to social rewards at the single-neuron level remains to be seen.

One immediate implication of these results is for patients with dysfunction of these brain regions. The striatum is among the targets of some neurological disorders, such as Parkinson's disease (PD). Overtreatment of PD with dopamine agonists is known to induce abnormal economic decision-making, including compulsive gambling (Voon et al., 2006). If the same brain structures are responsible for the reward-value of love and reputation, pharmacological manipulation of the striatum may also have social consequences.

The broader questions raised by the current results concern the relationship between two basic domains of human cognition: the social and the economic. Beyond the common currency, what distinguishes the processing of social versus monetary reward? How and when does sensitivity to these different domains of reward emerge, during child development or in evolution? And finally, what neural processes are engaged when an individual must trade off one kind of reward against the other? Taken together, the tools of behavioral economics, psychology, and neuroscience could provide an answer to how we decide, in the end, whether to choose love or money.

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Schizophrenia: Genome, Interrupted

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Structural chromosomal variation is increasingly recognized as an important contributor to human diseases, particularly those of neurodevelopment, such as autism. A current paper makes a significant advance to schizophrenia genetics by establishing an association with rare copy number variants (CNV), which are over-represented in neurodevelopmental genes.

Geneticists have become increasingly aware of a large amount of previously unidentified and unanticipated structural variation within the human genome. These variations, duplications and deletions of relatively small genomic segments that range from 1 kb to several million bases, are referred to as copy number variants (CNVs). CNVs, like other genetic variants, come in many forms: they may be inherited or de novo, rare or common. Similar to single base pair changes, rare de novo CNVs are often interpreted in the same way as Mendelian mutations that may play a causal role in disease and have been associated with several neurodevelopmental disorders, including intellectual disability and autism (de Vries et al., 2005; Jacquemont et al., 2006; Stankiewicz and Beaudet, 2007; Sebat et al., 2007; Szatmari et al., 2007). Some CNVs arise in chromosomal regions of segmental duplications that allow for inexact crossovers when the gametes are being formed (Mehan et al., 2004; Sharp et al., 2006). Sporadic cases of single-gene neurological disorders such as Charcot-Marie-Tooth neuropathy and Smith-Magenis syndrome derive from de novo CNVs generated by this mechanism (Lupski, 2007). However, most of the rare de novo CNVs arise in the absence of such repeat regions, consistent with what appears to be random DNA breakage.

The role of CNVs in common complex disorders is an area of intense investigation. Using the molecular technology of microarray-based methods designed for both single-nucleotide polymorphism

(SNP) association studies and CNV detection, they are beginning to be cataloged in psychiatric and neurological disorders (Sebat et al., 2007; Szatmari et al., 2007; Marshall et al., 2008). It is on this research background that Walsh et al. (Walsh et al., 2008) report an excess of CNVs in patients with schizophrenia in the journal *Science*. Schizophrenia represents a typical complex genetic disorder, with most cases previously thought to be due to the action of multiple genes interacting with each other and the environment. The incidence of schizophrenia is about 1%, and the sibling recurrence risk is about 5%–10%, making the case for its familiality, and twin studies indicate a high heritability (about 80%) (Sullivan, 2008). Genetic heterogeneity and the complexity of the phenotype have challenged whole genome linkage studies, which have been inconsistent, and despite a large number of published candidate gene studies, only a few genes, including DISC1 and neuregulin1 are considered strong candidates (Sullivan, 2008). Particularly relevant to the current report, DISC1, perhaps the schizophrenia-causing gene with the strongest evidence, was identified by a dominantly inherited chromosomal abnormality in a single pedigree. It is therefore anticipated that the disruption, deletion, and duplication of whole genes in the individuals reported by Walsh and colleagues (Walsh et al., 2008) represents a significant advance in the field.

This manuscript reports a CNV analysis of two samples: the first with mixed ages of onset of schizophrenia, and the second consisting of only subjects with childhood onset schizophrenia. The first "test" group included 150 individuals with schizophrenia and 268 controls who were ancestry matched and 35 or older, without signs of neurological or psychiatric illness. Because many of the CNVs identified are rare or are only observed in one subject or family, investigators are not able to provide statistical evidence of an association with a specific CNV. Rather, they investigate whether such CNVs are increased in aggregate in those with the disease compared to the controls. Their working hypothesis is that "some mutations predisposing to schizophrenia are highly penetrant, individually rare, and of recent origin, even specific to single cases or families (Walsh et al., 2008)." To establish this, the rate of rare CNVs considered collectively should be higher in those with the disorder than in those who show no evidence of it. Similar designs have been applied in autism spectrum disorders (ASD). In addition to the increased rate of rare de novo CNVs in ASD (about 10% in simplex families), recurrent CNVs on chromosome 16p and 15q have been identified, each accounting for about 1% of patients (Weiss et al., 2008).

The resolution of the molecular platform they used allows them to detect CNVs of a size greater than 100 kb, which is about 30 times the resolution of standard cytogenetic techniques. Here, common variants seen at 1% or greater did not differ in frequency in the cases compared to controls, so the focus remained on rare variants. Those variants that delete or duplicate genes were seen at a rate of 22/150 (or 15%) in cases and 13/268 (or 5%) in controls. The rates for those CNV disrupting genes were 11% in cases and 4% in controls. Both of these case and control differences are statistically significant, indicating that those with schizophrenia are more likely to harbor novel CNVs of a size greater than 100 kb than controls.

Replication of this finding focused on those with childhood onset schizophrenia (COS), a relatively rare condition, defined as those developing schizophrenia before 12 years of age. In the original case/control sample, there are 76 individuals falling into an early onset category (onset prior to age 19), and ~20% have a rare deletion. In the replication sample of 83 COS parent-child trios, 23/76 affected children aged 12 or less (or 28%) have a rare CNV, which is higher than the 20% in those with early onset in the original sample, where the age cutoff was 18 years. The control groups between the original and replication samples are not comparable in that the one in the replication sample is artificial and derived from those chromosomes not transmitted to the schizophrenic children from their parents, but the association of rare CNVs and schizophrenia is replicated.

Because parental information was not available in the first sample, but is in the COS sample (because the parents and the proband were assayed), it was also possible to identify those CNVs that are de novo mutations in the affected child. So, the investigators used the parent child trio data to present the specific CNV in the affected children classified by whether they are inherited or de novo (see the Supplemental Tables in Walsh et al., 2008). The majority are inherited from a parent, with only two that are de novo, suggesting that most of the CNVs are not highly penetrant, or the transmitting parent would exhibit symptoms of schizophrenia. In addition, several patients have more than one such CNV, again suggesting that any predisposing CNV is likely to be interacting with other modifying genetic or environmental factors to cause schizophrenia. Overall, the relative risk of schizophrenia in those carrying a rare CNV ranges between 3% and 4%, not consistent with a Mendelian model for the CNVs taken in aggregate. This does not preclude the possibility of a few individual CNVs operating in a Mendelian fashion, but such a mechanism has not been proven here. One interesting observation is that those cases with early or childhood onset, which can be considered a more severe form of the disorder, had the highest rate of rare CNVs. Similarly, large de novo CNVs are increased in severe ASD, especially in those with syndromic forms, relative to the less severe, familial cases (Jacquemont et al., 2006; Sebat et al., 2007), which is consistent with the notion that some large de novo CNVs are highly penetrant, relatively severe mutations.

The CNVs identified for schizophrenia in this study are within genic regions ranging from 135 kb to the entire Y chromosome (58 Mb) and include from 1 to 20 genes. In controls, CNVs range from 197 kb to 3.6 Mb and span the same range for the number of genes duplicated or deleted. Because not all genes are dosage sensitive, it is recognized that, within a region containing many duplicated or deleted genes, only a subset, or perhaps as few as one or none, are likely to contribute to the changes in phenotype observed in disease. Therefore, the authors focus most of their analysis on genes actually disrupted by the CNV breakpoints, because these genes are most likely to be functionally deranged. However, it must also be appreciated that genes within the CNV in addition to those ruptured by the chromosomal breakage may also be contributing to disease.

The authors use pathway analysis bioinformatics tools to establish that, while the

disrupted genes in controls are random, those that are seen in schizophrenia are overrepresented in pathways associated with brain development. These include neuregulin signaling, ERK/MAPK signaling, synaptic long-term potentiation, axonal guidance signaling, integrin signaling, and glutamate receptor signaling, several of which have been previously implicated in studies of schizophrenia biology (Lewis and Gonzalez-Burgos, 2006; Norton et al., 2006).

Several of the CNVs result in predictable alterations in gene product function. One particularly interesting CNV disrupts ERBB4, a receptor for neuregulin1, which is one of the few genes having a replicated common variant associated with schizophrenia (Munafo et al., 2006). Walsh and colleagues (Walsh et al., 2008) show that the transcript arising as a consequence of this medium-sized CNV (400 kb) encodes an alternate transcript that is predicted to act in a dominant-negative fashion. But, it is not described whether this represents a sporadic or familial case, and thus assessment of the segregation of this variant with disease is not possible, although it would clearly alter protein function.

However, several genes important for neurodevelopment were uniquely disrupted in controls, for example ROBO1 and SOX5, emphasizing that caution must be taken when connecting a single rare event with disease. Thus, among the genes disrupted by CNVs in those with schizophrenia are likely to be those that are random, as seen in controls, and some that are perhaps specific to schizophrenia. The authors recognize this in their discussion, pointing out that these data cannot implicate a role for any specific gene. What is remarkable, however, is that this single study provides statistical evidence supporting the involvement of several key neurodevelopmental pathways in schizophrenia, providing a circumscribed set of candidate genes within these pathways for further investigation. Their successful analysis exhibits an important approach for the study of rare variants in psychiatric disorders. In addition, as sequencing technologies provide the possibility of deep resequencing of large numbers of candidate genes, a similar approach to identify rare, single base pair mutations becomes accessible. The success of Walsh et al. (2008) in establishing that rare genetic variants are associated with schizophrenia, in contrast with the ambiguity thus far observed using approaches based on common variants, suggests that developing analytic methods focused on identifying rare mutations is warranted.

The specificity of the identified variants for schizophrenia remains unknown. For example, CNVs in Neurexin 1 and recurrent CNV on chromosome 16p11 previously reported in ASD and other neurodevelopmental disorders were also observed in this study. This is not problematic, but rather it presents a significant opportunity to understand the relationship of these disorders at a molecular level. If the same genes carry mutations for the development of schizophrenia or autism, it suggests genetic pleiotropy, where multiple disorders derive from mutations in the same gene, and the disorder is conditional upon the presence of other modifying alleles, environment factors, or chance. It also should be recognized that childhood schizophrenia shares some clinical features with ASD and has been considered part of the ASD spectrum in the past. Thus, from a neurobiological perspective, these genetic data support the notion of a link between disorders involving neurodevelopmental processes that are currently considered to be clinically distinct. This work makes significant inroads in breaking down the somewhat artificial clinical distinctions between neuropsychiatric diseases and provides support for defining core phenotypes related to the common genetic mechanisms.

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