22q11 and Schizophrenia: New Role for microRNAs and More

23 May 2008. Microdeletions at chromosome 22q11 that are associated with schizophrenia in humans alter the production of gene-regulating microRNAs in mice, according to a new report in the May 11 issue of Nature Genetics. The work, from Joseph Gogos and Maria Karayiorgou of Columbia University, New York, zeroes in on deletion of the microRNA-processing gene Dgcr8 as responsible for changes in miRNA expression and contributing to the behavioral and neuronal phenotypes of 22q11 deletion in mice. The work is the first time that microRNAs have been implicated in cognitive dysfunction associated with schizophrenia, and may provide a new handhold on the complex molecular basis of the disease.

In a separate paper, a human genetics study ties alleles of GNB1L, another gene deleted in 22q11 deletion syndrome (22q11DS, encompassing velocardiofacial syndrome and DiGeorge syndrome, among others), to the risk of schizophrenia in several case-control studies. The 22q11 region has been genetically linked to schizophrenia in the general population, and the new results suggest that the alleles, which alter expression of GNB1L, may account for at least some of that linkage. The work, from Nigel Williams and colleagues at Cardiff University in Scotland, was published online last November, and appears in the April print edition of Human Molecular Genetics.

Microdeletions of a 1.5 to 3 Mbase span of DNA at 22q11.2 result in a highly variable syndrome—cardiac or facial/palatal abnormalities are seen in most cases, but there is a long list of other health issues that may affect a given individual with the deletion (see SRF related news story, as well as GeneReviews). The finding of schizophrenia or schizoaffective disorder in about one-third of cases has prompted researchers to comb the region for schizophrenia genes. The work has led to several candidates, identified by their effects on cognitive phenotypes in animals or genetic association studies in humans, or both. In addition to the genes discussed here, recent association studies have cast suspicion on other genes within the 22q11DS region, including the myelin associated gene PIK4CA (Jungerius et al., 2007), the Nogo-66 receptor gene RTN4R (Hsu et al., 2007), and HTF9C, a gene for an RNA binding protein (Liu et al., 2007).

Of mice...
To further study the deletion phenotype, Gogos and Karayiorgou made a mouse model of 22q11DS by removing a 1.5 Mb region of mouse chromosome 16 corresponding to most of the functional genes in the human deletion. First authors Kimberly Stark and Bin Xu headed up the team that found that the mutant mice showed several behavioral phenotypes associated with the cognitive alterations seen in people with schizophrenia. This included a defect in sensory gating detected by the paired pulse inhibition test, as well as effects on learning.

Transcriptional profiling of the hippocampus and prefrontal cortex of the mice revealed a number of changes, and not just in genes that were part of the hemizygous deletion. "One striking finding of our analysis was the divergence in the transcriptional responses in the prefrontal cortex and hippocampus of the mutant mice, which suggests that different pathways (energy metabolism versus synaptic transmission) may be affected or activated (as
compensations) in these two brain regions," Gogos told SRF.

In particular, the researchers noticed alterations in levels of microRNA-related transcripts. The researchers reasoned that upregulation of these transcripts might be due to the deletion of the \textit{Dgcr8} gene, the product of which is involved in processing of pre-microRNAs to their mature microRNAs. To test this idea, they directly measured levels of pre-microRNAs in hippocampus and PFC, and found that several were indeed elevated. A comprehensive analysis of 386 mature miRNAs revealed 30 that were downregulated in hippocampus, and 59 in prefrontal cortex.

In support of the idea that downregulation of a subset of miRNAs stemmed from loss of \textit{Dgcr8}, the researchers found similar changes in a \textit{Dgcr8} heterozygous knockout mouse. When that mouse was tested for behavioral and cognitive changes, it replicated some but not all of the deficits observed in the deletion mouse, including the paired pulse inhibition defect and a deficit in spatial working memory in a T maze. Thus, loss of \textit{Dgcr8} explains part of the mouse deletion phenotype, consistent with the idea that different genes in the region make individual contributions to the overall phenotype.

The researchers also looked at the effect of the genetic manipulations on neuronal morphology. In the 22q11 deletion model, they found a reduction in dendritic spine density and width in hippocampal neurons, as well as alterations in dendritic complexity. The authors note unpublished data showing that deficiency of another gene in the deletion, \textit{Zdhhc8}, affects dendritic structure and complexity. However, \textit{Dgcr8} also had some impact, with the knockout mice revealing decreased dendritic spine width and dendritic complexity. The latter, found in both the \textit{Dgcr8} and \textit{Zdhhc8} models, as well as the full deletion model, may signal a developmental effect, the authors note. (Interestingly, the first report of a postmortem study of neuropathology of three patients with 22q11 deletion syndrome and schizophrenia reveals evidence for neuronal migration defects in one patient and vascular abnormalities in two others, suggesting both developmental and ongoing processes may play a role in this syndrome. That work, published online in Cerebral Cortex on May 14, comes from Anne Bassett and colleagues at the University of Toronto in Ontario, Canada.)

The 22q11 deletion phenotype in humans is highly variable and clearly involves multiple interacting genes. The new data implicating miRNAs, each of which controls multiple target genes in the brain, adds yet another layer of complexity to the story. At the same time, understanding whether and which miRNAs are affected in people with the 22a11 deletion syndrome and/or schizophrenia could offer a new path to discovery of an additional set of genes, the changing expression of which may contribute to disease.

...and men

The second study focuses on other genes in the 22q11 region that have been tied in one way or another to schizophrenia. In mice, hemizygous deletion of two adjacent 22q11 genes, those for the transcription factor \textit{Tbx1} and the G-protein b-subunit-like \textit{Gnb1L}, causes defects in prepulse inhibition, leading Williams and colleagues to look into a possible genetic link between human \textit{TBX1} and \textit{GNB1L} alleles and schizophrenia. By single nucleotide polymorphism (SNP) association studies, he and his colleagues identified a psychosis-associated marker. The association, held up in three different case-control studies, but only for males. A fourth study, a parent-proband study, showed allelic association but not at that marker. The most significant SNPs were also associated with psychosis in males in a sample of 22q11 deletion syndrome patients. Full sequencing of the \textit{TBX1} and \textit{GNB1L} exons showed no changes that could account for the allelic linkage, but the psychosis-related alleles were associated with changes in \textit{GNB1L} expression, but not TBX1 in human postmortem tissue. The authors conclude that the data...
provide significant evidence for association between schizophrenia and *GNB1L* genotype, and that abnormal gene expression could be a possible mechanism. However, that is not the only possible explanation for their data, and more work will be needed to sort out effects of the alleles on disease.—Pat McCaffrey.

**References:**


**Comments on News and Primary Papers**

**Comment by: Linda Brzustowicz**
Submitted 21 May 2008               Posted 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

Comments on Related News

Related News: Chromosome 22 Link to Schizophrenia Strengthened

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

Posted 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.

Related News: Chromosome 22 Link to Schizophrenia Strengthened

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

Related News: Chromosome 22 Link to Schizophrenia Strengthened

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

Related News: Chromosome 22 Link to Schizophrenia Strengthened

Comment by: Anne Bassett
Submitted 7 November 2005
☑️ 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-hemizygosity 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

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

Comment by: Doron Gothelf
Submitted 27 October 2008
Posted 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


http://www.schizophreniaforum.org/new/detailprint.asp?id=1436


View all comments by Doron Gothelf

Print this page