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Nature

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Dear Editor-in-Chief,

Please find enclosed the manuscript “Informative missing genotypes: hopes for the craving revolution of genome-wide risk models”, which we would like to be considered for publication in Nature.

We started this work in 2004 with the main aim of find out a sound method to build predictive models of individual risk to complex diseases, based on genome-wide data sets. After 13 years of a very hard work we have had very little success, as it has occurred to other labs that have approached the same goal and have also obtained predictive rates much lower than they should be, according to heritability and disease prevalence. However, we have obtained, by pure chance, results that may open hopes to this challenging goal. In fact we have found the clue of this generalized lack of success may be in the genotyping algorithms used. We have observed that, in the two diseases we could analyze, both autoinmune ones, that use Affymetrix technology, there is a very sound informative missing pattern favouring missingness in affected individuals. With other technologies this pattern does not appear. We claim current genotyping algorithms either bias genotyping favoring wild alleles, or just fail more often when calling the minor alleles. We show this informative missing pattern may explain the whole lack of predictive accuracy.

But what it is, in our modest opinion, much more important to a broader public, is the way we obtained these results and decided to finish this work and submit it, instead of just giving up at light of these, at first glance, bad results. The first author, aimed by a priest, Prof. P. Ildefonso Camacho SJ, she really trusted and who insisted in the need to publish this work when she was only able to look at it as a big defeat, started writing a research notebook. She decided to do that because she really wanted to pleasure him but she was unable to write any result at all. Therefore she decided to start telling the story of the work and the relationship her personal life as a way to get some strength and having hopes that meanwhile a good result could arise. She tells in the notebook the relationship she has discovered between this work and her spiritual life. She was an agnostic when she started this work and went through a strong conversion after a serious breast cancer. Once she has accepted no good results good arise other than the detection of the informative pattern in missing genotypes, she has understood perhaps that, what it is interesting in this research, is the research notebook itself, as a way to claim that science, even experimental, exact or technological science, is never conducted by a cold rational mind, as a matter of unaffected, untouched positivist science but instead is conducted by very deep soul movements and wishes and that perhaps is time to change the way to publish research results. The current procedure consists on first to carry out a research work and later to write how that work was conducted and its results. In theory we should describe the steps done but we usually omit several experiments that turn out to be failures and just tell positive results. We propose to use and publish a research notebook as a way to be closer to the real way the research is conducted. We could use a blog and give its web page reference in the final paper, but this time I just wrote the research notebook with the strong decision of never change something written before, except for grammar and typographical errors.

Thank you very much for your consideration,

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