this and because of the dynamic nature of gene–environment interplay, evidence implicating a role for particular genes with respect to the social behavior and genotype–brain–phenotype associations does not imply any inevitable effects. In fact, although strong evidence links the genetics of Williams syndrome to atypical brain development and behavior, evidence of the importance of environmental influences emerges even in the case of hypersociability in individuals with Williams syndrome.

In fact, despite suggestions that individuals with Williams syndrome are (genetically) hardwired to be socially oriented, their social behavior is not immutable—individuals with the syndrome can acquire safety skills after participating in stranger safety training (12). The fact that individuals with Williams syndrome improve in social skills and adaptive behavior and have fewer behavioral difficulties with age also indicates that social behaviors can change (36). Indeed, such findings are in line with studies showing that parents' evaluate their children who have Williams syndrome as more socially reserved in adulthood than in childhood (37). Thus, the social feedback individuals with Williams syndrome receive growing up regarding the inappropriateness of their hypersocial behavior may enable them to downregulate such behavior later in life.

Also highlighting the importance of environmental factors in accounting for the hypersocial behavior of children with Williams syndrome is research on the narratives of these children and their typically developing peers in three different cultures (cultures in which the children speak American English, French, and Italian). Even though all the children studied used social evaluation excessively—in the form of affective prosody, interjections, exclamatory phrases, onomatopoeias, and intensifiers—intercultural differences also emerged. For instance, Italian children with Williams syndrome used more exaggerated affective language than their American counterparts, whereas French children with Williams syndrome used less than the Italian and American children in the study (38).

Perhaps the most compelling evidence documenting the influence of the environment on the development of hypersociability comes from research on children living in institutions in the first years of life or growing up with biological parents in economically disadvantaged families. Both conditions are associated with hypersocial, indiscriminate social behavior (i.e., disinhibited social engagement disorder, according to the *DSM 5*; 39), reflecting the same behaviors as those observed in children with Williams syndrome; these include a readiness to approach and engage unfamiliar adults without reticence, as well as a tendency to wander from caregivers without checking back, and to seek attention from and direct affection toward strangers to the same extent as toward people who are familiar (39).

Although this work implies a general influence of particularly adverse environmental contexts in a manner consistent with diathesis–stress thinking (i.e., some individuals are more vulnerable than others to the negative effects of contextual adversity), it is important to appreciate the core lessons associated with the thinking related to Gene \times Environment interaction, namely that the same developmental experience or environmental exposure can affect genetically different children differentially (1). Indeed, in recent work on differential susceptibility to environmental influences (both negative and positive), some individuals, for genetic and other reasons, are more susceptible to the effects of both adverse and supportive environments (40, 41). In fact, $G \times E$ evidence indicates that variation in the effect of institutional rearing on indiscriminate social behavior proves consistent with differential susceptibility rather than diathesis–stress models of Person \times Environment interaction (41, 42): Children homozygous for the short allele of the serotonin transporter gene, 5-HTTLPR, who also carried a BDNF met allele—both genes outside the critical region of Williams syndrome—behaved the least hypersocially when they were in foster care and the most hypersocially when they remained institutionalized.

However, we would be remiss if we failed to mention that $G \times E$ findings related to differential susceptibility involving 5-HTTLPR (42) could not be reproduced (43). This $G \times E$ study may have yielded findings consistent with diathesis–stress rather than differential susceptibility thinking as a result of design differences across studies. After all, the initial work (42) involved

a randomized controlled trial, whereas the follow-up study (43) was observational. We should also consider the range of environments under investigation, a matter often not addressed in $G \times E$ studies. Much $G \times E$ research focuses on environmental extremes (e.g., adversity vs. absence of adversity), likely because of the prominence of diathesis–stress thinking in psychiatric genetics, and thus often fails to capture the supportive contextual conditions that may need to be measured to detect differential susceptibility effects (40).

In any event, the $G \times E$ work we have mentioned, like other $G \times E$ research (41), raises the possibility that hypersociability may be influenced by genetic systems outside the critical region of Williams syndrome, genetic pleiotropy (i.e., the same gene affecting many phenotypes), genetic epistasis (i.e., Gene \times Gene interaction), and ultimately, the quality of distal and proximal environmental conditions. Indeed, the environment may interact with genotype to influence social behavior, or this statistical observation may be the result of genotypic variation in how the environment influences the epigenome (44).

CONCLUSION

In this article, we argued that research on Williams syndrome can offer developmental psychopathological insights into the multilevel nature of both typical and atypical social development (1) by illuminating the interrelated roles of genetics, the brain, and the environment in fostering extreme social behavior that takes the form of hypersociability. Toward that end, we highlighted links connecting Williams syndrome or social behavior with several candidate genes within chromosome 7, particularly within the critical region of Williams syndrome, and connecting Williams syndrome with brain structure/function (32). We also highlighted associations between some of these genes and brain structure/function, while making clear that considerable variability exists in Williams syndrome, not only in social behavior but also in its underlying structural and functional correlates in the brain (45). Moreover, in at least some instances, hypersocial behavior also depends on contextual conditions, with at least some environmental effects moderated by genetic makeup. We need more research on all these matters, as well as research addressing whether—and how—epigenetic processes contribute to the emergence of variation in social behavior.

It would be a mistake to infer that only the candidate genes, neurological factors, and contextual conditions we have discussed likely play a role in the emergence and development of hypersocial behavior. Research should move beyond these foci: We need multilevel, prospective, and cross-cultural studies beginning early in life to advance understanding of the environmental, behavioral, neural, and genetic factors and processes underlying hypersocial behavior in both typical and atypical development, as well the impact of the environment on having a neurodevelopmental disorder.

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