GENETICS

COMMON DISEASE + COMMON VARIANT = COMMON MISUNDERSTANDING?

12.08.2008

Three large studies on schizophrenia now all agree that rare structural variants (CNVs) have a causal role in disease causation – probably by affecting large regions at 1q21 and 15q11 that contain all some "neuro"-genes (Harvard, Decode, Seattle). There are two major points that let me wonder if these papers even mark a turning point in our understanding of genetic causes of human diseases that is largely influenced by the Chakravarti hypothesis of common disease and common variants (CDVC). The Seattle paper had the most clever comment on that

> We propose an alternative model: that some mutations predisposing to schizophrenia are highly penetrant, individually rare, and of recent origin, even specific to single cases or families.

So after arguing many years against the CDCV hypothesis there seems to be some light at the end of the tunnel. It has not escaped our attention that

> Controls had on average 0.99 CNVs whereas cases showed a 1.15-fold higher rate.

Rare CNVs are already frequent in controls (that may have other diseases as well) – so there is a good chance that this not phenomenon observed in schizophrenia cases alone. Second, as CNV counts are based on rather low coverage SNP panels (~5% of all available SNPs), there is some good chance for even many more microdels known so far

> We mined the existing 13 million end sequences34 and identified 4.0 million non-redundant single nucleotide variants and 796,273 smaller insertion/deletion events (more than 1 bp to less than 100 bp in length).

Yea, yea.