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Copy number variation at 22q11.2: from rare variants to common mechanisms of developmental neuropsychiatric disorders

N Hiroi[1,2,3], **T Takahashi**[1], **A Hishimoto**[1], **T Izumi**[1], **S Boku**[1], and **T Hiramoto**[1]

[1]Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY, USA

[2]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA

[3]Department of Genetics, Albert Einstein College of Medicine, Bronx, NY, USA

Abstract

Recently discovered genome-wide rare copy number variants (CNVs) have unprecedented levels of statistical association with many developmental neuropsychiatric disorders, including schizophrenia, autism spectrum disorders, intellectual disability and attention deficit hyperactivity disorder. However, as CNVs often include multiple genes, causal genes responsible for CNV-associated diagnoses and traits are still poorly understood. Mouse models of CNVs are in use to delve into the precise mechanisms through which CNVs contribute to disorders and associated traits. Based on human and mouse model studies on rare CNVs within human chromosome 22q11.2, we propose that alterations of a distinct set of multiple, noncontiguous genes encoded in this chromosomal region, in concert with modulatory impacts of genetic background and environmental factors, variably shift the probabilities of phenotypes along a predetermined developmental trajectory. This model can be further extended to the study of other CNVs and may serve as a guide to help characterize the impact of genes in developmental neuropsychiatric disorders.

Keywords

autism; copy number variant; intellectual disability; mouse model; schizophrenia; ADHD

The onset of many neuropsychiatric disorders can be traced to childhood. Symptomatic features of autism spectrum disorder (ASD), intellectual disability (ID), attention deficit hyperactivity disorder (ADHD) and anxiety start to appear during infancy and childhood. Although the clinical diagnosis of schizophrenia occurs at an average of 18 years in males and 24 years in females, children and adolescents who later develop schizophrenia often exhibit prodromal symptoms and some exhibit symptoms to the extent that a clinical diagnosis of schizophrenia is appropriate during childhood (i.e., childhood-onset schizophrenia).[1,2] We use the term developmental neuropsychiatric disorders to collectively refer to neuropsychiatric disorders whose symptoms are first observed during childhood.

Correspondence: Professor N Hiroi, Department of Psychiatry and Behavioral Sciences, Dominick P. Purpura Department of Neuroscience, Department of Genetics, Albert Einstein College of Medicine, Golding 104, 1300 Morris Park Avenue, Bronx, NY 10461, USA. noboru.hiroi@einstein.yu.edu.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Despite many years of genetics studies of common variants, the etiology of developmental neuropsychiatric disorders is still poorly understood. Although there are many reports of association between common genetic variants and disorders, few have withstood rigorous replication testing. Recent large-scale analyses indicate individual common variants have very small effect on disorders.[3–5] It is now clear that rare (<1% population frequency) copy number variants (CNVs) have robust, reproducible impacts; carriers of rare CNVs have shown odd ratios of up to 20 for susceptibility to developmental neuropsychiatric disorders. In contrast to typical syndromes such as Smith–Magenis syndrome, Williams syndrome and Phelan–McDermid syndrome, recently discovered rare CNVs are usually associated with not one but many developmental neuropsychiatric disorders, suggesting the tantalizing possibility that there may be common denominators among symptomatically diverse disorders. Studies of rare chromosomal segment deletions and duplications involving multiple genes present a glimpse of psychiatry's promised land where clinically defined disorders are reduced to genetically, and possibly pathophysiologically, defined cases.

Although genome-wide analysis of CNVs for ASD and schizophrenia started to appear in the literature in 2007[6] and 2008,[7] respectively, an especially interesting CNV was known long before that time. Shprintzen *et al.*[8] reported that some adult patients with velocardiofacial syndrome developed schizophrenia. In the same year, it was recognized that both velocardiofacial syndrome and DiGeorge syndrome, two clinical syndromes focused on overlapping, yet nonidentical, constellations of heart, thymus and velopharyngeal defects, are associated with human chromosome 22q11.2 deletions,[9–11] establishing a previously unknown association between schizophrenia and 22q11.2 deletions.

As extensive analyses have accumulated for 22q11.2 CNV over the past 20 years, we discuss here the current understanding of this rare variant as it relates to mechanisms of developmental neuropsychiatric disorders and describe mechanistic insights we gained from mouse models of this CNV. We first characterize pleiotropic symptoms and traits seen in individuals with this CNV in relation to developmental neuropsychiatric disorders. We then review attempts to identify specific causal genes for behavioral phenotypes seen in 22q11.2 CNV in humans and mice. Finally, we refine and extract general hypothetical principles derived from mouse studies.

CNV-ASSOCIATED DIAGNOSES OF DEVELOPMENTAL NEUROPSYCHIATRIC DISORDERS

In many cases, a CNV is associated with more than one clinical diagnosis.[12,13] Schizophrenia, ASD, ID and ADHD are all associated with CNVs at 1q21.1, 15q13.3, 16p11.2 and 22q11.2. Many other CNVs are associated with some, if not all, developmental neuropsychiatric disorders; CNVs at 3q29, 15q11.2, 16p13.11-p13.2 and 17q12 are associated with schizophrenia, ASD and ID. Others are associated with fewer clinical diagnoses, but their clinical characterization is incomplete and additional diagnoses might be added as more clinical evaluations become available, as was the case with 22q11.2 CNV.

Schizophrenia

High rates of schizophrenia in 22q11.2 deletion have been consistently replicated.[14–19] A recent estimate indicates that ~25% of adults with 22q11.2 deletions develop schizophrenia, which is considered to represent one of the genetically identifiable causes of schizophrenia.[20] This deletion is detected as a rare variant (0.2–0.3%) in the general adult schizophrenic population[7,21,22] and might be present at even higher rates among individuals with childhood-onset schizophrenia.[23–25] On the other hand, studies report that 22q11.2

duplications are not enriched in the schizophrenic population, [7,21,22,25–28] and there exist few reported cases of schizophrenia among individuals with 22q11.2 duplication.

Autism spectrum disorder

Children with 22q11.2 hemizygosity (with only one copy present in diploid cells) and duplications exhibit many behavioral problems in the social behavior and language development domains.[29–36] A series of studies using established ASD scales determined that 14–50% of children with 22q11.2 hemizygosity met diagnostic criteria.[33,37–42] Duplications of 22q11.2 are also associated with ASD.[43,44] Conversely, studies have identified 22q11.2 duplications and hemizygosity in ASD populations.[6,27,45–51]

Although, according to some studies, 22q11.2 deletions are not statistically enriched in the general ASD population,[52] enrichment of any given CNV in the general ASD population is difficult to establish due to its very rare occurrence. Another technical confounding factor is the sample structure. Although simplex and multiplex do not necessarily equate with *de novo* and inherited cases, respectively,[13] the rate of *de novo* CNVs tends to be higher in simplex than multiplex samples.[51] As deletion and duplication at 22q11.2 are overwhelmingly *de novo* (~80%) and inherited (>90%), respectively,[53] studies including both simplex and multiplex families might underestimate the overall rate of deletion cases. A complementary approach to avoid false negatives involves characterization of clinical phenotypes for any given CNV. In light of consistently replicated, extremely high rates (14–50%) of ASD in 22q11.2 deletion cases,[33,37–42] this association is undeniable.

Vorstman *et al.* reported that many autistic symptoms present during childhood are similar to those seen in 22q11.2 deletion patients with and without schizophrenia. Moreover, childhood ASD features tended to be associated with lower rates of psychosis during adulthood, indicating that ASD and schizophrenia in individuals with 22q11.2 deletion are, at least in some cases, two distinct and unrelated phenotypic manifestations.[54]

Intellectual disability

ID, defined by a quantitative measure (i.e., intellectual quotient (IQ)), is one of the most prevalent diagnoses among children, adolescents and adults with this CNV. Approximately half of the individuals with 22q11.2 hemizygosity have an IQ ≤70; the majority of the remainder are distributed between 71 and 100, with the overall average IQ near 70.[33,35,41,55–60] Children with 22q11.2 deletions also exhibit declines in IQ as they grow.[61] Although a majority of 22q11.2 deletion patients have lower performance IQ than verbal IQ, a sizable subpopulation shows the reverse pattern.[59] Cognitive impairments, developmental delay and ID have been noted among 22q11.2 duplication cases.[43,44,62–75] Screening of ID samples has revealed individuals with 22q11.2 deletions and duplications.[53]

Attention deficit hyperactivity disorder

ADHD is seen in children and adolescents with 22q11.2 deletion at rates ranging from 30 to 55%,[19,33,41,58,76–83] and individuals with this deletion meet clinical diagnostic criteria at much higher rates during childhood than adolescence or adulthood.[19] These are significantly elevated rates compared with ~10% in the general population. However, although 22q11.2 CNV has been identified in ADHD cases, its statistical enrichment compared with controls has not been significant in genome-wide searches.[84,85]

Anxiety

Various forms of anxiety disorders are seen in approximately half of the 22q11.2 hemizygous cases;[83] 5.6–29% of 22q11.2 hemizygous children, adolescents and adults are

diagnosed with generalized anxiety disorder.[15,18,19,33,78,81,83] Rates remain stable from childhood to adulthood.[19] Rates for obsessive–compulsive disorder in children, adolescents and adults with 22q11.2 hemizygosity range from 9.7 to 32.6%.[15,19,83] Various forms of phobias are also seen in this population.[15,17,33,78]

Depression

Rates of major depressive disorder in 22q11.2 hemizygous individuals of all ages range from 4 to 20%.[16,18,19,76–78,80,82] However, the rates of mood disorders are generally higher in individuals with somatic disorders,[86] and it remains unclear whether 22q11.2 deletion directly contributes to anxiety and depression.

WHY SO MANY DISORDERS AT THE GROUP BUT NOT AT THE INDIVIDUAL LEVEL?

As the same deletion sizes of 22q11.2 are associated with multiple diagnoses,[87] the difference in deletion size does not adequately account for the diagnostic diversity. This begs the question of why the same-sized genetic variant is associated with so many clinically distinct disorders. One possibility is that common mechanisms are shared by many developmental neuropsychiatric disorders, meaning that these developmental neuropsychiatric disorders are not necessarily mechanistically distinct entities.

However, some individuals with the same deletions exhibit not all the disorders but a combination of some diagnoses. For example, in cases of 22q11.2 deletion, subgroups exist for codiagnosis of ASD and ID, ID and ADHD, ASD and ADHD or schizophrenia and ASD;[41,54,88] therefore, there must exist factors that make each CNV manifests differently in different individuals.

It has been hypothesized that several sources of genetic background modifiers influence the impact of CNVs. Clinical features of a disorder may depend on the presence of an additional CNV, as shown in the case of 16p12.1 microdeletion.[89] The rate of a second CNV hit is higher than that in asymptomatic controls among 16p11.2 distal duplication, 15q11.2 deletion and 17q12 duplication.[53] However, rates of a secondary CNV do not differ from asymptomatic control cases for 16p13.11 duplication and deletion, 15q13.3 deletion, 1q21.1 deletion, 16p11.2 deletion, 1q21.1 duplication and 22q11.2 deletion and duplication.[53,90] Alternatively or additionally, as a genome-wide set of common single-nucleotide polymorphisms (SNPs) could act as a determinant for disorders,[91] such a factor might differentially modify phenotypic expression of a CNV in individuals.

QUANTITATIVE MEASURES OF TRAITS ASSOCIATED WITH DISORDERS

Intelligence, memory, attention and social cognition are not, by themselves, quantitative traits, but they can be treated as such when they are assessed using quantitative experimental tasks. CNV carriers are atypical for these traits in that they deviate from the population average. However, there is not a clear-cut boundary between a case and a control in these traits, and there is no solid basis on which to group individuals as ‘impaired’ or ‘abnormal’.

Many traits deviate from the population average during childhood before diagnosis of adulthood- and childhood-onset schizophrenia, including motor and speech development, academic scores, intelligence and sociability. The average score for social and cognitive tests in preschizophrenic individuals deviates slightly from that of controls,[92–95] so that a larger proportion of preschizophrenic children have low-end scores compared with controls.[94–97] Low IQ scores during childhood predict the likelihood of developing schizophrenia during adulthood but are also prevalent in unaffected siblings and those who

develop affective disorders during adulthood.[97] Thus, low scores for these traits do not provide an all-or-none predictor for a disorder but instead provide probabilistic (not categorical) predictors for future schizophrenic onset.

Scores of various cognitive tests and subtests tend to be lower than the population average in children with 22q11.2 hemizygosity. The manner in which 22q11.2 deletions affect IQ is not all or none, and it only lowers the average IQ to approximately 70.[33,35,41,55–60] Longitudinal studies show that low verbal IQ during childhood is associated with the emergence of psychosis in adolescence and adulthood,[98,99] suggesting that it is a predictor for the emergence of schizophrenia. Moreover, low scores on executive function tests during childhood best predict psychotic symptoms during adolescence.[81] Among adults with 22q11.2 deletions, scores of tests designed to evaluate social cognition (i.e., theory of mind), motor skills and verbal learning tend to be lower in 22q11.2 deletion with schizophrenia than without this diagnosis.[100]

Working memory performance typically shows gradual, but steady, development from childhood (e.g., 6-year old) to adulthood (i.e., 20-year old) in typically developing individuals.[101–108] This developmental maturation of working memory capacity is compromised in individuals with ASD.[109] Children who later develop idiopathic schizophrenia exhibit stable low scores over time in cognitive tests such as working memory tasks.[110–112] Children with idiopathic ADHD score lower in visual–spatial tests than those for auditory–verbal working memory.[113] In individuals with idiopathic ID, scores for many forms of working memory capacity are consistently lower than in typically developing individuals throughout development.[114] Similarly, children, adolescents and adults with 22q11.2 deletions score lower in various working memory tasks than controls.[32,115–120]

Attention is another cognitive domain in which test results are atypical in many developmental neuropsychiatric disorders.[121] Diminished performance in cognitive flexibility, psychomotor speed and shifting of attention is common in children with ASD.[122,123] Scores of subcomponent tests correlate with specific symptomatic elements within a disorder. For example, lower scores on attention tests are correlated with negative, but not positive, symptoms of schizophrenia.[124] Children with 22q11.2 deletions score low in mental flexibility and visual attentional focus but not in tasks that test orienting or altering attention.[34,36,125–127]

Social motivation and skills are psychological processes thought to underlie idiopathic ASD.[128] Scores on social cognition tests are lower for both ASD[129,130] and schizophrenia[131–135] patients than for controls. Compared with non-deletion controls, children with 22q11.2 deletions have more difficulties in understanding facial expression and are developmentally delayed in acquisition of social-cognitive skills.[34,136] Average scores on tests designed to evaluate various aspects of social perception skills are lower in children with 22q11.2 deletions than in non-deletion controls.[136] Individuals with 22q11.2 hemizygosity exhibit deficits in social motivation as well as social skills.[137]

Prepulse inhibition (PPI), in which a startle response evoked by a loud sound is attenuated by presentation of a preceding subthreshold sound, is lower in many psychiatric disorders, so it is a nonspecific research tool. For instance, lower-than-average PPI scores were reported in individuals with schizophrenia, obsessive–compulsive disorder, bipolar disorder, ADHD and Huntington's disease,[138] but lower PPI scores are not consistently seen in individuals with ASD.[139–141] Children with 22q11.2 deletions score lower than controls on auditory PPI tests.[142]

IDENTIFYING SPECIFIC GENES WITHIN 22Q11.2 CNV

Approximately 90% of 22q11.2 deletions are ~3 Mb, and the remainder includes a nested ~1.5 or ~2Mb deletion or some atypical, non-nested distal deletions. Psychiatric diagnoses and their correlation with various sizes (1.5–3 Mb) of 22q11.2 deletions were previously examined[77,87,143] (Figure 1). A potentially informative approach involves correlation of small deletions and various diagnoses. In a study by Michaelovsky *et al.*,[87] the typical 3-Mb deletion was associated with schizophrenia, ADHD, major depressive disorder, anxiety disorders, obsessive–compulsive disorder and ASD. In smaller deletion (~1.5 and ~2.0 Mb) cases, disorders that are present at high frequencies (e.g., ID, ADHD and anxiety) are detected but disorders that occur in less than one-third of in 22q11.2 deletion cases are not (e.g., schizophrenia and ASDs). As pointed out by the authors, this might simply reflect small sample sizes: there were only four cases of ~1.5 Mb deletions and four cases of ~2Mb deletions. Although CNVs smaller than ~1.5Mb at 22q11.2 have been found in individuals with schizophrenia[7,144] and in ASD samples,[6,48–50] such small CNVs are few in number and are also found in control samples (see http://projects.tcag.ca/variation/?source=hg18).

Extremely rare cases of functional mutations at single 22q11.2 genes have been identified with specific clinical features. A single individual with ASD and a frameshift mutation of *TBX1* that reduces expression of TBX1 has been identified in a family with multiple carriers.[145] A single child with homozygous deletion confined to *SEPT5* and *GP1BB* but not adjacent genes also exhibited social interaction deficits.[146] As a mutation of *GP1BB* alone is characterized by prolonged bleeding and large platelets (i.e., Bernard–Soulier syndrome) but with no psychiatric diagnosis, *Sept5* is a possible candidate gene for the behavioral phenotype in this individual. To date, there are no reports of other single 22q11.2 gene mutations associated with psychiatric disorders. Although these findings are suggestive, each mutation was reported in only a single subject. More cases are needed to ascertain the causative role of these mutations in developmental neuropsychiatric disorders. Moreover, as the ENCODE project has identified many more new transcripts at 22q11.2, the role of those additional genes in disorders should also be explored.

Attempts have been made to associate common variants of specific 22q11.2 genes in individuals with developmental neuropsychiatric disorders without 22q11.2 CNV. Results are inconsistent, and both negative and positive associations exist for *PRODH*,[147,148] *TBX1*,[149] catechol-*O*-methyltransferase (*COMT*),[150–152] *ZDHHC8*,[153] *DGCR8*[154,155] and *RTN4R*.[156–162] Although not many studies are available, reports to date regarding association of *GNB1L* SNPs with schizophrenia have all been positive.[163–165] Comprehensive screenings of SNPs on 22q11.2 in individuals without 22q11.2 hemizygosity have identified association of SNPs on *DGCR6, PRODH, ZDHHC8* (*KIAA1292*) and *RTN4R* (*NOGO-R*) with schizophrenia and childhood-onset schizophrenia.[162,166] However, none of these common variants was found to be associated with schizophrenia[4,167] or ASD[3,168,169] in recent large-scale genome-wide association studies, confirming that SNPs on 22q11.2 genes are unlikely to contribute to risk for schizophrenia or ASD.

SNPs on the remaining copy of 22q11.2 hemizygous individuals have also been examined. Many studies consistently report that the Met/Val alleles of *COMT* are not associated with clinical diagnosis of schizophrenia or schizotypy, depressive disorders or anxiety disorders among adults with 22q11.2 hemizygosity[16,170–172] except for one report where the Val and Met alleles were associated with the presence and absence, respectively, of schizophrenia.[173] In children and adolescents with 22q11.2 hemizygosity, the Met allele is associated with the incidence of prodromal psychotic symptoms during adolescence in one study[98] but not in another.[81]

Overall, identification of small critical segments or SNPs on single genes within 22q11.2 in humans has not been conclusive. Moreover, it is difficult to know whether weak association of an SNP with a disorder reflects a weak impact of an SNP on protein function or a weak contribution of the protein to specific disorders. As hemizygosity of 22q11.2 is sufficient to cause phenotypes, SNPs on the remaining copy would indicate how such variants *modify* the phenotype caused by hemizygosity but would not identify single genes whose dominant effect *causes* the phenotype.

MOUSE MODELS OF DEVELOPMENTAL NEUROPSYCHIATRIC DISORDERS

Mouse models are essential to experimentally evaluate how specific genes *causally* relate to phenotypes beyond observing correlations in humans. There are three criteria to consider when judging whether a mouse model is or is not valid: construct validity, predictive validity and face validity.

A genetically generated CNV or dose alteration of encoded individual genes satisfies the construct validity of mouse models in that the human genetic alteration is recapitulated in a mouse.

Predictive validity is difficult to satisfy in mouse models, because therapeutic drugs do not provide disorder specificity. Hyman[174] pointed out that therapeutic drugs do not respect boundaries defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM). For instance, antidepressants are an effective treatment for depression, anxiety disorders and obsessive–compulsive disorders. Moreover, drugs often do not comprehensively affect all symptomatic elements of a clinically defined disorder. Typical neuroleptics attenuate positive symptoms of schizophrenia (e.g., delusions and hallucinations, disorganized thought and speech, and disorganized behavior) but do not have much effect on negative symptoms (e.g., affective flattening, avolition and social withdrawal) or cognitive impairments (e.g., poor executive functioning, attention and memory problems). Atypical neuroleptics improve the positive and negative symptoms of schizophrenia, but cognitive impairments are resistant to these drugs.

Use of face validity (i.e., phenomenological similarity) in judging a mouse model is equally misguided. Certainly, for some disorders, it is currently not possible to mimic some human symptoms; for example, there is no rodent model that mimics human delusion or hallucination. For other symptomatic elements, humans and mice use different species-specific modes.[175] For instance, humans use visual and auditory senses for social interaction, whereas rodents heavily rely on olfactory cues. From an evolutionary perspective, species-specific manifestation of certain functions is still informative to understanding biology across species.[175] In cases where some but not all symptomatic elements are exhibited in a single gene deletion mouse model, this is often interpreted as a reason to invalidate face validity. However, as it is questionable to assume that any gene should mechanistically contribute to all symptomatic elements of a given disorder, it is not necessary to attempt achievement of maximal phenotypic similarity in a single mouse model.

GENETIC MOUSE MODELS OF CNVS

Many mice developed to carry large deletions or duplications in murine chromosomes orthologous to human CNVs, including CNVs at 15q11.2-q13.1,[176,177] 16p11.2,[178] 17p11.2[179,180] and 22q11.2,[181–184] do indeed exhibit behavioral phenotypes related to developmental neuropsychiatric disorders. CNV at 22q11.2 has been most extensively and

systematically studied in mouse models, and identification of small segments and individual genes is unparalleled compared with other CNVs.

Systematic alteration of a copy number of small segments within 22q11.2 turned out to be a highly effective approach. Both segmental overexpression and hemizygosity at this locus have been modeled in mice (Figure 2). Hiroi *et al.*[183] reported that overexpression of a 200-kb segment of human 22q11.2 that included *TBX1, GP1BB, SEPT5* and *GNB1L* causes social behavioral deficits as well as repetitive hyperactivity and its spontaneous exacerbation, the latter of which was attenuated by chronic treatment with the antipsychotic drug clozapine.

Overexpression of an adjacent ~190 kb segment of human 22q11.2 that included *TXNRD2, COMT* and *ARVCF* produced a unique set of phenotypes in a BAC transgenic mouse.[184] This mouse exhibited lower scores for the rewarded alternation task, an index of working memory. In this task, wild-type (WT) mice showed spontaneous improvement from 1 month to 2 months of age.[184] This age-dependent improvement in working memory performance was not due to a carryover effect from previous learning because separate sets of mice were tested at 1 month and 2 months of age. Remarkably, the BAC transgenic mouse did not show such developmental maturation in working memory performance, in which they exhibited lower levels of working memory at 2 months, but not at 1 month, of age than WT mice.[184] This phenotype was highly selective; BAC transgenic and WT mice were indistinguishable in results of testing for PPI, social interaction or motor activity.

Stark *et al.*[185] demonstrated that overexpression of a 22q11.2 segment containing *Zdhhc8, Ranbp1, Trmt2a (Htf9c), Tango2 (T10), Arvcf* and *Comt* had no effect on PPI; overexpression of another (*Vpreb2* and *Prodh*) instead increased PPI. Relevance of the high PPI level to human phenotypes remains unclear at this point, as PPI in 22q11.2 duplication cases has not been reported.

Taken together, these overexpression studies identified the ~200-kb region and the adjacent ~190-kb region, collectively termed a murine critical region, as causative for distinct sets of behavioral phenotypes relevant to developmental neuropsychiatric disorders.

Paylor *et al.*[145] reported an elegant study that examined the impact of variously sized deletions of partially overlapping segments within murine chromosome 16, the ortholog of human 22q11.2, and found that PPI was reduced only when large deletions encompass a commonly affected segment (Figure 2), which turned out to be the ~200-kb portion of the murine critical region.[183]

Several genes encoded in the murine critical region were individually examined (Figure 3). Heterozygosity of either *Tbx1* or *Gnb1l* alone lowered auditory PPI levels in non-congenic mice in one study,[145] but another study with a different non-congenic mouse line showed that *Tbx1* deficiency had no effect on auditory PPI.[181]

Hiramoto *et al.*[186] also demonstrated that heterozygosity of *Tbx1* lowered reciprocal social interaction and communication and increased anxiety-related behavior (i.e., thigmotaxis) and tendency to repetitive behavior in congenic mice. Moreover, congenic *Tbx1* heterozygous (HT) mice exhibited lower levels of working memory performance and heightened levels of interaction with a non-mouse object; there was no change in locomotor activity.[186]

As an example where not all symptomatic elements are recapitulated in one gene manipulation, *Sept5* deficiency lowered reciprocal social interaction but, contrary to 22q11.2 hemizygosity in humans, increased levels of auditory PPI, reduced levels of anxiety-related

behavior and had no effect on locomotor activity, working memory or repetitive behavioral tendency in both congenic and non-congenic mice.[187,188] Moreover, the phenotypic expression of *Sept5* deficiency is attenuated or amplified when genetic background is systematically altered.[187–189] As virally guided overexpression of *Sept5* alone against a coisogenic genetic background is sufficient to raise social interaction,[187] phenotypic differences between WT and *Sept5*-deficient mice do not simply reflect the collective impact of alleles other than *Sept*5.

Overexpression of *COMT* reduced performance on a working memory task[184,190] and might be relevant to phenotypes of 22q11.2 duplication. However, deletion of *Comt* had no effect on PPI[190–192] or sociability[192–194] and increased working memory performance,[190,193,194] whereas humans with 22q11.2 deletion show low levels of PPI,[142] social behavior[33,37–42] and working memory.[120]

Although a large hemizygous deletion outside the murine critical region has no effect on PPI[145,195] (Figure 2), genes encoded outside the critical region nevertheless might have a weak impact on specific phenotypes. Non-congenic *Dgcr8* HT mice exhibited lower levels of working memory and lower PPI levels than WT mice at 74 and 78 dB but not at 82 or 86 dB prepulse levels.[196] Non-congenic *Zdhhc8*-knockout, but not HT, mice exhibited lower PPI levels at 78 dB but not at 82 dB prepulse intensities.[197] Given that a large deletion including *Dgcr8* and *Zdhhc8* has no effect on PPI,[145] these partial effects might reflect the impact of unequal alleles (other than the targeted genes) in genetic background of non-congenic mice or other nongenetic factors.[198–201] PPI was reduced in non-congenic *Prodh*-deficient mice in one study;[202] however, no PPI deficit was seen in congenic *Prodh*-deficient mice with 129/SvEv background by the same group.[203] Deficiency of *Rtn4r*[161] and *Gsc2*[181] did not affect PPI. Working memory capacity was unaffected by *Prodh*[203] or *Rtn4r*.[161] Anxiety-related behaviors were heightened by deficiency of *Zdhhc8*[197] but not of *Gsc2*,[181] *Prodh*,[202] *Rtn4r*[161] or *Dgcr8*.[196]

One important caveat to consider these results is that deletion of two copies (i.e., homozygous deletion) and one copy (i.e., HT deletion) in mice should not be equated with homozygous and hemizygous deletions in humans. Although, in some cases, heterozygosity was not and homozygosity was sufficient to cause a specific phenotype in mice (e.g., *Sept5* and *Zdhhc8*),[188,197] the mechanism by which gene-dose alteration causes a phenotype depends on genetic background,[187–189] which is not identical in humans and mice.

GENERAL HYPOTHETICAL RULES OF 22Q11.2 CNV–PHENOTYPE RELATION

Mouse behaviors do not necessarily directly address clinically defined disorders. Nonetheless, some general rules governing genotype–phenotype relationships can be extrapolated from mouse studies involving 22q11.2 CNVs (Figure 3). We present these rules as testable hypotheses that can be used to guide analyses of mouse models of this and other CNVs.

Hypothesis 1: noncontiguous gene effect

Dose alteration of a unique set of noncontiguous critical genes causes a phenotype in that dose alteration of other interdigitated genes has no effect on, or even opposes the phenotype.

Mouse studies present a far more complex gene–phenotype relation than expected from a contiguous gene syndrome where a contiguous set of genes contributes to a specific phenotype. This is illustrated for PPI, working memory and anxiety (Figure 3). For any given phenotype, genes whose deficiency results in an expected effect are not continuously

distributed; they are intercepted by genes whose deficiency has no apparent or even opposing effect. Moreover, nonidentical sets of genes seem to contribute to different phenotypes. The question remains whether 22q11.2 CNV is still considered a contiguous gene syndrome if all phenotypes are lumped as a syndrome, underscoring the necessity to analyze more than one behavioral phenotype.

It should be noted that the genes listed here have nonidentical anatomical distributions and neuronal functions and, thus, the ways they contribute to behavioral phenotypes are likely diverse. Some genes might have more robust impacts on phenotypes than others, partly because specific neuronal processes, in which each of these genes plays a role, are differentially involved in behavioral phenotypes.

An obvious implication of this hypothesis is that given that there are genes within 22q11.2 whose deficiency has no apparent or even an opposing role in behavioral phenotypes, neuronal, cellular and molecular phenotypes seen in mice with hemizygosity of a large segment or single gene deletions might not necessarily be relevant to behavioral phenotypes, not to mention clinical diagnoses.

Hypothesis 2: gene-dose alteration

The dose of each gene has an optimal range on a linear or nonlinear function for a given phenotype.

Viewed from a simplistic mechanistic perspective, a reduction and an increase in a gene dose would be expected to cause opposite effects. In fact, COMT overexpression and deletion, respectively, lowers and raises levels of working memory-dependent performance.[184,190,193,194] *Sept5* deficiency and overexpression, respectively, reduces and raises levels of social interaction.[187,188] However, given that individuals with 22q11.2 duplications and deletions exhibit similar cognitive atypicality, some genes might induce the same phenotypes with gene-dose deviation in either direction from the optimal level.

Hypothesis 3: pleiotropy

Some, but not all, critical genes have more than one phenotypic target.

Tbx1 heterozygosity, for example, causes phenotypes in social interaction and communication, repetitive behavior tendency and working memory[186] (Figure 3). Deletion of *Zdhhc8* affects both PPI and anxiety-related behavior,[197] and deletion of *Dgcr8* lowers scores for PPI and working memory.[196] Moreover, various genes within this CNV do not seem to necessarily target the identical set of phenotypes. A corollary of this hypothesis is that the pleiotropic actions of multiple genes within this CNV cause multiple diagnoses.

Hypothesis 4: mass action

The ultimate phenotype of a CNV reflects the impacts of additive and opposing impacts of many genes.

Sept5 deficiency increases PPI and reduces levels of anxiety-related behavior[188] (Figure 3). Similarly, *Comt* deficiency enhances performance levels of working memory (Figure 3). In individuals with 22q11.2 deletions, heightened levels of anxiety[15,18,19,33,78,81,83] and lower levels of performance of PPI[142] and working memory[32,115–120] are seen. Given that *Sept5* and *Comt* are nevertheless deleted in 22q11.2 deletions in humans, their effects are likely overridden by the effects of other genes. These opposing effects and facilitating effects of other genes are likely to sum to the ultimate phenotype.

Hypothesis 5: phenotypic variation

Genetic background and environmental factors modulate phenotypic expression of a CNV.

Genetic background, including common variants throughout the entire genome, might modulate phenotypic expression of a gene deficiency. We demonstrated this by systematically altering genetic background in the setting of *Sept5* deficiency.[187–189] This modulatory effect of genetic background provides a plausible explanation for the seemingly inconsistent observations that deletion of *Prodh* or *Tbx1* causes PPI deficit in one but not another mouse line with different genetic backgrounds.[145,181,202,203] This hypothesis underscores the necessity to analyze mice under several genetic backgrounds.[187–189]

Environmental factors also modulate phenotypic expression. In mice, a housing condition known to increase stress levels reduced Sept5 protein levels and decreased social interaction.[187]

This hypothesis is consistent with the observation that CNVs at 22q11.2 are associated with many developmental neuropsychiatric disorders when examined in a large group of patients overall, but individuals with the same CNV exhibit only one or a few clinical diagnoses. If the impact of a CNV or a gene alteration is variably modified by stochastic processes, genetic background and environmental factors, the ultimate summation of various phenotypes would be expected to individually differ, perhaps resulting in variable penetrance and expressivity of many disorders among 22q11.2 CNV carriers.

Hypothesis 6: phenotype beyond average

The impact of 22q11.2 gene alteration is to shift data distribution with or without a change in variance.

Comparison of averages between a WT and a genetically modified group is the standard practice for evaluating impact of a gene manipulation. However, gene manipulation could alter the data structure in various ways. Even with the same gene deletion, the effect on various phenotypes may not be identical. For example, in our own data, *Tbx1* heterozygosity produced a large shift in PPI scores from WT to HT mice so that a sizable portion of HT mice fell below the lowest score of WT mice (Figure 4a). For vocal call frequencies, this shift was not robust, so the results for WT and HT mice are distributed within the same range but the average of HT shifted to the left (Figure 4b). Another type of data restructuring included alteration of data variance and an average shift; the duration of social interaction in HT mice was more tightly clustered below the lowest data point for WT mice (Figure 4c).

Hypothesis 7: developmental trajectory

Gene alteration causes a phenotype at specific developmental stages when the gene function is required.

We demonstrated that overexpression of the ~190 kb region, including COMT, lowers performance of working memory at 2 months of age, but not at 1 month of age. This observation highlights the need to evaluate phenotypes at several developmental time points. Moreover, this hypothesis is consistent with observations in humans that low scores of working memory capacity start to appear at and after adolescence in ASD patients[109] and that the high-activity COMT allele is associated with poor visual–spatial working memory after, but not before, 10 years of age compared with the low-activity COMT allele.[104]

The seven hypotheses outlined above are derived from mouse models of 22q11.2 CNV. Given that some distinct mechanisms are likely to be in play for different CNVs,[53] these

hypotheses might require revision for other CNVs. Concerning the testability of these hypotheses in humans, unless more single gene deletion cases are discovered, a critical evaluation of hypotheses 1, 2, 3 and 4, where the role of specific genes is concerned, can only be tested in genetically engineered mice. Hypotheses 5, 6 and 7 can be tested in humans insofar as it is assumed that genetic variants are a determinant for symptomatic elements of developmental neuropsychiatric disorders; there is no reason to doubt that these hypothesized gene–phenotype mechanisms exist in humans as well. The ultimate test of mouse-derived hypotheses would be to evaluate the effectiveness of therapeutic options, derived from these hypothetical mechanisms, in humans.

Based on these hypotheses, we propose a quantitative model to explain how deficiency of specific genes encoded in a CNV affects behavioral phenotypes (Figure 5). According to this model, when gene dose is altered, some genes (e.g., gene a) affect more phenotypes more severely than others (genes b, d and e); other genes (c and f) have no impact on phenotypes (green flat plane) or have an effect opposite to that of other genes (yellowish upward protrusion at gene b and phenotype 5, Figure 5a). The ultimate phenotype score is determined by the net effects of all phenotypic deviation of genes or predominantly by genes that have major impacts on a phenotype. Alleles in the genetic background, environmental factors (in some cases, via epigenetic alterations) or both could shift the scores of phenotypes evenly across genes and phenotypes so that phenotypic deviation (blue in the lower plane) from the averages disappears or becomes less severe (Figure 5b). Alternatively, genetic background and/or environmental factors could unevenly affect specific phenotypes (Figure 5c; e.g., phenotype 3) or the phenotypic impacts of specific genes (Figure 5d; e.g., gene a). Any combination of these effects could shift the score plane evenly or tilt it unevenly upward or downward, resulting in unique phenotype sets in individuals with varying genetic backgrounds and environmental influences.

DOES DNA ‘READ’ THE DSM?

The hypothesized mechanisms, based on mouse studies of 22q11.2 CNV, dictate that alterations of a distinct set of multiple, noncontiguous genes encoded in this CNV unequally shift the probabilities of various phenotypes, through modulatory impacts of genetic background and environmental factors, along a predetermined developmental trajectory.

Historically, the nosology of neuropsychiatric disorders, exemplified by those included in the DSM, has evolved largely based on prevailing opinions about how to categorize symptoms and what to consider the primary component of a disorder;[204] this trend has continued because of clinical reliability. However, clinical diagnoses based on symptomatic clustering have contributed to many unexplained by-products, such as many comorbid traits and failure to find statistically significant and reproducible genetic associations.[174,204]

Our overall hypothesis predicts that genes do not necessarily follow the logic by which disorders are clinically categorized. In a sense, the DNA does not ‘read’ the DSM from chapter to chapter; instead, it ‘reads’ the DSM from the index section that ignores the clinical boundaries of developmental neuropsychiatric disorders.

Dimensional measures of neurophysiological, biochemical, endocrinological, neuroanatomical, cognitive or neuropsychological traits have been proposed as a reliable alternative that may better approximate genetic mechanisms in the hope to establish stronger association with gene variants.[205] Mouse and human studies of 22q11.2 CNV have reinforced the validity of a quantitative, dimensional approach. However, although a quantitative deviation from the average for each trait is associated with a disorder, such trait atypicality does not predict any clinically defined disorder with sufficient specificity. Is it because we have not devised a quantitative task that adequately taps aspects of perception,

attention, memory and social cognition that are so specifically affected in clinically defined disorders? We are left with this question, but instead of initiating a debate, perhaps a more practical approach is to explore mechanisms of causation for quantitative traits and evaluate how therapeutic options devised for such traits affect symptoms of clinically defined developmental neuropsychiatric disorders. Such an approach is likely to provide not only mechanism-based effective therapeutic options but also new insights into the relationship between quantitative traits and symptoms.

Twenty years of 22q11.2 CNV research has provided hypothetical rules and lessons that serve as a guiding torch for a path to psychiatry's promised land.

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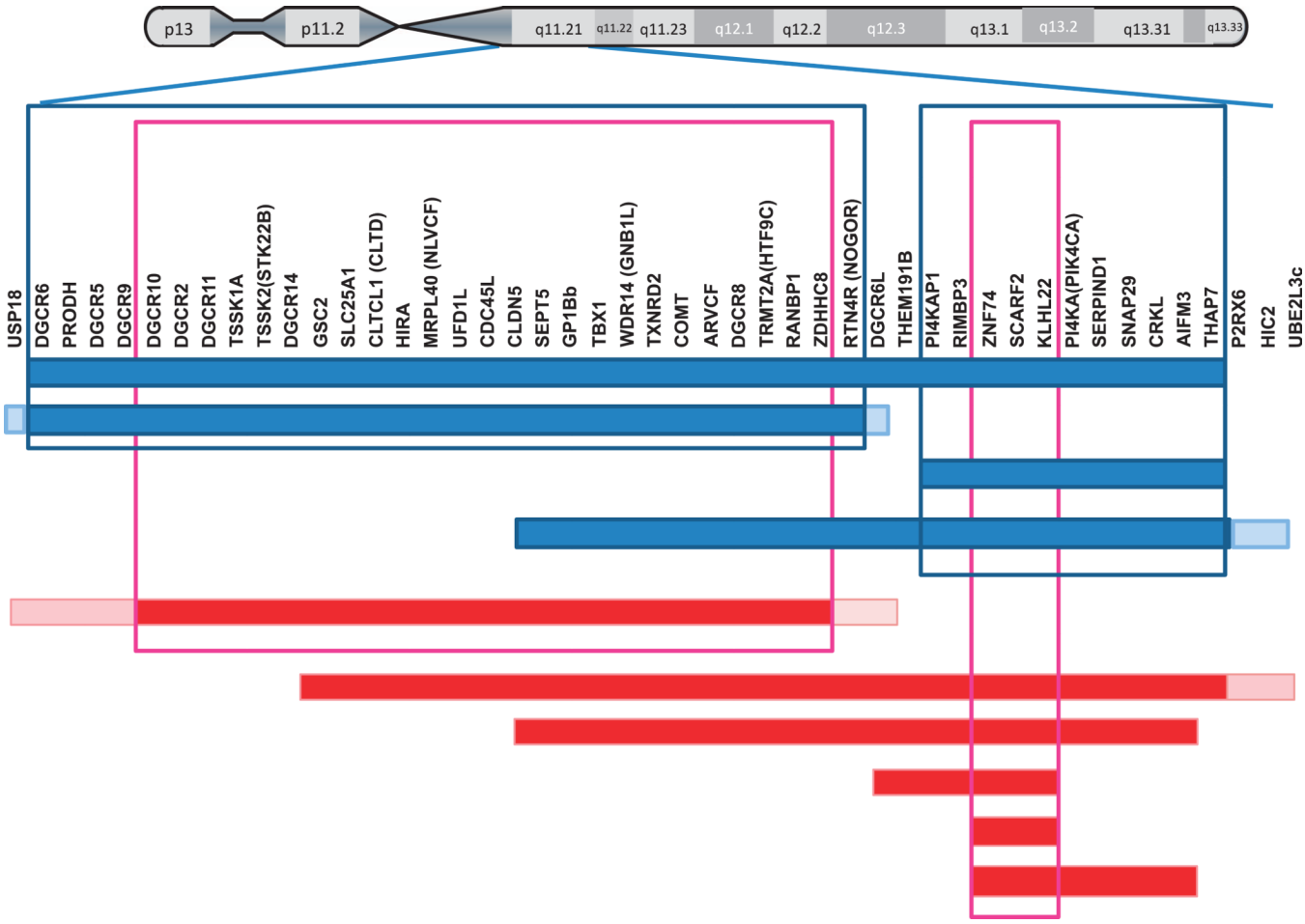

Figure 1.

Schematic representation of 22q11.2 deletions and duplications in individuals with schizophrenia (blue bars) or ASD (red bars). Cases and boundaries are based on published studies with dense probes.[6,7,26,48–51,87,143] The blue and pink frames indicate chromosomal segments that are commonly deleted in schizophrenia and ASD cases, respectively. A boundary with a pale color indicates individually variable ends.

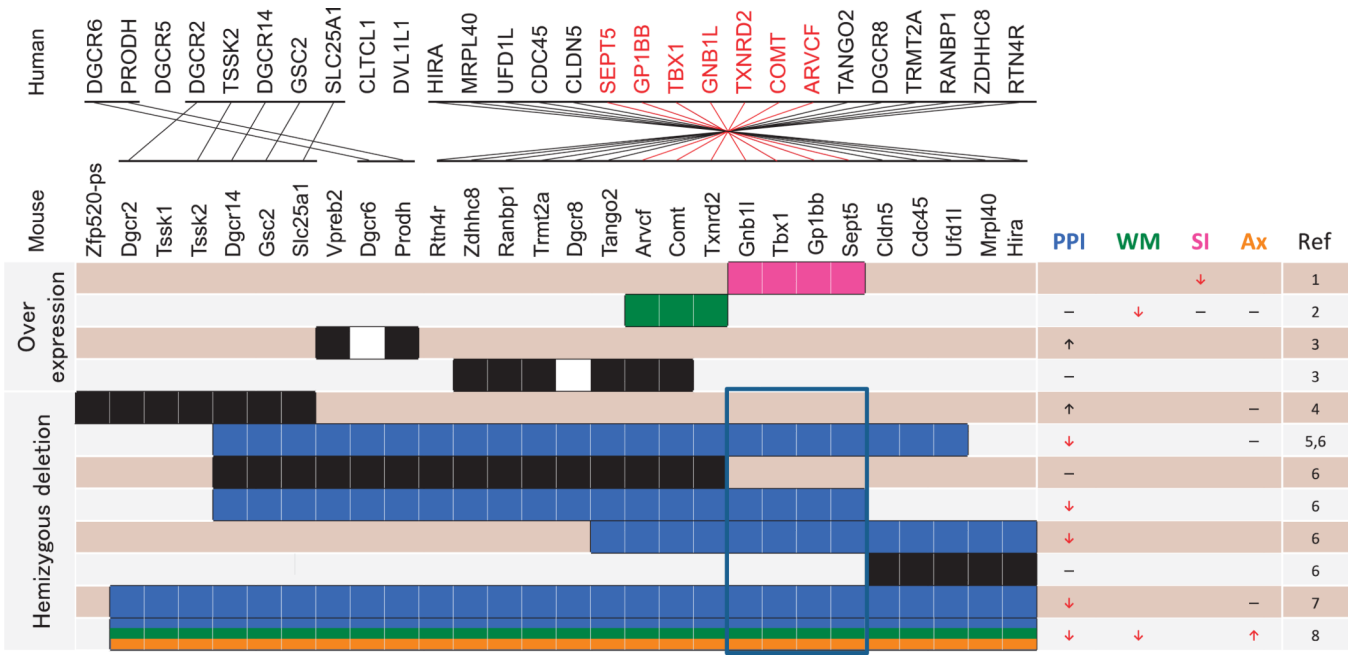

Figure 2.

Organization and location of corresponding genes between human 22q11.2 and murine 16. Mouse models of segmental overexpression and deletions are shown. Purple (social interaction), green (working memory), blue (PPI) and orange (anxiety) bars represent chromosomal segments whose murine copy number variation results in phenotypes consistent (see red arrows) and inconsistent (see black arrows) with 22q11.2 CNVs in humans or no effect (see black horizontal lines). The blue frame represents a segment whose deletion is commonly seen in mouse models with a PPI phenotype consistent with that in humans. PPI, prepulse inhibition; WM, working memory; SI, social interaction; Anx, anxiety. (1) Hiroi *et al.*;[183] (2) Suzuki *et al.*;[184] (3) Stark *et al.*;[185] (4) Kimber *et al.*;[195] (5) Paylor *et al.*;[182] (6) Paylor *et al.*;[145] (7) Long *et al.*;[181] (8) Stark *et al.*[196]

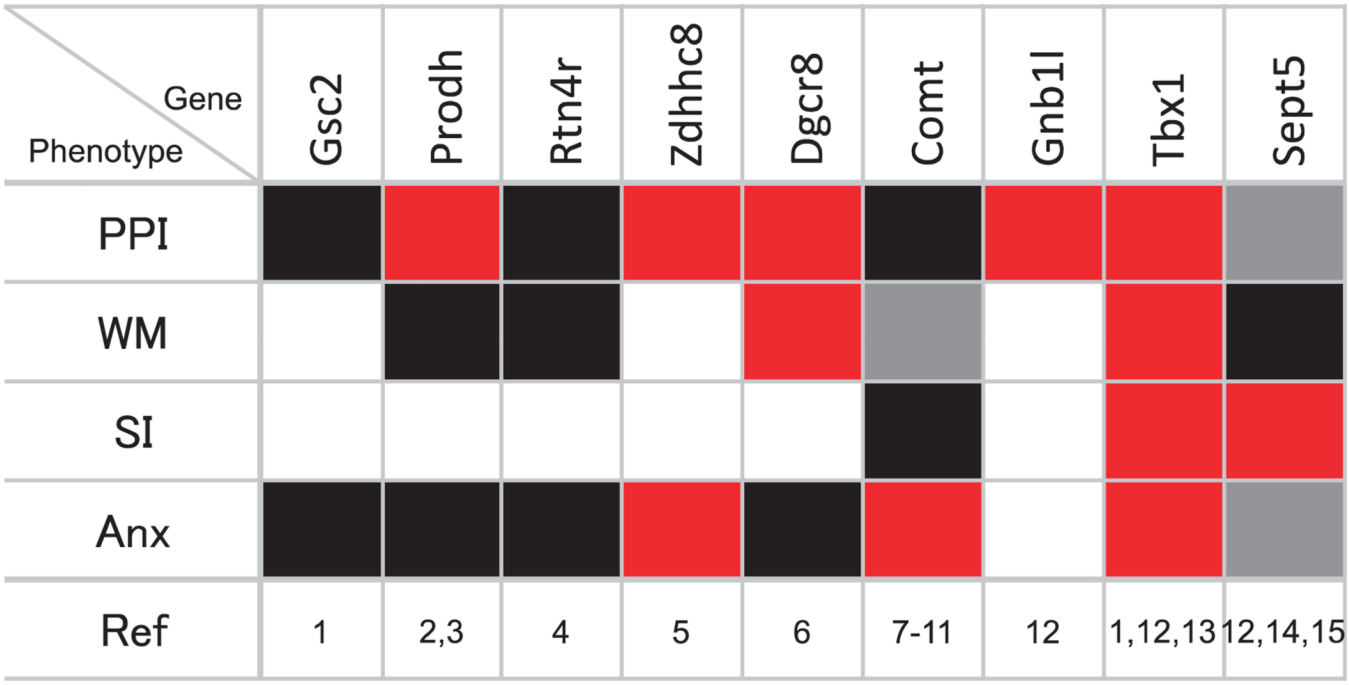

Figure 3.

Mosaic pattern of phenotypes caused by deletion of specific genes in mouse models. Phenotypes consistent (red) and inconsistent (gray) with what is seen in 22q11.2 hemizygous patients are shown; black squares represent cases where a gene deletion caused no effect. Blank squares represent cases where phenotyping was not conducted. PPI, prepulse inhibition; WM, working memory; SI, social interaction; Anx, anxiety. (1) Long *et al.*;[181] (2) Gogos *et al.*;[202] (3) Paterlini *et al.*;[203] (4) Hsu *et al.*;[161] (5) Mukai *et al.*;[197] (6) Stark *et al.*;[196] (7) Gogos *et al.*;[191] (8) Papaleo *et al.*;[190] (9) Babovic *et al.*;[194] (10) O'Tuathaigh *et al.*;[193] (11) O'Tuathaigh *et al.*;[192] (12) Paylor *et al.*;[145] (13) Hiramoto *et al.*;[186] (14) Suzuki *et al.*;[188] (15) Harper *et al.*[187]

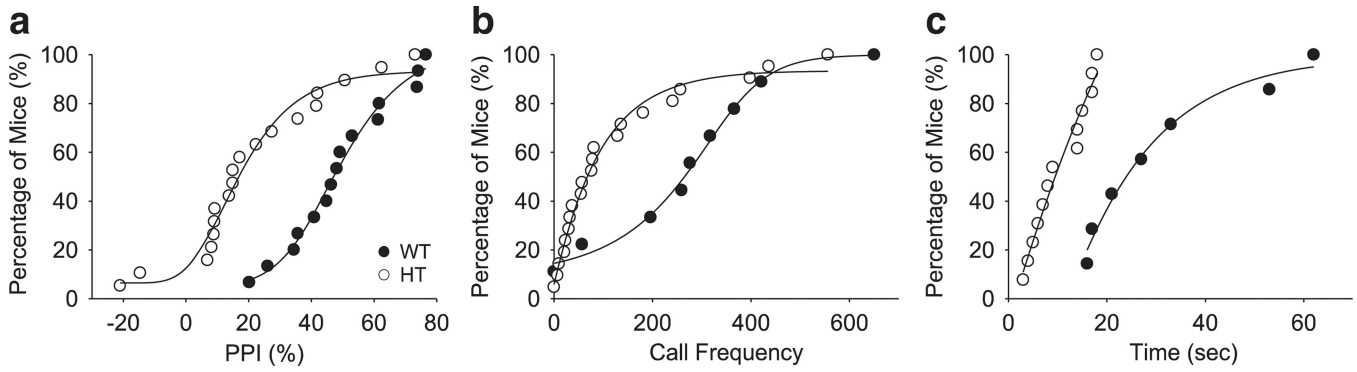

Figure 4.

Shifts in data structure of various phenotypes caused by *Tbx1* heterozygosity. Figures are based on raw data of our published study.[186] Black circles represent WT mice and open circles represent HT mice for the three graphs. (**a**) For PPI, *Tbx1* heterozygosity shifts data lower so that the cumulative data curve shows a parallel shift to the left, with many HT cases below the lowest data point of WT mice. (**b**) Vocal calls: *Tbx1* heterozygosity shifts the average of data slightly to the left, but data largely overlap between WT and HT mice. (**c**) Social interaction: *Tbx1* heterozygosity shifts the data distribution of WT to the left, with a minimal overlap between HT and WT mice. Note that variance is also reduced in HT mice.

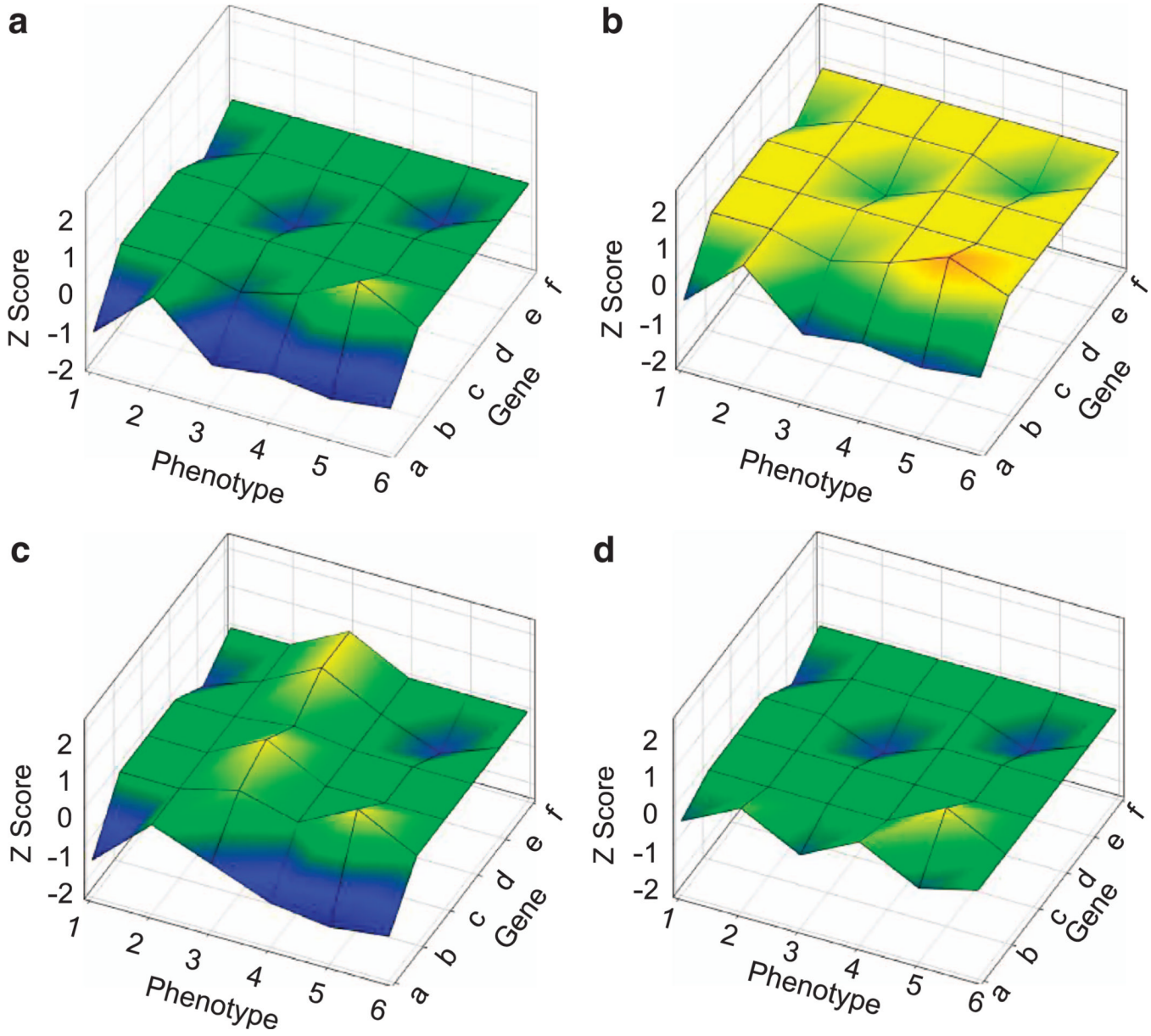

Figure 5.

Hypothetical genotype–phenotype relation. Three dimensions indicate genes, phenotypes and *Z*-scores of phenotypic expression. The yellow–green zones indicate average scores exhibited in organisms at a normal gene dose. Lower (blue) and higher (red) *Z*-scores indicate more severe phenotypic deviation. The plane expands as more genes are involved in a CNV and more phenotypes are affected. (**a**) A hypothetical impact of a CNV on phenotypes. (**b**) Genetic background and/or environmental factors evenly shift the impact of a CNV on all phenotypes, compared to panel **a**. (**c**) Genetic background and/or environmental factors selectively shift the impact of a CNV on a specific phenotype (see phenotype 3), compared to panel **a**. (**d**) Genetic background and/or environmental factors selectively shift the impact of a specific gene (see gene a), compared to panel **a**. Not depicted here is a developmental trajectory along which a gene-dose alteration starts to affect a phenotypic score.