of the autosomal genome in ROH exceeding a specified size—using a fixed threshold of 2–5 Mb, the computation can be performed using, as the threshold, the boundary size separating class C ROH from shorter ROH in classes A and B. This boundary size varies across populations, typically in a range from 0.9 to 2.2 Mb.[3] Therefore, we suggest that use of a population-specific threshold obtained from a systematic calculation will be more informative for inference of parental relatedness than the use of a shared predetermined threshold applied equally in all populations. For 64 worldwide groups, Supplementary Table S1 online of Pemberton et al.[3] provides such population-specific thresholds. Genetic estimation of ancestry will be informative for guiding threshold choices in analyzing a particular genome.

Third, although Rehder et al.[1] frame the identification of ROH in terms of detection of "absence of heterozygosity," genotyping errors or mutations can place one or a few heterozygous sites inside a long segment that otherwise has been inherited identically by descent. Because complete absence of heterozygosity can be too stringent a condition for ROH identification, current methods accommodate a small number of heterozygous sites within a largely homozygous region by reducing the chance that the segment is identified as an ROH but not eliminating the region from consideration entirely.[3] A perspective of positive identification of ROH, probabilistically allowing for occasional heterozygotes, enables a sensitive data-driven approach to detecting autozygosity.[3]

Because even without consanguinity, distributions of baseline autozygosity levels vary considerably across individuals and populations, for definitive evaluation of parental relatedness, it will continue to be advisable to test additional family members. However, taking into account population variation, ROH size classes, and occasional heterozygous sites in ROH can aid in reducing the potential for errors in the initial determination of a close parental relationship on the basis of a single genomic test.

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DISCLOSURE

The authors declare no conflict of interest.

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Response to Rosenberg et al.

To the Editor: We appreciate the comments of Rosenberg et al. in their letter, "Runs of Homozygosity and Parental Relatedness,"[1] as they provide important points regarding the complex origins of runs of homozygosity. We agree that the percentage of the genome consisting of homozygous segments varies across different ethnic populations and that the best estimates of parental relatedness would take this background contribution (both percentage of the genome and size of the homozygous segments) into account; however, this is probably impractical for most clinical laboratories, which frequently receive limited demographic information. The comments by the authors further highlight the complexity of these assessments and reinforce our recommendation that genomic testing that can detect runs of homozygosity should never be used to definitively assign a specific relationship between the parents of a proband.

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