NEWS

Rare, spontaneous mutations rife in schizophrenia cases

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5 JUNE 2008

Rare, spontaneous mutations could account for at least ten percent of cases of schizophrenia, according a study published online last week[1].

These mutations are deletions or duplications of DNA segments, dubbed copy number variations (CNVs).

Although submicroscopic in stature, CNVs have for the past two years been implicated in neurological disorders such as **autism and schizophrenia** in one high-profile publication after another.

Since discovering a schizophrenia-related deletion in chromosome 22q11 more than a decade ago[2], **Maria Karayiorgou**, professor of psychiatry at Columbia University Medical Center, suspected other CNVs could also play a role in schizophrenia, but detecting them was tricky.

"It was not until very recently that we had the technology to actually look genome-wide for such variants," she says. Methods using microarrays can now detect CNVs as small as 30 kilobases.

In the new study, Karayiorgou and her colleagues tracked *de novo* CNVs: those that are not found in unaffected parents, but instead occur spontaneously in the children.

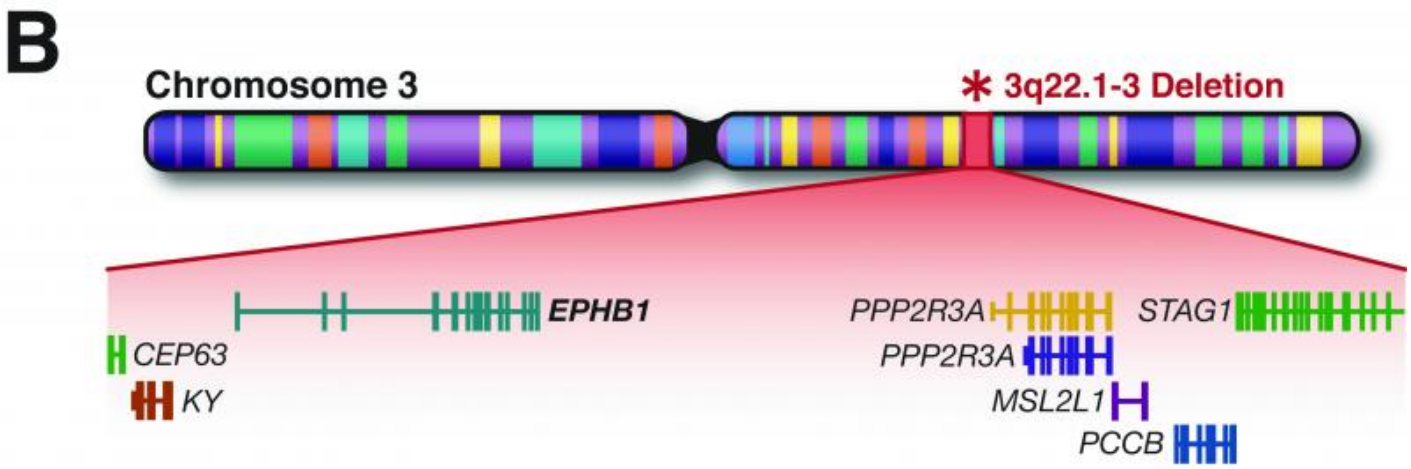
They found 17 such CNVs, and say that together, these CNVs could account for at least ten percent of sporadic cases of schizophrenia, which strike a family with no prior history of the disorder.

"The *de novo* just brings you so much closer to establishing causality to the disease," says Karayiorgou.

The *de novo* CNVs are specific to sporadic schizophrenia, appearing eight times more frequently in sporadic cases than in controls. No *de novo* CNVs turned up in familial cases of schizophrenia.

Of the 17 CNVs identified, 3 are deletions in chromosome 22q11, which Karayiorgou had previously linked to schizophrenia. Each of the rest is found in only one study participant. This heterogeneity is "a bit of an eye opener," Karayiorgou says.

Numbers game:



Of 19 copy number variations identified, 3 are deletions in chromosome 22q11.

Fine focus: Of 19 copy number variations identified, 3 are deletions in chromosome 22q11.

A study published in April also found that rare CNVs occur more frequently in individuals with schizophrenia than in controls, and that virtually each CNV is different[3].

Connecting such rare genetic events to the disorder is a numbers game.

"All of this information is not causal, it's statistical," says **Rita Cantor**, professor of human genetics

at the University of California, Los Angeles, who was not involved in either study.

"If something is rare," Cantor says, "it's hard to detect an effect or an association unless you have many rare events, and that's what both of these papers are built upon ? many rare events."

Genes implicated in both studies appear to be involved in signaling pathways that control development of the brain. Despite different designs and populations in the studies, their similar findings support a role for CNVs in schizophrenia.

"We are delighted to see our hypothesis validated by independent researchers, in a completely independent series of patients," says **Jon McClellan**, associate professor of psychiatry at the University of Washington, a researcher on the second study.

The distinction between sporadic and familial cases of schizophrenia also echoes **findings in autism** published last year. That study found a higher incidence of *de novo* CNVs in simplex families ? in which only one child has autism but siblings and parents are unaffected ? than in multiplex cases or controls[4].

Large databases of samples from simplex families, such as the **Simons Simplex Collection**, could turn up even more *de novo* CNVs associated with autism, says Cantor.

Schizophrenia and autism share similar CNVs, for instance affecting the neurexin 1 gene and **chromosome 16p11**, suggesting that the two disorders could stem from different variations of the same genes.

References:

1. Xu B. *et al. Nat. Gen.* Epub ahead of print (2008) **PubMed ?**
2. Karayiorgou M. *et al. Proc. Natl. Acad. Sci. USA* **92**, 7612-7616 (1995) **PubMed ?**
3. Walsh T. *et al. Science* **320**, 539-543 (2008) **PubMed ?**
4.

Sebat J. *et al. Science* **316**, 445-449 (2007) **PubMed ?**