radiological findings indicate disease that is currently present, whereas incidental genomic findings indicate disease that may some day be present. In fact, some of the radiological incidental findings do not diagnose disease; some are false positives that could lead to unnecessary invasive procedures. The time to discuss such incidental findings in radiology is when the clinician receives the radiology report, and is able to interpret the report in light of the patient's clinical status, personality, and life experience. I posit that the same is true for genomic incidental findings, recognizing that the American College of Medical Genetics and Genomics recommendations apply to a very narrow list of highly penetrant, well-annotated, and medically actionable findings.

Townsend et al.[1] also raised the point that the working group did not seek input from consumers (patients). This possibility was considered, but it was difficult to know who actually speaks for the general public on this issue. We ultimately decided to begin the discussion with input from scientific and medical experts, realizing that the recommendations would serve as a reference point for many perspectives. Townsend et al.[1] suggest that the recommendations be withdrawn and revised. I do not believe that they should be withdrawn, but as we stated in the report, I anticipate that they will be refined and revised in response to additional input and evidence. I especially agree with them that further research on patient perspectives and decision making should be encouraged. The working group felt, however, that genome sequencing is here with us now and that some statement was needed to provide a guideline to laboratories and clinicians actively struggling with this question. I hope that the recommendations will come to be seen in that light.

DISCLOSURE

The author declares no conflict of interest.

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Runs of homozygosity and parental relatedness

To the Editor: Several reports have drawn attention to the possibility that incidental evidence of parental relatedness can be uncovered in an individual who undergoes genomic testing for other purposes, and a recent article, "American College of Medical Genetics and Genomics: Standards and Guidelines for Documenting Suspected Consanguinity as an Incidental Finding of Genomic Testing,"[1] provides guidelines to clinical laboratory professionals for cases in which this scenario occurs. We wish to discuss new findings on runs of homozygosity (ROH) that could improve upon these recommended guidelines, thereby reducing the occurrence of false-positive and false-negative suggestions of parental relatedness on the basis of genomic testing.

Rehder et al.[1] recommended that the proportion of an individual genome located in homozygous segments whose lengths exceed a fixed threshold of 2–5 Mb can be compared with textbook autozygosity levels to suggest the level of relationship for the sampled individual. As recognized by Rehder et al.[1] and noted in studies of ROH features,[2,3] production of ROH is affected by forces acting on multiple time scales, including not only recent parental relatedness but also parental relatedness within a population at a level generally too distant for the parents to know of the relationship ("background relatedness"), and chance pairing of ancient haplotypes that have been magnified in frequency by founder events and subsequent population expansions. Recent parental relatedness, background relatedness, and founder events contribute primarily to ROH with long, intermediate, and short sizes, respectively, and in this context, the choice by Rehder et al.[1] to only consider ROH longer than a fixed threshold is an effort to identify only those ROH arising from recent parental relatedness. In relation to other studies that focused on a 1.5-Mb threshold,[2] the 2- to 5-Mb threshold level suggested by Rehder et al.[1] is comparable but more stringent.

The approach of applying a fixed threshold uniformly to all individuals can be improved in at least three ways. First, we have found that because of differences in the contribution of the various population-genetic processes to ROH patterns, the proportion of the genome consisting of homozygous segments differs across populations.[3] As a result, the demarcation of homozygous segments that are sufficiently long that they probably arose from recent parental relatedness lies at different sizes in different groups. For example, Native Americans, at the far extreme of the ancient out-of-Africa migration, have elevated homozygosity owing to ancient founder effects, and therefore their threshold length for attributing homozygous segments to recent parental relatedness is higher than that of Africans, who carry fewer long ancient homozygous regions. In small or isolated populations, the threshold can be higher than that in larger populations because limited mate choice can lead to high baseline levels of homozygosity even in the absence of consanguinity.

Second, we have developed a method that seeks to explicitly account for the different processes giving rise to ROH, separating ROH into three categories that largely correspond to different underlying processes—short "class A" ROH due to pairing of ancient haplotypes, intermediate "class B" ROH due to background relatedness in a given population, and long "class C" ROH due to recent parental relatedness.[3] In place of the recommendation of Rehder et al.[1] to compute F_{ROH}—the proportion

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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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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