Chromosome 22 Link to Schizophrenia Strengthened

4 November 2005. There is now overwhelming evidence that genetic inheritance plays a major role in susceptibility to schizophrenia. And though no schizophrenia genes have yet been confirmed, there are plenty of candidates. Multiple lines of evidence, for example, suggest that a region in the small arm of chromosome 22 (22q11.2) might confer susceptibility to the disease. Two recent Nature Neuroscience papers bolster that connection.

The link between schizophrenia and chromosome 22q11.2 is particularly interesting because that segment of DNA harbors genes for two enzymes that can influence neurotransmission—catechol-O-methyltransferase (COMT) and proline dehydrogenase (PRODH). COMT, of course, is crucial for dopamine metabolism, so any genetic variance that alters the activity of this enzyme could tip the balance toward too much, or too little, of this neurotransmitter. The PRODH link is less obvious, but again, loss or reduction of PRODH activity could lead to an increase in the level of proline, and it was recently shown that this amino acid accumulates in glutamatergic synapses where it probably modulates glutamate transmission (see, for example, Renick et al., 1999). Now, together, the two papers add weight to the COMT/PRODH link.

Allan Reiss and colleagues at Stanford University, California, together with collaborators at Tel Aviv University, Israel; the University of Geneva, Switzerland; and the University of Washington, Seattle, report on a study of adolescents with 22q11.2 deletion syndrome. The disorder is often referred to as velocardiofacial syndrome (VCFS), a term that encompasses some of the most common early childhood manifestations such as cleft palate, heart defects, characteristic facial appearance, minor learning problems, and speech and feeding problems. The constellation of some 30 different identifying features, not all of which appear in any given child, are traceable to the deletion of that region of chromosome 22. About one third of all babies born with these deletions will go on to later develop schizophrenia (see, for example, Murphy et al., 1999).

First author Doron Gothelf and colleagues considered whether polymorphisms, or variations, in the undeleted copy of COMT may help to explain why some with the 22q11.2 deletion will develop schizophrenia, while others do not. They followed patients known to have the deletion, correlating the emergence of the disease with a known single nucleotide polymorphism—one that results in a methionine amino acid instead of a valine at position 158 and that ablates about one third of the enzyme’s activity.

Gothelf and colleagues tested 24 patients with 22q11.2 deletion syndrome. During childhood, none showed evidence of a psychotic disorder, but in early adulthood, seven did. The authors found that the COMT variant with low enzyme activity (COMTL) correlated with lower verbal IQ and language skills and lower prefrontal cortex volume in these seven adolescents. The results suggest that “extreme deficiency in COMT activity, as present in the COMTL subjects with 22q11.2DS, is an important neurodevelopmental risk factor for decline in PFC [prefrontal cortex] volume and cognition and for the emergence of psychotic symptoms during
adolescence,” write the authors.

In the second paper, Maria Karayiorgou’s group at Rockefeller University, New York, and Joseph Gogos’s group at Columbia University, New York, collaborated to model the effect of altering the expression of PRODH. First author Marta Paterlini and colleagues found that in mice, loss of the enzyme leads to increases in neuronal proline and that this, in turn, increases the probability that glutamate will be released into synapses in the hippocampus. In addition, the authors discovered that synaptic plasticity, as defined by the ability of neurons to modulate their activity in response to the activity of other nearby neurons, is compromised. They found, for example, that both paired-pulse facilitation and long-term potentiation, two commonly used measures of plasticity, were inhibited. The authors also found that loss of PRODH and increases in proline were accompanied by behavioral changes—the mice were generally less active, exploring about 25 percent less than normal mice, and they reacted less frequently in conditioned responses to stimuli such as mild shock. The animals also had a poorer response to psychotomimetic drugs, such as MK801, which increase glutamate release (this could be because the PRODH-deficiency already causes more release of glutamate than normal), but when given amphetamine, locomotor activity increased almost twofold more than in normal animals. “This is reminiscent of the increased susceptibility to the disorganizing effects of D-amphetamine observed in individuals with schizophrenia,” note the authors.

Gothelf and colleagues, in their 22q11.2 deletion paper, emphasize that many other genes in the vicinity of COMT and PRODH should be evaluated, and Paterlini and colleagues do just this, using a transcriptional profiling method to evaluate what genes may be turned on or off by the loss of PRODH in their animal model. And one of the genes that interacts most strongly with PRODH was none other than COMT, which was upregulated in the prefrontal cortex of the PRODH-deficient animals. This not only buttresses the argument for COMT and PRODH as key risk factors for schizophrenia, but also suggests that the two genes may interact.—Tom Fagan.

References:


Comments on News and Primary Papers

Comment by: Anthony Grace, SRF Advisor
Submitted 5 November 2005

The fact that the PRODH alteration studied in Gogos et al. leads to alterations in glutamate release, and this corresponds to deficits in associative learning and response to psychotomimetics, provides a nice parallel to the human condition. The Reiss paper examines humans with the 22q11.2 deletion, and shows that the COMT low-activity allele of this deletion syndrome correlates with cognitive decline, PFC volume, and development of psychotic symptoms. This is a nice addition to the Weinberger and Bilder papers about how...
COMT can lead to psychosis vulnerability.

View all comments by Anthony Grace

Comment by: Caterina Merendino  
Submitted 5 November 2005  
Checked  I recommend the Primary Papers  
Posted 5 November 2005

Primary Papers: COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome.

Comment by: Jeffrey Lieberman  
Submitted 6 November 2005  
Checked  I recommend this paper  
Posted 6 November 2005

Isn't the association of the low-activity COMT allele with development of psychotic symptoms in the paper by Gothelf et al. inconsistent with the finding of Egan et al., and subsequent replications? The latter's findings of decreased cortical information processing efficiency and vulnerability to schizophrenia was with the high-activity allele. How is this apparent inconsistency in the 22q11.2 deletion subjects reconciled?

View all comments by Jeffrey Lieberman

Comment by: Leboyer Marion  
Submitted 6 November 2005  
Checked  I recommend the Primary Papers  
Posted 6 November 2005

Comment by: Anne Bassett  
Submitted 7 November 2005  
Checked  I recommend the Primary Papers  
Posted 7 November 2005

I echo Jeff Lieberman's comment regarding previous reports of a weak association between the Val COMT functional allele and schizophrenia. Notably, the most recent meta-analysis (Munafo et al., 2005) shows no significant association. Even in 22q11.2 deletion syndrome (22qDS), our group (unpublished) and Murphy et al. (1999) have reported that there is no association between COMT genotype and schizophrenia, and Bearden et al. reported that Val-hemizygous patients performed significantly worse than Met-hemizygous patients on executive cognition (2004) and childhood behavioral problems (2005). Though important as an initial prospective study, there is a risk in the Gothelf et al. small sample size and multiple testing for type 1 errors. Certainly, there is little evidence, even in 22qDS, for COMT (or PRODH) as "key" risk factors for schizophrenia. There may be some evidence for small effects on cognitive or other measures. Regardless, there is not "extreme deficiency" in COMT activity in the many individuals with Met-hemizygosy in 22qDS, or Met-Met homozygosity in the general population.

Regarding the news item, there are a few widely held misconceptions about 22qDS. Our recent article (Bassett et al., 2005) shows that, accounting for ascertainment bias, the rate of schizophrenia was 23 percent, and congenital heart defects was 26 percent. Of the other 41 common lifetime features of 22qDS (found in 5 percent or more patients), neuromuscular palatal anomalies were common but overt cleft palate was so rare it did not meet inclusion criteria; intellectual disabilities ranged from severe mental retardation (rare) to average intellect (rare) with most patients falling in the borderline range of intellect; and on average,
patients had nine of 43 common features. We propose clinical practice guidelines for adults with 22qDS which may be directly applicable to the 1-2 percent of patients with a 22qDS form of schizophrenia.

References:


Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry. 1999 Oct 1;56(10):940-5. Abstract

View all comments by Anne Bassett

Primary Papers: COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome.

Comment by: Daniel Weinberger, SRF Advisor
Submitted 14 November 2005

Drs. Lieberman and Basset raise an important question about why the met allele in the VCFS early adult cases is associated with cognitive decline and risk for psychosis, while the val allele tends to be associated with both characteristics when there is a positive association to COMT in adult subjects. I believe that the data of Gothelf and colleagues are entirely consistent with predictions about what would be expected in VCFS based on evidence that dopamine signaling in prefrontal cortex relates to prefrontal function as an inverted U-shaped dose-response curve. Too little dopamine, as might be seen in normal aging, in Parkinson's disease and possibly in schizophrenia, is associated with relatively abnormal prefrontal function, and too much dopamine, as might be seen in amphetamine or other acute psychotic states, also is associated with relatively abnormal prefrontal function. Landmark experiments from the laboratory of the late Patricia Goldman-Rakic at Yale demonstrated this in the monkey, and Mattay et al., 2003 showed similar effects in normal human beings.

In the study of Gothelf et al., in late childhood, val hemizygous individuals with VCFS were more impaired on cognitive testing compared to met hemizygous individuals (consistent with other VCFS studies of children), but the reverse relationships emerged later in adolescence. What explains this? The evidence that dopaminergic innervation of the primate prefrontal cortex increases during adolescence is well established (e.g., Lambe et al., 2000), and this developmental enhancement of cortical dopaminergic activity would be expected to move
everyone further to the right on the inverted U-shaped dopamine cortical response curve.

What would this mean for individuals hemizygous for COMT? As dopamine activity goes up, val individuals are rescued by being hemizygous, because their normally increased COMT activity (i.e., reduced synaptic DA) is compensated by the null COMT chromosome. In contrast, COMT met hemizygous individuals are compromised by having one low-activity COMT chromosome and one null activity chromosome, and pushed to the far downslope of the curve. The study of Gothelf et al. illustrates that the critical factor in genetic risk for abnormal brain function is the biologic state of the gene, not necessarily a particular allele or haplotype, and how this biologic state relates to the biologic context of the neural functions involved.

View all comments by Daniel Weinberger

Primary Papers: COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome.

Comment by: Doron Gothelf, Allan Reiss
Submitted 18 November 2005

Reply to comments by Lieberman and Bassett

I have just seen Dr. Weinberger's reply and our reply follows the same vein.

22q11.2DS subjects are unique in that they are hemizygous for the COMT gene, that is, have half the dosage of the gene and are thus different from the general population and from non-22q11.2DS schizophrenia patients. The model we think best integrates our "met" findings with the "val" findings in non-22q11.2DS schizophrenia is that of the hypothetical inverted U-shape relationship between prefrontal dopamine levels and cognitive functioning/neuropsychiatric risk. Too much dopamine, as presumably occurs in the prefrontal cortex of the 22q11.2DS "met" subgroup, or too little prefrontal dopamine, as presumably occurs in the general schizophrenia population, puts subjects outside the "optimal" dopamine range and in a less favorable state in terms of cognitive functioning and risk for psychosis. As Dr. Bassett noted, there are indeed studies that found higher cognitive performance in 22q11.DS children with the "val" as compared to "met." In our study, the same trend was evident when we looked only at Time-1 evaluations conducted during childhood. However, during adolescence, those with "met" had a more robust decline in VIQ and expressive language. Thus, it was the longitudinal follow-up of subjects during adolescence that enabled us to identify this intriguing developmental trend.

Dr. Bassett suggests that 22q11.2DS met subjects are not in extreme deficiency of COMT enzyme activity. There is no definite information about this because there are no measures of enzyme activity in this population. However, in the COMT knockout model published by Gogos et al. (1998), a 100-200 percent increase in prefrontal dopamine was measured in males, and this was accompanied by aggressive behavior. We think that the state of the COMT knockout mouse may resemble that of 22q11.2DS as these subjects are "knocked-out" of the COMT gene by virtue their deletion in this region. As to Dr. Bassett’s remark about sample size, we strongly ascribe to the principle that “more is better,” particularly in genetic association studies where samples tend to be biologically heterogeneous and where the variance of key measures is often relatively large. However, in contrast to the study of persons with phenomenologically (i.e., DSM-IV) defined “schizophrenia,” our investigation focuses on a group where a specific genetic risk factor for schizophrenia can be identified.
(22q11.2DS), and is shared amongst affected individuals. Thus, relative to a DSM-IV defined sample, a 22q11.2DS group would be likely to demonstrate less variance in key cognitive, neuropsychiatric, and biological measures, with smaller sample size requirements for demonstrating effects of interest. Accordingly, we believe that 22q11.2DS is a powerful model from which to discern genetic and pathophysiological mechanisms associated with schizophrenia.

In our longitudinal study, the met allele was robustly associated with three pivotal phenotypic features of schizophrenia: 1) emergence of psychotic symptoms, 2) decline in cognitive abilities, and 3) reduction in prefrontal gray matter volumes. Each of these phenotypic features has been linked with dopamine dysregulation. Thus, it is logical to presume that a unique hyperdopaminergic state, induced by severe deficiency of COMT activity in 22s11.2DS, would trigger a series of pathophysiological events that increase risk for schizophrenia. We believe that the likelihood of a type 1 error in our study is greatly reduced by the homogeneity of our sample (with respect to shared “risk” for psychosis), the consistency of our findings across core phenotypic features of schizophrenia, and the consistency of our findings within a rigorous neurobiological framework. Of course, we agree that replication should be tested in larger, independent samples of subjects, including those with different ethnicities.

View all comments by Doron Gothelf
View all comments by Allan Reiss

Primary Papers: COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome.

Comment by: Carrie Bearden
Submitted 21 November 2005

I recommend this paper

Gothelf and colleagues present a novel study (the first longitudinal investigation of psychopathology, cognition, and brain volume in adolescents with 22q11.2 deletions) with a very interesting result. As they correctly assert in their manuscript, their baseline finding of a trend toward better cognitive function in the COMT H (Val) subgroup is consistent with our previous finding of a tendency toward higher full-scale IQ in Val-hemizygous patients with 22q11.2 deletions versus Met-hemizygous patients (mean = 77.6 [SD = 10.5] versus 71.8 [SD = 11.4], respectively; F = 2.98, df = 1, 42, p = 0.09; Bearden et al., 2004). Despite this, as Dr. Bassett described above, we also found that Met-hemizygous patients performed significantly better than Val-hemizygous patients on measures of executive function (specifically Digit Span and Trailmaking B), after controlling for overall effects of IQ. In addition, we found that Val genotype was associated with a greater-than-fourfold increase in risk for clinically significant behavior problems, as measured by the Child Behavior Checklist (CBCL), in 38 children (16 Met/-, 22 Val/-) with confirmed 22q11.2 deletions. While inconsistent with the findings of Gothelf et al. of increased rates of schizophrenia in 22q11.2DS patients with the low-activity (Met) allele, our data are nonetheless consistent with previous findings of increased psychopathology associated with the Val genotype in normal adults. Clearly, this is a complicated story, though, and much of the puzzle still awaits to be solved, as at least two published studies (Baker et al., 2005; Murphy et al., 1999) have found no association between COMT genotype and psychopathology in 22q11.2DS. Thus, it is not clear whether COMT genotype in the intact chromosome in patients with 22q11.2 deletion syndrome has a similar influence on executive cognition and psychiatric symptoms to that...
observed in other populations.

While intriguing, several questions remain regarding the findings presented in Gothelf et al. First, what is the mechanism by which one would predict that COMT would cause verbal IQ and prefrontal volume decline over time in 22q11DS patients with the low-activity (Met) allele? Dr. Weinberger eloquently elaborates on the idea of the hypothetical U-shaped dose-response curve, in which relatively abnormal prefrontal function may be seen at both ends of the curve. However, if developmental enhancement of cortical dopaminergic activity does indeed move everyone further to the right on the inverted U-shaped dopamine cortical response curve, I am not sure this explains why cognitive performance (and prefrontal cortical volume) would remain stable in the Val-hemizygotes over time.

In addition, it is not clear whether Gothelf and colleagues mean to suggest that somehow COMT exerts independent effects on cognition and psychotic symptoms (as implied by their statement that VIQ decline precedes development of psychosis). Clearly, further study would be needed in order to address that question.

The finding of concomitant declines in verbal IQ and expressive language are quite unusual, as these measures of crystallized knowledge/verbal abilities are highly unlikely to truly decompensate over time—it is not clear that the decline over time observed in both cognition (on VIQ and CELF-E scores) and prefrontal volume is not entirely accounted for by the greater rate of development of psychotic disorder in the Met allele subgroup. I assume that the significantly higher BPRS scores at follow-up for the Met patients would correspond to this (although data regarding rates of psychotic disorder in low- versus high-activity COMT subgroups were not specifically reported). While this in itself would not detract from the importance of the finding, it seems that acute psychiatric symptomatology may be the best explanation for the IQ/cognitive decline witnessed in the 22q11 L group. This type of decline on such highly stable measures is quite atypical except under unusual circumstances, and is rare even in typical young adult patients who develop psychotic illness (e.g., Kurtz, 2005).

Finally, I am curious as to the reason that the authors would a priori hypothesize that verbal IQ and expressive language (CELF-E) would be associated with COMT genotype, and not the complementary measures (performance IQ and receptive language; CELF-R), which most likely also were administered at the same time.

Nevertheless, this study represents a very important step toward a better understanding of the effects of specific genetic influences on human cognition, and pathophysiological mechanisms associated with the development of psychosis.

References:


http://www.schizophreniaforum.org/new/detailprint.asp?id=1202

Murphy KC, Jones LA, Owen MJ. High rates of schizophrenia in adults with velo-cardio-facial syndrome. Arch Gen Psychiatry. 1999 Oct 1;56(10):940-5. Abstract

View all comments by Carrie Bearden

Primary Papers: COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome.

Comment by: Patricia Estani
Submitted 23 November 2005
I recommend this paper

I agree with the comments of Dr. Weinberger about the COMT gene and schizophrenia. This relationships is consistent with the data of Gothelf et al. More experiments must be carried out to separate these variables.

View all comments by Patricia Estani

Primary Papers: COMT genotype predicts longitudinal cognitive decline and psychosis in 22q11.2 deletion syndrome.

Comment by: William Carpenter, SRF Advisor (Disclosure)
Submitted 27 December 2005
I recommend this paper

Comments on Related News

Related News: New Genetic Variations Link Schizophrenia and Bipolar Disorder

Comment by: Mary Reid
Submitted 28 September 2006
I agree with the comments of Dr. Weinberger about the COMT gene and schizophrenia. This relationships is consistent with the data of Gothelf et al. More experiments must be carried out to separate these variables.

View all comments by Mary Reid

Related News: New Genetic Variations Link Schizophrenia and Bipolar Disorder

Comment by: Patricia Estani
Submitted 5 October 2006
I recommend the Primary Papers

Related News: 22q11 and Schizophrenia: New Role for microRNAs and More

Comment by: Linda Brzustowicz
Submitted 21 May 2008
While some have expressed frustration over the lack of clear reproducibility of linkage and association findings in schizophrenia, the importance of the chromosome 22q11 deletion syndrome (22q11DS) as a real and significant genetic risk factor for schizophrenia has often been overlooked. While the deletion syndrome is present in a minority of individuals with schizophrenia (estimates of approximately 1 percent), presence of the deletion increases risk of developing schizophrenia some 30-fold, making this one of the clearest known genetic risk factors for a psychiatric illness. As multiple genes are deleted in 22q11DS, it can be a challenge to determine which gene or genes are involved in specific phenotypic elements of this syndrome.

The May 11, 2008, paper by Stark et al. highlights the utility of engineered animals for dissecting the individual effects of multiple genes within a deletion region and provides an important clue into the mechanism likely responsible for at least some of the behavioral aspects of the phenotype. While some may argue about the full validity of animal models of complex human behavior disorders, these systems do have an advantage in manipulability that cannot be achieved in work with human subjects. A key feature of this paper is the comparison of the phenotype of mice engineered to contain a 1.3 Mb deletion of 27 genes with mice engineered to contain a disruption of only one gene in the region, DGCR8. The ability to place both of these alterations on the same genetic background and then do head-to-head comparisons on a number of behavioral, neuropathological, and gene expression assays allows a clear assessment of which components of the mouse phenotype may be attributed specifically to DGCR8 haploinsufficiency. Perhaps not surprisingly, DGCR8 seems to play a role in some, but not all, of the behavioral and neuropathological changes seen in the animals with the 1.3 Mb deletion. The fact that the DGCR8 disruption was able to recapitulate certain elements of the full deletion in the mice does raise its profile as an important candidate gene for some of the neurocognitive elements of 22q11DS, and makes it a potential candidate gene for contributing to schizophrenia risk in individuals without 22q11DS.

Also of great interest is the known function of DGCR8. While the gene name simply stands for DiGeorge syndrome Critical Region gene 8, it is now known that this gene plays an important role in the biogenesis of microRNAs, small non-coding RNAs that regulate gene expression by targeting mRNAs for translational repression or degradation. As miRNAs have been predicted to regulate over 90 percent of genes in the human genome (Miranda et al., 2006), a disruption in a key miRNA processing step could have profound regulatory impacts. Indeed, as reported in the Stark et al. paper and elsewhere (Wang et al., 2007), homozygous deletion of DGCR8 function is lethal in mice. What perhaps seems to be the most surprising result is that haploinsufficiency of DGCR8 function does not induce a more profound phenotype, given the large number of genes that would be expected to be affected if miRNA processing were globally impaired. The Stark et al. paper determined that while the pre-processed form of miRNAs may be elevated in haploinsufficient mice, perhaps only 10-20 percent of all mature miRNAs show altered levels, suggesting that some type of compensatory mechanism may be involved in regulating the final levels of the other miRNAs. Still, the 20-70 percent decrease in the abundance of these altered miRNAs could have a profound effect on multiple cellular processes, given the regulatory nature of miRNAs. In the context of the recent evidence for altered levels of some miRNA in postmortem samples from individuals with schizophrenia (Perkins et al., 2007), the Stark et al. paper adds further support for studying miRNAs as potential candidate genes in all individuals with schizophrenia, not just those with 22q11DS. This paper should serve as an important reminder of how careful analysis of a biological subtype of a disorder can reveal important insights that will be
relevant to a much broader set of affected individuals.

References:


View all comments by Linda Brzustowicz

Related News: Are Membrane Molecules Unmoored in 22q11DS Mouse?

Comment by: Doron Gothelf
Submitted 27 October 2008

The common theory held until recently regarding the genetic underpinning of neuropsychiatric disorders was based on the “common disease-common variant” model. According to that theory, multiple common alleles in the population contribute small-to-moderate additive or multiplicative effects to the predisposition to neuropsychiatric disorders. With the advances in genetic screening technologies this theory is now being challenged. Recent findings indicate that rare copy number variations (CNVs) may account for a substantial fraction of the overall genetic risk for neuropsychiatric disorders including schizophrenia and autism (Consortium, 2008; Stefansson et al., 2008; Mefford et al., 2008). The 22q11.2 microdeletion was the most common CNV identified in patients with schizophrenia in a recent large scale study of patients with schizophrenia (Consortium, 2008). The 22q11.2 microdeletion is also the most common microdeletion occurring in humans and up to one third of individuals with 22q11.2 deletion syndrome (22q11.2DS) develop schizophrenia by adulthood. Thus the syndrome serves as an important model from which to learn the path leading from a well defined genetic defect to brain development and eventually to the evolution of schizophrenia.

It is still uncertain whether the neuropsychiatric phenotype associated with 22q11.2DS is a result of a strong effect of haploinsufficiency of one or a few genes from the microdeletion region as some studies suggested (Gothelf et al., 2005; Paterlini et al., 2005; Raux et al., 2007; Vorstman et al., 2008), or the result of cumulative small effects of haploinsufficiency of multiple genes, each contributing a small effect, as other studies suggested (Maynard et al., 2003; Meechan et al., 2006).

The current very elegant study by Mukai and colleagues suggests that haploinsufficiency of a single gene from the 22q11.2 deleted region, Zdhhc8, is responsible for the microscopic neural hippocampal abnormalities present in a mouse model of the disease. Remarkably, these abnormalities were prevented with the reintroduction of enzymatically active ZDHHC8
protein. The works of Gogos and his colleagues (Paterlini et al., 2005; Stark et al., 2008) are consistently and brilliantly getting us closer to revealing the complex association between genes from the 22q11.2 region and the neuropsychiatric phenotype. If indeed haploinsufficiency of single genes like Zdhhc8, COMT, or Dgcr8 have a strong effect on abnormal brain development and the eruption of schizophrenia, it conveys an enormous potential for developing novel pathophysiologically based treatments for this refractory disease. Such treatments will target the enzymatic deficit conveyed by the genetic mutation.

References:

[No authors listed]. Rare chromosomal deletions and duplications increase risk of schizophrenia. Nature. 2008 Sep 11;455(7210):237-41. Abstract


Paterlini et al. (2005); Stark et al. (2008).


View all comments by Doron Gothelf

Print this page