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Reply to Herlihy and Halliday

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We thank the authors for their comments on our paper. They query as to why we do not mention paternal age as a possible explanation for the increase in prevalence of Klinefelters compared to XYY and XXX. We agree that it may be a partial explanation, but we do not believe that there is a substantial body of evidence of an association of paternal age with the birth of a child with Klinefelters. Of the five studies referenced in a recent meta-analysis, only one study found a significant positive association between paternal age and Klinefelters.[1]

The authors were correct in the assumption that we did not reference the study by Bojesen *et al*,[2] because it did not give the corresponding numbers of XYY and XXX diagnoses and the basis of our paper was to compare the prevalences of the three sex chromosome trisomies. The study by Bojesen *et al* covers the time period from 1970 to 2000 and they estimate a prenatal prevalence of 2.1 per 1000 (not specifying what proportion of diagnoses are from CVS or from amniocentesis), which compares to the data in our paper of 3.1 per 1000 observed in an amniocentesis series in women over age 35 from 1976–1981. It is difficult to directly compare these two figures as Klinefelters is associated with maternal age and has a fairly high fetal loss rate, so the gestational age at diagnosis is important.

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Hypotheses in genome-wide association scans

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Dear editor,

With great interest we have read your commentary on genome-wide association studies (GWAS), published in the January 2008 issue of this journal.[1] In view of the recent interest in GWAS and the consequent impact on the side of both publishers and funding bodies, however, we think that some of the points raised in your buoyant contribution are worth further reflection.

Contrary to the view expressed in your commentary, GWAS do need an *a priori* hypothesis about the pathology of the disease under study, namely, that at least one causative genetic variant is statistically associated with at least one of the markers used. In fact, this is the *conditio sine qua non* of any GWAS. As good Popperians, we then hope for the GWAS to falsify the corresponding null hypothesis, that is, the complement of the above supposition. With linkage analysis (or 'positional cloning'), the situation is slightly different. There, physical proximity becomes the primary factor, rather than statistical correlation, so that the falsehood of the null hypothesis becomes a truism for virtually all marker panels currently used for genome-wide linkage analysis in humans.

In our view, understanding Popper's philosophy mainly as a strategy to optimize the unravelling of new truths is a gross misinterpretation. A cornerstone of his philosophy has been that scientific knowledge can only be achieved through falsification. If genetic epidemiologists feel that positive GWAS results still require 'replication', this is because they (rightly) regard the ensuing null hypotheses as falsifiable, and therefore 'scientific', claims in the sense of Popper.

Even with the impressive coverage provided by today's genotyping technologies, GWAS do not come anywhere near 'collecting all data required'.[1] This is true, not only for rare genetic variation, but also for much of the common genetic variation in populations of non-European extraction.

Finally, 'thoroughly assessing [the] irrelevance' of putative genetic risk factors[1] requires adequate data to be able to do so. Consideration of candidate genes becomes prohi-

bitive, however, if scientists are systematically doomed to drown in a sea of false-positive results before reaching the shore of genuine effects. Many causative genetic variants of moderate effect will inevitably have to be discarded by GWAS due to insufficient sample sizes. This has already become evident by the strength of successfully replicated disease associations which, for most published GWAS, were at the limit of what these studies were powered to detect. The need for qualified hypothesis generation does not vanish with a growing wealth of data! With realistic sample sizes, it will be hampered instead by the multiple-testing problem. In other words, most GWAS will not substantially reduce ignorance; they will make it recur faster.

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Reply to Nothnagel *et al*

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Thank you for your comments most of which are quite well understood in the GWAS community. I would gladly confess that I understated Poppers' conceptual framework of hypothesis-driven research for the sake of being a bit provocative. Indeed, several readers have pointed out that the idea of 'always finding what you are looking for, by studying all data and discarding data only after assessing their relevance … ' is a hypothesis *per se*. That is probably true, and then, after all, we are all doing hypothesis-based research.

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