Response to Prakash et al.

To the Editor:

We thank Prakash et al.¹ for their letter and for raising these important points. As they state, 45,X/46,XX mosaicism is common in the Turner syndrome clinic and we acknowledge that phenotypic predictions on the basis of karyotype are extremely important to families and clinicians, yet are limited by current knowledge.

The morbidity and mortality associated with undiagnosed or minimally investigated Turner syndrome mosaics is obviously of paramount importance. We agree that our data does not yet justify an immediate change in clinical management, or deviation from established clinical protocols that aim to reduce risk to patients with Turner syndrome, particularly with respect to cardiovascular complications.

Our paper was an attempt to describe this mosaic chromosomal finding within the background community to add to information available regarding phenotypic variability.² We are aware from our own experience that coincidentally ascertained mosaic cases may well be a different cohort to those ascertained on the basis of a suggestive phenotype. This phenomenon of phenotypic widening, specifically the identification of milder cases that may overlap more with healthy subjects than with historically described cases, as genetic testing becomes more widespread, is well recognized in a range of chromosomal and genetic disorders; just considering sex chromosome aneuploidy examples, prenatally detected cases of triple X and 45,X/46,XX mosaicism, especially when identified as an incidental finding on chorionic villus sampling (CVS) tests performed for maternal age, are often less affected than those cases detected following chromosomal analyses performed in childhood when tests often follow developmental or medical concerns.^{3, 4}

Individuals in UK Biobank were not recruited because of particular clinical features and thus provide an opportunity to inform clinicians presented with a patient with aneuploidy, revealed as an incidental finding. We are not aware of other studies on this scale that have investigated women without clinical ascertainment bias. It was not our intention to imply that *all* individuals with 45,X mosaicism were phenotypically normal; neither did we wish to imply that such patients would not require follow-up. Although full phenotypic data of these mosaic individuals is not available, height was reliably recorded. Our data included several individuals who were around 175 cm tall with 50% mosaic 45,X/46,XX in their blood, which indicates that any effect on height is not fully penetrant in these women. On the basis of height these women would not be suspected as having Turner syndrome

and yet the genetic analysis would classify them as having the condition.

Overall we did find a small difference in height in the women with mosaic 45,X/46,XX compared with controls, which might indicate additional underlying anomalies, not recorded in the Biobank, in a proportion of these mosaic women: a full clinical examination was not carried out, and in particular echocardiograms were not performed/available for all these patients; however, participants did have significant phenotypic information available, including self-reported conditions, hospital records, and blood pressure, arterial stiffness, and anthropometric measurements recorded at a clinical assessment appointment. Primary amenorrhea was not specifically recorded, but age of menarche was; whilst a simple recording of age does not provide information about induction of puberty, it is interesting that more than half of the women with apparently full 45,X frequently answered this question with “don’t know” or “prefer not to answer” (16/30 cases), compared with only 9 of the 186 women with mosaic 45,X/46,XX answering in this way and over 95% of mosaic cases giving a specific age. This percentage was not different from the 98.3% of 46,XX women who gave a specific age. This lack of a difference in answering a simple question about menarche between 45,X/46,XX and 46,XX women would suggest that primary amenorrhea was not a common feature in the mosaic 45,X/46,XX women.

We fully acknowledge that the UK Biobank does not represent the entire population. The study required individuals to be over the age of 40 and others have reported it favors healthy individuals and we reiterated this point in our paper.⁵ This ascertainment bias does mean that the incidence of severe congenital heart disease or cardiovascular disease may be underestimated. Furthermore, any women or children who died before the age of 40 years old would not be represented. There are however cases of dissection of the aorta in UK Biobank and any individuals who have died since recruitment will have cause of death through linkage to the National Death Registry. There was no “screening out” of any particular disease or conditions in UK Biobank, and having a pre-existing condition did not preclude inclusion into the study.

We also acknowledge that the level of mosaicism is likely to vary between tissues and may have an impact on phenotypic severity. Interestingly, there is some evidence in fact that all 45,X pregnancies that survive to term and livebirth are in fact mosaics;⁶ however, unfortunately we were not able to assess this as the UK Biobank only has DNA available from peripheral blood samples.

The UK Biobank has given us the opportunity to study X chromosome aneuploidy in large numbers of older women not ascertained in the clinic for the first time. As women with

X chromosome mosaicism are followed up longitudinally, causes of death will further inform the phenotype/genotype relationship. We identified women who appear unaware that they have this genetic finding, many of whom were not short and had several pregnancies. We believe that our findings extend the phenotypic spectrum of 45,X/46,XX mosaicism, and fully support the need for a more systematic genotype/phenotype study to inform any guideline review relating to future management of this group.

DISCLOSURE

The authors declare no conflicts of interest.

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