European Journal of Human Genetics (2008) 16, 1173–1175

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LETTER

# Is paternal age playing a role in the changing prevalence of Klinefelter syndrome?

*European Journal of Human Genetics* (2008) **16,** 1173–1174; doi:10.1038/ejhg.2008.96; published online 21 May 2008

We were very interested to read the recent article published by Morris *et al*[1] suggesting that the prevalence of Klinefelter syndrome (KS), XXY, may be increasing. We are currently carrying out analyses using routinely collected data in Victoria to ascertain an estimate of XXY prevalence in Australia. Studies like these highlight the value in systematic collection of various types of information for public health purposes. Certainly, preliminary analysis of our more recent data (unpublished) suggests a higher prenatal prevalence than has been previously indicated in prenatal studies extending back to 1970.[2]

By separating the earlier and later newborn chromosome surveys, Morris *et al* showed a difference in prevalence of XXY between the two time periods. However, although all three sex trisomies were seen at similar frequencies in the earlier surveys, neither the prevalence of XYY nor XXX changed in the later surveys. The observed increase in the frequency of XXY was supported by data series of prenatal diagnoses, spontaneous abortions and perinatal deaths.

On the basis of this finding, the authors hypothesise that the increase in frequency of XXY is due to an increase in non-disjunction at paternal meiosis I, and that this may be caused by the same factors that have been attributed to the falling sperm counts in men. Such factors may include prenatal exposure to environmental chemicals or perinatal exposure to known environmental xeno-oestrogens.[3]

The effect of maternal age on KS is well established but would cause a similar increase in the frequency of XXX, which was not seen by Morris *et al*. However, the authors do not mention paternal age effect as a possible explanation, or at least contributing factor, for the increase in the frequency of XXY conceptions. Increasing paternal age trends in Australia are similar to those seen in the United Kingdom, with the average age of fathers of live births reaching an all time high of 33.1 years in 2006 years, and the number of men in their 50s having children up by around 20% in the last decade.[4]

The effect of paternal age on recombination frequency (reduced in XY disomic sperm) and non-disjunction is a controversial area, with not all study findings supporting a relationship, yet there remains a substantial body of evidence that indicates an association between paternal age and the birth of a child with KS.[5] If the increased frequency of XXY that has been observed is due to a paternal age effect acting only at meiosis I, this would explain the lack of corresponding increases in frequencies of XYY and XXX.

Finally, we are curious about the lack of reference to the comprehensive study of Bojesen *et al*[2] in 2003 that utilised the extensive prenatal and postnatal diagnoses Danish databases, and covers a considerable time period. We presume that this was excluded because it only considered karyotypes associated with KS and not the other two sex chromosome trisomies. However, in our organisation, we use this publication as our benchmark for KS prevalence, and would be interested to hear the perspective of Morris *et al* on how this study compares to theirs in regards to the prevalence of KS.

Above all else, the possible increasing frequency of XXY only further highlights the need for increased awareness and detection of males with the condition at an age and stage of development most appropriate for treatment and intervention. The best time to be diagnosed has yet to be determined and there remains a lack of research on the psychosocial impacts of having KS, and how quality of life and life outcomes might be affected by age of diagnosis. If this condition is truly becoming even more common, it is vital that we identify the needs of this group of males.

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# Reply to Herlihy and Halliday

*European Journal of Human Genetics* (2008) **16,** 1174; doi:10.1038/ejhg.2008.99; published online 21 May 2008

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

*European Journal of Human Genetics* (2008) **16,** 1174–1175; doi:10.1038/ejhg.2008.97; published online 14 May 2008

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-