

Interview

A Rare Find

Discovering rare variation associated with schizophrenia.

INTRODUCTION

Sven Cichon, Ph.D., Professor of Genomic Imaging at the Research Center Juelich and at the Institute of Human Genetics, Department of Genomics (Life & Brain Center), University of Bonn, is trying to find the genetic variation underlying common neuropsychiatric disorders such as schizophrenia, bipolar disorder, depression, and alcoholism. Recent genome-wide association studies (GWAS) in schizophrenia have led to major breakthroughs. There is now molecular evidence that both common risk alleles of small effect as well as rare alleles of moderate to large effect contribute to the heritability of this psychiatric condition.

Together with his colleagues Markus Nöthen (U Bonn) and Marcella Rietschel (CIMH Mannheim), Cichon is involved in a large European consortium on schizophrenia genetics (SGENE) which has uncovered rare structural risk variants that play a role in some schizophrenia patients. Their findings were enabled using Illumina's Infinium® HD BeadChips.

i. Why did you decide to pursue genome-wide association studies (GWAS) to investigate neuropsychiatric disorders?

SC: In our community, researchers have tried to find disease-associated genetic variants using candidate gene approaches for a long time. There were some promising results, but none of them were undisputed in the field because of the lack of consistent replications. As an alternative strategy, we started to use genome-wide associa-

tion studies (GWAS) which allow a broad, systematic search for genetic risk variants across the entire genome.

In the larger research community, successes in other complex diseases, such as type 2 diabetes, suggested that the genetic risks conferred by common variants are often significantly smaller than previously estimated (for example, odds ratios of 1-1 or less for type 2 diabetes). With these insights, researchers in our field began to form large consortia [such as the SGENE consortium to study schizophrenia or the Psychiatric Genetics Consortium (PGC) to study several neuropsychiatric phenotypes] to meet the sample size requirements necessary to detect small genetic effects reliably.

By taking the GWAS approach, we are finally beginning to identify the first genes involved in psychiatric conditions, which has been very exciting. At the same time, we constantly increase the knowledge about the genetic architecture of these diseases. The genetic risk factors identified to date explain only a fraction of the overall heritability. It is possible that many more common variants of very small effect exist. The sum of rare variants may also contribute substantially, as well as strong effects of combinations of genetic risk factors (gene-gene interaction). So there is still a lot to discover before we can claim that we understand the genetics of psychiatric disorders.



Dr. Sven Cichon is currently Professor of Genomic Imaging at the Research Center Juelich and at the Institute of Human Genetics, Life & Brain Center at the University of Bonn

i: You used Illumina's Infinium HD BeadChips for your studies. What types of variation were you able to find, and were the results surprising?

SC: The type of genetic variation we expected to find contributing to neuropsychiatric disorders was variation at the single nucleotide level. What was more of a surprise was discovering the presence of rare copy number variants associated with schizophrenia¹. In the SGENE consortium, we followed up on a hypothesis that rare variants of large genetic effect may account for a fraction of the genetic risk in schizophrenia.

What we discovered using Illumina's HumanHap300 and HumanHap550 BeadChip signal intensity data were rare copy number variants (CNVs) on chromosomes 1 and 15 that repeatedly occur *de novo* and are likely to be under negative selection pressure. To date, they are the strongest genetic risk factors known for schizophrenia (odds ratios of 10–15). It was quite exciting to find molecular evidence for a hypothesis that was first proposed several decades ago based on epidemiological data.

At the moment, it looks like there is a mutation spectrum with common disease variants and rare disease variants that contributes to the development of schizophrenia.

i: What impact does data quality has on your work?

SC: We are really happy with the performance of Illumina's Infinium HD BeadChips. Although they were initially designed to monitor common SNP variants, they can also be used to detect common and rare CNVs. We can study single nucleotide and structural variation with one array and the data quality is outstanding.

With GWAS you're performing many statistical tests. A certain proportion of these tests is expected to produce statisti-

cally significant results just by chance (and has nothing to do with disease association). This is an inherent problem in our research field and we've accounted for it by rigid correction methods for multiple testing combined with replication in independent data sets.

The problem becomes more pronounced if you have a genotyping platform that does not work optimally, because then you get additional association signals from technical problems. It has been shown that minimal genotyping errors, even if the error rate is a little bit elevated, can produce a number of false positives. We believe that's not a problem with the Illumina platform. From the technical point of view we can truly rely on the data, and that's an important step. We think we don't have many technical artifacts, if any.

Because the data quality is good, we spend less time analyzing the data, which allows us to use our time efficiently and spend more time on more exciting things.

i: Illumina BeadChips allow you to study common SNPs and CNVs. In the future, are you interested in incorporating information from rare SNPs into your studies?

SC: We have been pleased with Illumina's current genotyping arrays and how they've enabled us to study both common SNPs and CNVs. We are thrilled to see that as a part of its 2010 GWAS product roadmap Illumina will be incorporating rare variants identified by the 1000 Genomes Project into its new line of OmniExpress BeadChips. Association studies with these new arrays could further elucidate the role of rare variants (at the single-base level) in neuropsychiatric disorders.

REFERENCES

1. Stefansson H, Rujescu D, Cichon S, Pietiläinen OP, Ingason A, et al. (2008) "Large recurrent microdeletions associated with schizophrenia." *Nature* 11:455 (7210): 178-179.

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ADDITIONAL INFORMATION

To learn more about Illumina's DNA analysis solutions, please visit www.illumina.com/DNA.

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Pub. No. 070-2010-004 Current as of 02 March 2010

