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Behavior, Brain, and Genome in Genomic Disorders: Finding the Correspondences

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Abstract

Objective—Within the last decade or so, there has been an acceleration of research attempting to connect specific genetic lesions to patterns of brain structure and activation. This article comments on observations that have been made based on these recent data and discusses their importance for the field of investigations into developmental disorders.

Method—In making these observations, we focus on one specific genomic lesion, the well-studied, yet still incompletely understood, 22q11.2 deletion syndrome (22q11.2DS).

Results—We demonstrate the degree of variability in the phenotype that occurs at both the brain and behavioral levels of genomic disorders, and describe how this variability is, upon close inspection, represented at the genomic level.

Conclusion—We emphasize the importance of combining genetic/genomic analyses and neuroimaging for research and for future clinical diagnostic purposes, and for the purposes of developing individualized, patient-tailored treatment and remediation approaches.

Recent advances in technology have impacted the genetic/genomic and neuroimaging sciences such that the amount of information that can be obtained on a human genome or a human brain has reached an unprecedented level of quantity and quality. These advances have also resulted in an accumulation of data that has initiated a paradigmatic shift in the field's understanding of the biological bases of childhood developmental disorders. In a nutshell, this shift reflects the field's growing appreciation of the multitude and variability of both the genetic/genomic mechanisms that appear to contribute to the etiology of developmental disorders, as well as its understanding of the behavioral manifestations that seemingly result from what appears to be a single mechanism. Correlating genetic mechanisms and developmental outcomes has grown exponentially more complex (rather than less) as a result of the last 10–15 years of research in genetics/genomics and neuroimaging and clinical practice in the field of developmental disorders. And yet this complexity is very reassuring, as it is the direct outcome of the field's striking advances in

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understanding how the genome, the brain, and the environment work together to generate complex human behavior, both typical and disordered.

Within the last decade or so, there has been an increased accumulation of data attempting to connect specific genetic lesions to distinct patterns of brain structure and activation[1]. These observations are particularly important for understanding the connections between the genome and typical and atypical development because genes do not impact behavior directly; their connection to behavior is mediated by the brain. Exploring the degrees of variation at the levels of the genome, the brain and behavior, and then correlating these multiple sources of variation is important for understanding the degree of malleability of developmental disorders and identifying treatment targets, both pharmacological and behavioral.

Finding the Correspondences

The majority (up to 70%) of human genes are expressed in the brain[2]. Correspondingly, it is reasonable to assume that structural variation in these genes is directly related to variation in brain development, structure and function. Although the idea of correlating genetic/genomic and neuroimaging findings is far from new, perhaps surprisingly, there is a relative shortage of literature in which such correlations have been obtained robustly. Perhaps one reason for such a shortage is the tremendous amount of variability across individuals who are alike in one set of indicators (i.e., brain structure and function) but not another (i.e., genomic characteristics), and vice versa.

In the attempts to correlate these sources of variability, two lines of research have emerged. The first line, seen quite often in the literature, ascertains samples of participants based on their phenotype (either behavior- or brain-based). In this line of research[3–4], brain- or behavior-based phenotypes are viewed as the homogenizing factor, and these phenotypes are associated with sources of variability in the genome. The originating point here is typically behavior (or disorder), which is characterized by a particular brain phenotype; attempts to correlate both behavior and brain phenotypes with the genome are then made. These types of studies are referred to as neurogenetics/neurogenomics[5–6]. Recently, a second line of research referred to as imaging genomics[a] has emerged[2], which starts with the genome, and the genomic structural variation is then related to a brain structure/activation pattern and, subsequently, to a disorder or disorder-related componential phenotype.

Consider illustrations of the first line of research (working from brain phenotypes to the genome). In a recent study[7], 29 agenesis of the corpus callosum (ACC) cases were identified through routine prenatal (fetal) magnetic resonance imaging (MRI) at 20–36 weeks of pregnancy. Although the diagnosis of ACC was used to identify these cases, a number of fetuses had additional brain development abnormalities. Most importantly for the discussion here, the observed cases of ACC were associated with a variety of causes, ranging from known genetic syndromes (e.g., Aicardi, Walker-Warburg, MASA, and oral-facial-digital syndrome Type I) to metabolic disorders of unknown etiologies and cases suggestive of

[a]A form of genetic association analysis, where the phenotype is defined not only behaviorally, but also neurophysiologically, registering neurophysiological responses of the brain or its specific structures during specific information processing.

acquired etiology. Yet another informative illustration comes from studies of paragangliomas—rare neuroendocrine neoplasms that may develop at various body sites, including the head, neck, thorax and abdomen[8]. It has long been believed that the majority (up to 90%) of these neoplasms are sporadic in nature. However, recent data suggest that up to 30% may be familial[9]. Familial paragangliomas have been associated with the malfunctioning of the succinate dehydrogenase (SDH) protein—complex II of the mitochondrial respiratory chain (this complex is responsible for funneling electrons into the respiratory chain via ubiquinone). This complex is constructed from four different subunits (SDH A-D), each of which is controlled by a specialized gene. Mutations in the *SDHA* gene cause Leigh syndrome, a rare and severe metabolic disorder associated with the inability to thrive and/or developmental regression. Mutations in the genes *SDHB, SDHC*, and *SDHD* all cause paragangliomas. However, paragangliomas also appear in a number of other genetic syndromes (i.e., von Hippel-Lindau, VHL, syndrome, multiple endocrine neoplasia type 2, MEN-2, and neurofibromatosis type 1, NF1), each of which is caused by mutations in different unrelated genes (the *VHL* gene, *RET* gene, and *NF1* gene, respectively). Thus, paragangliomas are not specific to mutations in SDH genes, although these mutations are considered major familial causes of neuroendocrine neoplasms. Moreover, there is a substantial amount of phenotypic variability in the type and malignancy of paragangliomas associated with mutations in different SDH genes[10], and the modes of genetic transmission appear to be different for different genes[9]. Yet, what is most intriguing about this is the observation that these variable genetic lesions associated with the formation of paragangliomas are all related to a single common pathway that is thought to be responsible for the developmental organization of precursor cells[11].

There are also informative illustrations of research conducted within the second line of investigations (from the genome to brain phenotypes). What the imaging genomics literature currently contains are primarily studies of brain-based differences in structure and function when the samples of imaged individuals are stratified by a known source of genetic variation, most often by a single common polymorphism[12–13]. There is also a growing line of inquiry endeavoring to associate known genomic lesions characteristic of specific constitutional genomic disorders[b] with the brain phenotypes observed in these disorders. These disorders are typically diagnosed via cytogenetic methods, although the corresponding genetic tests are requested when there is a suspicion that an individual has a syndrome. However, the last 10–15 years of research investigating the specifics of the genetic lesions underlying genetic syndromes, as well as the specifics of the cognitive and behavioral manifestations of these lesions, has also resulted in an appreciation of the amount of variability in both the genetic/genomic mechanisms and the associated phenotypes.

Here we use one example of a genomic disorder, the 22q11.2 deletion syndrome. Studies of this syndrome provide illustrations of both types of approaches to mapping the correspondence (from the disorder/the brain to the genome and from the genome to the brain/disorder).

[b]This term is used to mark a gain (duplication) or loss (deletion) of a specific chromosomal region paired with a clinical genetic syndrome typically manifested in congenital anomalies and developmental impairments.

22q11.2 Deletion Syndrome

Structural particularities of certain chromosomal regions appear to predispose them to specific genomic rearrangements, causing aberrations in copy number or genetic dosage[c]; these aberrations, in turn, result in distinct clinical phenotypes. For example, some structural characteristics of chromosome 22q, and in particular in the pericentromeric region 22q11, are thought to predispose it to rearrangement[14]. A number of genomic disorders have been associated with such rearrangements, for example, Cat Eye syndrome (arising from the supernumerary bisatellited marker chromosome), the Emanuel Syndrome or malsegregation-derived supernumerary der(22)t(11;22) syndrome (arising from the recurrent t(11;22)), and the 22q11.2 deletion syndrome, 22q11.2DS (also referred to as velo-cardio-facial syndrome, VCFS, the conotruncal anomaly face syndrome, as well as DiGeorge syndrome, arising from variably-sized deletions of regions of 22q11). Of these genomic disorders, 22q11.2DS is the most frequent disorder; its population incidence has been estimated at 1 in 2,000–4,000 live births, with only 6–25% of deletions having been inherited and the rest arising *de novo*.

Clinical Presentation and Associated Phenotypes

22q11.2DS is characterized by multiple (>180) developmental aberrations, including specific craniofacial features (cleft palate, velo-pharyngeal insufficiency; 69–100%), thymic and parathyroid defects including hypocalcemia (17–60%), congenital cardiovascular malformations (49–83%), mild to moderate renal anomalies (36–37%), and a range of cognitive and behavioral impairments. The most striking feature of the syndrome is the tremendous degree of phenotypic variability, both at the levels of the brain and behavior[15–17]. The associated phenotypes range from combinations of serious anomalies to the presence of isolated mild impairments[18]. Another central feature of the syndrome is the prominent presence of psychopathology (9–50%), with the most frequently observed conditions being developmental delay in infancy (75%) and childhood (45%), speech and language disorders (79–84%), schizophrenia (6–30%), autism spectrum disorders (10%), attention deficit and hyperactivity disorder (25%), and learning disabilities (50–80%)[15, 19–22]. In addition, there are pronounced transformations of the syndrome's presentation across different developmental stages. The cause of such variability within the group of individuals with 22q11.2DS and across the lifespan within an individual is unclear[23].

One of the most consistent findings in the phenotypic presentation of 22q11.2DS is a low average to borderline range of general cognitive functioning[24]. Yet, this deficiency is not consistent across different domains of cognitive functioning, although, as a group, individuals with the syndrome tend to function at a lower level than typically developing individuals in all domains of cognitive performance. Verbal functioning in spoken and written domains (e.g., receptive language, decoding and spelling, auditory verbal rote memory, but not higher-level processing such as comprehension) has been observed to be a relative strength, whereas visual-spatial (e.g., space orientation, visuospatial memory, visuospatial perception), quantitative processing (e.g., number and magnitude

[c]Less frequent alterations include gene disruption, the creation of a fusion gene, a position effect, or the unmasking of a recessive gene mutation.

representation), and executive functioning (e.g., initiation, planning, working memory, and monitoring skills) have been marked as domains of particular weakness. Yet, once again, although this profile appears to be characteristic of individuals with 22q11.2DS as a group, within this group, there is variation in both the direction (i.e., reversed cognitive patterns have been reported) and the magnitude (i.e., the standard scores) of the discrepancy.

Molecular Mechanism

The syndrome's molecular mechanism is well studied on the cytogenetic level (i.e. at a resolution of hundreds of thousands of bp); the deleted material can range from the more commonly seen 3Mb deletion (~90%) to the less commonly seen 1.5Mb deletion (7%), with the rest having an even smaller deletion with an undetermined minimal size. The pericentromeric region of chromosome 22q, and in particular 22q11, is rich in regions of segmental duplication (SD). SD regions are stretches of the human genome that have one or several highly sequence-homologous (i.e. more than 90% of identical sequence) counterpart(s) elsewhere in the genome, either upstream or downstream on the same chromosome but also on other chromosomes. Such SDs are frequently associated with variability in copy number, even in the normal genome of healthy individuals, as well as with the formation of aberrations leading to genomic disease. An interesting question that cannot easily be settled is whether this association is because SDs are prone to copy number variation (CNV) or structural variation (SV)[15, 25], possibly through mechanisms such as Non-Allelic Homologous Recombination (NAHR) – or whether they are found in regions of high CNV/SV content because they are actually ancient CNVs themselves that have become fixated in regions of the chromatin that are--for as yet unknown reasons--particularly prone to such alterations.

In 22q11DS the 3 Mb typical deletion has both of its breakpoints in prominent SD regions. Also, most of the subtypical or atypical deletions have at least one of their endpoints in such a segmentally duplicated stretch of 22q11. The 3Mb deletion region contains more than 45 genes, whereas the 1.5Mb region contains 24 genes. Based on the research in mouse models, however, it appears that no single 22q11.2 deletion region is both necessary and sufficient for the expression of the major features of the syndrome[26]. Similarly, there appears to be no difference in the clinical severity of the disorder depending on the size of the deletion. The 'classical' approach to determining which gene is responsible for a given symptom would have been to whittle down the possible candidates by determining the minimum or critical region that is necessary to cause the phenotype in patients with atypical genomic lesions, then studying the remaining individual genes, for example in animal models, to determine which causes the phenotype at hand.

This approach, however, was met with mixed success in 22q11DS. Very convincing results have been achieved where the genetic basis for the malformations of the heart and outflow tracts in 22q11DS is concerned. Here the main gene responsible in mouse models has been shown to be *Tbx1* (see below for details); thus, it is assumed that human *TBX1* is the gene that factors most prominently into the cardiac phenotype of the syndrome[27] However, other facets of 22q11.2DS remain as etiological puzzles; and this is particularly true where the neuropsychiatric symptoms are concerned[23].

Multiple hypotheses with regard to the genetic bases and, more specifically, the causative gene(s) for 22q11.2DS are being entertained. One hypothesis stipulates that the deletion causes the disruption of a major regulatory gene, for example, the transcription factor *TBX1*[d] gene[28]. According to this hypothesis, such a disruption triggers a cascade of events that are only indirectly related to the deletion per se; thus, what is challenged then are specific genetic pathways upstream or downstream from the initial step in which a particular deleted gene might be involved[e].

Yet another hypothesis assumes that the syndrome and its associated psychiatric conditions are associated with one or more candidate genes in the deleted region[20]. Specifically, among these genes are *COMT* (the gene encoding catechol-O-methyl transferase), *PRODH* (the gene coding for proline dehydrogenase), *GNB1L* (a gene that encodes a protein of unknown function), *ZDHHC8* (the gene coding for zinc finger and DHHC domain-containing protein 8), and *ARVCF* (the armadillo repeat gene deleted in 22q11.2DS, which may have a role in cell-to-cell communication and intracellular transduction during embryonic development). The results of these candidate-gene studies are provocative, but inconclusive. Similar to the role of *TBX1*, it is possible that haploinsufficiency in specific genes results in specific features of 22q11.2DS[29]. Thus, haploinsufficiency for *GP1BB* might contribute to the mild thrombocytopenia seen in patients, and haploinsufficiency for *COMT* might contribute to cognitive aspects of the 22q11.2DS phenotype[15]. Moreover, the genes *PRODH*, *TBX1*, *GNB1L*, *COMT*, *ARVCF*, *DGCR8*, *RANBP1*, *ZDHHC8*, and *PIK4CA* are located in or relatively close to regions of SD. Consequently the obvious hypothesis is that the syndrome is caused by an alteration of the genetic dosage of a particular gene or a number of genes in the region.

Each of these mechanisms or a combination of them might contribute to the etiology of the syndrome.

However, with the genomic technology that is now allowing high-resolution analyses (i.e. with a resolution of just a few hundred bp and even down to the level of single bp, as contrasted to conventional cytogenetic analyses with a resolution not better than several tens of thousands and often as many as hundreds of thousands of bp) the picture is changing dramatically. For example it was shown by high-resolution array CGH[25] that the actual endpoints of the ‘typcial’ deletion, situated in SD which are notoriously difficult to resolve, can differ by up to several hundred thousand bp, which can mean a difference of up to 14 genes affected or not affected by the aberration.

At this point of the discussion, a consideration of the human genome as a whole seems pertinent. It has become clear over the last 5 years or so that there is a much larger degree of variation in the genomic sequence than was initially assumed. In addition to millions of SNPs there are possibly thousands of InDels (insertions and deletions ranging from a few bp to a few hundred bp) and hundreds of Copy-Number Variants[f] and Structural Variants[g]

[d] *Tbx1* is a member of the Tbox family of transcription factors, expressed in the pharyngeal apparatus and resulting in a phenocopy of the syndrome when inactivated in the mouse.

[e] For example, investigations of mouse models of 22q11.2DS involving the *Tbx1* genes suggest the possible involvement of the *Fgf8* and *Fgf10* genes—growth factor gene alterations that might explain the specific developmental patterning seen in the syndrome.

(CNV/SV). CNV/SV are comprised of deletions, duplications, insertions, inversions, and translocations, that range in size from several hundred to several hundred thousand bp, as well as Mobile Element variation[h] events (ME). This impacts the consideration of the genetic and genomic bases of 22q11.2DS in two ways. It means that each aberration has to be considered in the context of its genomic background, which, as we now know, will be very different between two individuals. And also, we now have to consider that there is a high likelihood of there being an additional, much smaller, sequence variation event within the boundaries of the large deletion, but on chromosome 22, which does *not* carry the large, main deletion. Such an additional variation event—under normal circumstances quite possibly benign—will now be rendered hemizygous and might thus take on a more enhanced role in shaping the molecular etiology of 22q11DS. Hence, it is not surprising that the genetic and genomic bases of the various symptoms of 22q11DS (excluding from that statement the remarkable success story of associating the cardiac malformation phenotypes and *TBX1*) are not yet known to any degree that might be called satisfactory and could form the basis for rational molecular interventions.

Neuroimaging Studies

While understanding the diversity of clinical presentation and the molecular mechanism of the syndrome, researchers have attempted to connect cognitive and behavioral presentations of 22q11.2DS with its brain signature. Neuroimaging studies have reported a number of abnormalities in the brain structure and function of individuals with 22q11.2DS[30]. As with genomic anomalies, the more precise characterization of brain abnormalities has been paralleled by the development of neuroimaging technologies. In the 1990s, neuroimaging studies of the syndrome most frequently reported high rates of nonspecific brain alterations, including but not limited to minor midline defects, focal white matter foci, cerebral and cerebellar atrophy, sulcal and ventricular enlargement, small posterior fossa, polymicrogyria, and hypoplasia of the cerebellar vermis and corpus callosum. More recent studies have offered both quantitative and qualitative specifications of these anomalies. In addition, recently a number of imaging-genetics studies focusing on the genes in the deleted region have been conducted. Here some of these studies are briefly reviewed.

Studies of Patients with 22q11.2DS—According to structural brain studies, the total brain volume of children and adolescents with 22q11.2DS appears to be 8–11% smaller than that of typically developing individuals, with the white matter being reduced more than the gray matter, and the parietal lobe, cerebellum, and vermis being the structures with the highest loss of volume. It has also been reported that changes in specific brain structures are not homogeneous, with specific substructures appearing to increase, decrease, or remain comparable in volume to typically developing individuals along a rostro-caudal gradient. For example, in the fusiform gyrus, the anterior section has been reported to be enlarged, the middle section unchanged, and the posterior section reduced. Similar changes along a

[f] A segment of DNA of which the number of copies has been found to differ when comparing two or more genomes, i.e. through the deletion or addition of a copy of said segment.
[g] Comprise CNVs and copy-number neutral variation events such as insertions, inversions or balanced translocations.
[h] Deletions and insertions of elements such as LINE 1 and Alu elements and Human Endogenous Retroviruses, ranging from several hundred to several thousand bp; ME variation events are very hard, if at all possible, to detect with chip based high-throughput technology.

gradient have been reported in the thalamus, the corpus callosum, and the caudate. Intriguingly, such a gradient-based pattern of changes is not observed in adults with the syndrome; what is seen in adults is brain volume loss. The reported volume loss appears to be ubiquitous, with the presence of pronounced changes in both the frontal and temporal lobes, especially in gray matter. These indicators of brain atrophy are similar to those registered in the brains of individuals with schizophrenia but without 22q11.2DS; however, at this point, it is unclear whether these alterations are associated with the syndrome or with psychosis. The literature also contains reports of major disorganization in the parietal white matter, as well as unhinged axonal tracts in the anterior frontal and anterior temporal areas. Moreover, there are consistent indicators of gyral alterations.

Functional brain studies are considerably fewer than structural ones and have been designed to probe into specific cognitive deficits characteristic of individuals with 22q11.2DS—arithmetic processing, face perception, executive functioning, and working memory. The results of these studies parallel both the observed structural findings as well as specific considerations from the literature. Specifically, compared to typically developing children and/or patients with other neurodevelopmental conditions, individuals with 22q11.2DS demonstrate altered and/or specific patterns of activity in (1) the inferior parietal regions of the brain while solving arithmetic tasks; (2) the fusiform gyrus, the right insula, and frontal regions while processing faces versus other objects; (3) the left inferior parietal lobule while performing the Go/No-Go task; and (4) in the ventral and dorsolateral prefrontal cortices and the operculum while engaging in nonspatial memory tasks.

In summary, neuropsychological and brain-imaging studies of 22q11.2DS together point to the presence of structural and functional differences in the posterior parietal lobe, which explain, at least partially, visual-spatial/quantitative difficulties; in the prefrontal-striatal networks, associated with attention difficulties; and in the prefrontal-parietal and prefrontal-subcortical circuits, associated with executive functioning.

Studies of Candidate Genes Associated with 22q11.2DS—As indicated above, a number of genes in the deleted region of 22q11 have been associated with 22q11.2DS. At this point, imaging genomics studies have been carried out with only one of these genes, *COMT*. This gene encodes the enzyme *catechol-O-methyltransferase*, which is involved in cortical dopamine catabolism by inactivating released dopamine in the brain; its activity is especially prominent in the prefrontal cortex (PFC)[31]. Because numerous cognitive deficiencies characteristic of 22q11.2DS (e.g., working memory, planning, and selective attention) are considered to be associated with the functioning of PFC[32], it is important to consider the imaging-genomics literature concerning the *COMT* gene in the context of this discussion. Among the numerous common polymorphisms in this gene, there is a functional polymorphism in codon 158 (*Val158Met*), in which a substitution of methionine (*Met*) for valine (*Val*) occurs. This substitution results in differences in the thermostability and activity of the COMT enzyme[33]. There is literature associating this polymorphism with individual differences in cognitive processes. It originated with evidence that the high-activity allele *Val*, associated with 3-to 4-fold higher COMT enzyme activity, was related to “inefficient” functioning of PFC and, correspondingly, “inadequate” prefrontal cognitive performance[12, 34]. Later, however, the literature diversified, suggesting that different

cognitive tasks trigger differential patterns of performance by carriers of different alleles. Current research underscores the importance of considering additional polymorphisms in the *COMT* genes that, in forming haplotypes, appear to modulate the *COMT* expression up to 20-fold by altering mRNA secondary structures[35].

Studies attempting to connect the COMT variation to structural variation in the brains of individuals with 22q11.2DS—A number of key observations have been made through various studies. First, there does not appear to be an overrepresentation of a particular type of hemizygous, either for the *Val* or for the *Met* allele, among individuals with the syndrome. Second, when the carriers of the *Val* and the *Met* alleles are compared with each other, the results are rather contradictory. Thus, there were reports that the *Met* allele appeared to be associated with the presence of bipolar disorder in adolescents with 22q11.2DS[36]. However, at least at this point, there is no evidence that the *Val158Met* polymorphism affects the prevalence of schizophrenia in adults with the syndrome[37–38]. In addition, the *Met* allele was suggested as a risk factor for the decrease in PFC volume[39–40] and verbal IQ[39]. It has also been reported that the *Val158Met* polymorphism is related to differential patterns of brain anatomy, specifically, grey matter density in the cerebellum, brainstem and parahippocampal gyrus, and white matter density in cerebellum[40] (all increased in Val-hemizygotes). Yet other reports did not observe any direct associations with the *Val158Met* polymorphism, but registered a gender-moderated effect of the genotype on the PFC anatomical structure, but not on the performance on PFC-related cognitive tasks[41].

Researchers have also considered the effects of the *Val158Met* polymorphism on the cognitive functioning of individuals with 22q11.2DS. Some studies stated that the *Met* allele is associated with better performance on PFC tasks[42–44] and higher verbal IQ[42]. These findings have been challenged by Glaser and colleagues (2006)[45], who compared Met-hemizygous and Val-hemizygous groups and reported no difference in performance on executive functioning. Moreover, it has been shown that the *Met* allele is associated with poorer performance on a task of language expression and spatial working memory[46], and worse performance on theory of mind, Trails B, olfactory identification, communication and social functioning[37].

In summary, the literature on the effect of the *Val158Met* polymorphism is far from straightforward. It has been hypothesized that the discrepancy between the results of the reported studies may have arisen because of the U-shaped relationship between dopamine and at least some aspects of PFC function (with optimal functioning occurring within a narrow range of dopamine activity)[47–48], differences in dopaminergic neurotransmission at different developmental periods[49], the dynamics of the maturation and optimization of PFC functioning[50–51], and specifics of the neuronal connectivity[i] found in 22q11.2DS patients and disorder-free individuals[52–54]. There is also a possibility that the diversity of the associations between the *COMT Val158Met* polymorphism and the brain and behavior

[i]It has been shown that, compared with heterozygous individuals, *COMT val* homozygotes are characterized by significantly decreased prefrontal-related connectivities, which primarily occur between prefrontal regions and the posterior cingulate/restrosplenial cortices.

phenotypes is, at least in part, attributable to the impact of other genes in the region of hemizygosity; for example, there is research in mice establishing functional interactions between the COMT and PRODH (another putative susceptibility gene within the 22q11.2DS region) proteins[55]. Moreover, this diversity can be attributed to the impact of other polymorphisms within the *COMT* gene. For example, a recent study conducted on a sample of typical individuals has demonstrated that haplotypes at *COMT* (i.e., haplotypes or combinations of variants that include markers additional to the *Val158Met* polymorphism) appear to have a stronger relationships to PFC functioning than the Val/Met locus alone[56], suggesting that the COMT function is influenced by other variants in the gene[35, 57–59].

It is important to note that, given the activity of the *COMT* gene and its polymorphisms, it has been studied not only in an attempt to understand the psychopathophysiology of 22q11.2DS, schizophrenia, and other psychiatric disorders, but also with an aim to better understand individual differences. There the data are quite complex as well. It is rather clear that the *COMT* gene is associated with variability in PCF functioning, but the preferential roles of the *Val* and *Met* alleles either in isolation or in combination with alleles at other polymorphisms within the *COMT* gene are not clearly delineated. At this point, however, it seems that the pursuit of *COMT* as the candidate gene for the neuropsychiatric phenotypes seen in 22q11.2DS has not been as successful as initially hoped. This is not to say that *COMT* can be ruled out as a factor in the molecular pathology of the symptom, but its role will probably only be fully understood once we have a complete picture of the network of genomic variants both inside the 22q11.2 region and possibly genome wide.

Concluding Remarks

In this brief commentary, we reviewed the literature on 22q11.2DS to illustrate both the importance and current lack of understanding concerning the link between genomic lesions and the structure and function of the brain as it moderates behavior. As it stands now, there is no common practice of collecting brain imaging data on individuals with genomic disorders. As technologies and cost permit, it is important that specific genome, brain, and behavior evaluations that clearly delineate the extent of a suspected genomic lesion, and its brain and behavior manifestations, are carefully researched. Although offered in the majority of clinical settings in major research institutions, such con-current evaluations are rarely done. Such multi-level evaluations, though, may offer patients and their families fine-tuned diagnostic information that can be used to design and deliver the most effective remediation strategies.

The investigation of the candidate genes deleted in 22q11.2 syndrome has triggered a number of informative research lines. Specifically, given the phenotypic presentation of patients with 22q11.2DS and the genetic association with one of these genes (*COMT*), neuroimaging studies, in which participants were stratified based on common variants in this gene, have been carried out and have thus informed the research in the field of schizophrenia[12, 60], as well as in the general field of studies of mechanisms of general cognitive functioning[61–62]. However, the most striking insight into the genetic and genomic etiology of 22q11.2DS gained by applying the newly available high-resolution genomics technologies is that a complex phenotype such as the one found in 22q11.2DS is mirrored by

an equally complex genotype, where the main aberration is much more variable in its extent than previously understood. This large degree of genome-wide variation will require study of the main aberration within the context of each patient's complement of genomic sequence variants, both genome wide and deleted region wide. It is conceivable that studies of the genomic variation in the region of 22q11.2DS on chromosome 22q *without* the main aberration might be of much greater importance than has been previously thought. The many plausible candidate genes will probably be only fully understood when examined within the complex interaction of genome wide sequence variation.

It is also of great interest that many genomic disorders, although associated with distinct regions of the genome, have many features in common, most notably developmental delays, intellectual disabilities, speech and language disorders, and academic learning disabilities, as well as malformations of the heart and outflow tracts. As we have demonstrated here, the available data on at least one such syndrome, 22q11.2DS, are far from definitive in delineating the specific phenotypic presentations of these disorders. As noted earlier, it has been assumed, based on limited amounts of data, that 22q11.2DS might present particular weaknesses in nonverbal abilities and visual-spatial representations, with relative strengths in verbal functioning. These considerations might be further refined by conducting both structural and functional neuroimaging investigations of patients with these syndromes, utilizing knowledge of the brain's functional pathways of linguistic and visual-spatial information processing.

Finally, and most importantly, interrogations of complex developmental disorders, such as genomic disorders, by means of molecular, neuroimaging, and behavioral data, will contribute to the quest for the best possible behavioral and educational interventions for individuals with genomic syndromes. Although no convincing examples are presented in the literature at this point, there has been at least some conversation about specific pedagogical programs that might work for children with specific genetic syndromes[63] and, ultimately, this is what these multi-method investigations should reap—better developmental and life outcomes for individuals with complex genomic architecture.

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