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45,X mosaicism in a population-based biobank: implications for Turner syndrome

To the Editor

One of the more common questions asked by providers, parents, and patients with Turner syndrome (TS) concerns the clinical significance of mosaicism. More than half of individuals who are diagnosed with TS have detectable mosaicism of their peripheral blood karyotypes, but the impact of mosaicism on TS-related cardiovascular, endocrine, autoimmune, and reproductive phenotypes is incompletely understood. Specifically, there is no evidence that testing additional tissues to identify "hidden" mosaicism is useful, and the lowest level of mosaicism that may cause disease remains uncertain. Because of these unresolved questions, there is no clear guidance on the appropriate type, frequency, or intensity of surveillance for mosaic individuals. An attempted analysis of the relevant evidence in the 2017 international guidelines was inconclusive, because the current data is based on a small number of studies of variable design.[1] Tuke et al. identified 326 individuals between ages 40 and 69 with altered X chromosome dosage in 244,000 peripheral blood microarray genotypes from the UK Biobank.[2] After analyzing the relationship between X chromosome mosaicism and available phenotypic data, they concluded that adult women with 45,X/46,XX mosaicism require "minimal" clinical management due to the few reported complications and paucity of stigmata related to TS.

While we agree that genotypic analysis of population-based cohorts can generate important new insights into genetic disorders, we believe that the authors' conclusions cannot be generalized to all individuals with mosaic X chromosome genotypes. For example, this study did not include infants, children, adolescents, or young adults, who may manifest the most serious TS-related complications, such as aortic dissection, and other congenital disorders predisposing to cardiovascular death. The mean age when TS patients experience an aortic dissection is 30–35 years. In addition, the limited UK Biobank data set did not include consistent data on diagnoses that are highly relevant to TS, such as primary amenorrhea, or cardiovascular phenotypes including bicuspid aortic valve, coarctation, and coronary artery disease, which are primary drivers of the markedly increased rate of cardiovascular mortality in TS women. Many of these conditions are asymptomatic while continuing to pose lifetime risks for sudden or premature death. Additional phenotyping and long-term follow up of mosaic TS individuals will be essential to determine if X chromosome aneuploidy is associated with adverse outcomes.

As the authors acknowledge, a substantial bias exists in the UK Biobank enrollment to "favor healthy individuals." Therefore, mosaic patients with pre-existing health conditions related to TS could have been systematically screened out of the data set. Because patients with TS and low-level mosaicism frequently lack the typical features of TS, they are also less likely to have been screened for TS-related conditions, many of which may be asymptomatic. Both of these factors tend to generate an unrealistically robust snapshot of mosaic patients in UK Biobank data. Moreover, a substantial proportion of the analysis relies on self-reported data or ICD-10 diagnostic codes from inpatient records. These are notoriously unreliable for documentation of chronic disorders such as hypertension. The significant height difference between mosaic and control groups indicates that the impact of mosaicism is not subtle and is more likely to cause additional undetected pathology that merits investigation. The small sample of 45,X individuals in this study not only limits the utility of comparisons between 45,X and 45,X/46,XX individuals, but also minimizes the substantial phenotypic variation that is apparent in larger cohorts of 45,X individuals, who may be mildly affected and indistinguishable from age-matched mosaic counterparts.[3,4] Tissue-specific mosaicism is common in TS and has been implicated as an important modifier of phenotypic severity.[5,6] In larger cohorts, the overlap between 45,X and mosaic individuals is more apparent, undermining the argument that peripheral blood genotypes are entirely responsible for differences between the two groups.[7,8] However, we do acknowledge that inclusion of individuals with less than 20% mosaicism in the 45,X group tends to mitigate the confounding effects of unmeasured mosaicism.

This study does not address significant questions about the potential impact of somatic mosaicism and also generalizes conclusions about clinical management of individuals with mosaic 45,X/46,XX genotypes that are not warranted by limited observations. The net effect may be to discourage future research on mosaicism in TS, when evidence-based guidance for the management of this important and increasingly recognized subgroup of patients is urgently needed.

DISCLOSURE

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