GENETICS

# MISSING HERITABILITY

12.06.2019

It is always nice if you are being cited after some years ;-)
There is an important article that I have been reading this morning "Missing heritability of complex diseases: case solved?" Emmanuelle Génin is correct by questioning the statistical models underlying our heritability measures.

It is therefore possible to directly quantify the contribution of these genetic variants to phenotypic variance and measure what is called "genomic heritability". Briefly, the idea is to infer the proportion of variance that can be explained by a linear regression on a set of markers used as explanatory variables.

This genomic heritability seems to be in fact a poor mathematical representation of a biological trait. >1000 hits in >500.000 individuals, does that make any sense at all in terms of biology?

More recently, it was proposed that rather than polygenic, the genetic architecture of common diseases could in fact be "omnigenic" with mainly all active genes affecting every complex traits.

which is fatalistic but justified IMHO. But there could be solutions. We proposed undetected rare variants

When adding these rare and low-frequency variants to the common variants associated with height, 27.4% of the variation can be explained.

while the results are not impressive. We proposed also structural variants (CNVs), but again no convincing effect so far. Allele dosage? Disappointing . GxE, interaction with genome background? Difficult, highly complex. Epigenetic environmental influences ? Sure but where to start?

The "GIGO (Garbage-In Garbage-Out) syndrome in genetics" as coined by Emmanuelle Génin is one of the main reasons why I mostly dropped out of the field.

We believe that the “missing heritability problem” is an ill-posed problem. Solving it by refining over and over again statistical models derived under the “polygenic paradigm” or using more and more sophisticated sequencing machines will not answer the fundamental and biological question of why that individual is affected by the disease and that other individual is not.

My last sentence would be: Phenotypic correlations between relatives determine heritability. So we should go back to family studies if we want to explain heritability.