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ACMG ARTICLE

Interpretation and reporting of large regions of homozygosity and suspected consanguinity/uniparental disomy, 2021 revision: A technical standard of the American College of Medical Genetics and Genomics (ACMG)

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Disclaimer: This technical standard is designed primarily as an educational resource for clinical laboratory geneticists to help them provide quality clinical laboratory genetic services. Adherence to this technical standard is voluntary and does not necessarily assure a successful medical outcome. This technical standard should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same results. In determining the propriety of any specific procedure or test, clinical laboratory geneticists should apply their own professional judgment to the specific circumstances presented by the individual patient or specimen.

Clinical laboratory geneticists are encouraged to document in the patient's record the rationale for the use of a particular procedure or test, whether or not it is in conformance with this technical standard. They also are advised to take notice of the date any particular technical standard was adopted, and to consider other relevant medical and scientific information that becomes available after that date. It also would be prudent to consider whether intellectual property interests may restrict the performance of certain tests and other procedures.

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ABSTRACT

Genomic testing, including single-nucleotide variation (formerly single-nucleotide polymorphism)–based chromosomal microarray and exome and genome sequencing, can detect long regions of homozygosity (ROH) within the genome. Genomic testing can also detect possible uniparental disomy (UPD). Platforms that can detect ROH and possible UPD have matured since the initial American College of Medical Genetics and Genomics (ACMG) standard was published in 2013, and the detection of ROH and UPD by these platforms has shown utility in diagnosis of patients with genetic/genomic disorders. The presence of these segments, when distributed across multiple chromosomes, may indicate a familial relationship between the proband's parents. This technical standard describes the detection of possible consanguinity and UPD by genomic testing, as well as the factors confounding the inference of a specific parental relationship or UPD. Current bioethical and legal issues regarding detection and reporting of consanguinity are also discussed.

The Board of Directors of the American College of Medical Genetics and Genomics approved this technical standard on 27 September 2021.
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Introduction

Previous American College of Medical Genetics and Genomics (ACMG) standards addressed the documentation of suspected consanguinity as an incidental finding of genomic testing, when using single-nucleotide variation (formerly single-nucleotide polymorphism)–based chromosomal microarray (CMA) and exome or genome sequencing (ES/GS).[1] Those standards were developed to harmonize practices within the clinical genetics laboratory community when reporting regions of homozygosity (ROH) detected by CMA.[2] At present, the use of CMA and ES/GS for constitutional analysis of children and adults with developmental delay, intellectual disability, congenital anomalies, and neurobehavioral disorders, along with prenatal specimens, is a routine practice.[3-7] Because the detection of ROH is no longer considered an incidental finding, there is an increased need to address the bioethical, social, and legal ramifications of these findings. Standards for the field when reporting ROH consistent with uniparental disomy (UPD) are also addressed.[8] The updated standards presented here are designed to assist clinical laboratories in the management of CMA and ES/GS findings that suggest parental consanguinity or UPD, with an emphasis on detection and reporting results back to the ordering clinician. The standards are not intended to address CMA and ES/GS findings in neoplastic testing.

Methods

The workgroup tasked with this update comprised laboratory geneticists, clinical geneticists, genetic counselors, and a law professor trained in bioethics. This technical laboratory standard was informed by a targeted review of the literature and current guidelines. Resources consulted included PubMed and relevant ACMG guidelines. The workgroup members also used consensus expert opinion and empirical data to inform their recommendations. Conflicts of interest for workgroup members were reviewed per ACMG policy and are listed at the end of the paper. The ACMG Laboratory Quality Assurance Committee reviewed the document, providing further input on the content, and a final draft was presented to the ACMG Board of Directors for review and approval to post on the ACMG website for member comment. Upon posting to the ACMG website, an email and a link were sent to all ACMG members inviting participation in the 30-day open comment process. All members' comments and additional evidence received were assessed by the authors, and these recommendations were incorporated into the document as deemed appropriate. Member comments and author responses were reviewed by representatives of the ACMG Laboratory Quality Assurance Committee and the ACMG Board of Directors. The final document was approved for publication by the ACMG Board of Directors.

Significance of ROH

Most CMA platforms use a combination of probes designed to assess copy number and probes to genotype single-nucleotide variations. In addition to copy number changes (ie, deletions, duplications, amplifications), these array platforms can identify ROH, often in the form of 1 or more long contiguous stretches of homozygosity. Detection of ROH is also possible using next-generation sequencing methods, including ES/GS.[9-12] These autozygous segments, synonymous with identity by descent (IBD), originate from a common ancestor and may indicate a consanguineous relationship between the proband's parents.[13] Consanguinity confers increased homozygosity, which leads to an increased risk of autosomal recessive (AR) disorders.[14] The detection of ROH can lead to the identification of AR candidate loci.[13,15,16] When observed on a single chromosome, large ROH can be indicative of UPD.[16] More commonly, when unique ROH are observed to be distributed throughout the genome, they represent segments of autozygosity/IBD. Detection of ROH and UPD by these platforms has become a useful clinical tool in the diagnosis of patients with genetic/genomic disorders.[17] In a study with a large population of patients tested for a broad range of clinical conditions, including intellectual disability and congenital anomalies, approximately 4.4% of tested samples (651/14,574 consecutive cases) showed multiple ROH of >10 Mb in length suggesting IBD, and ~1.2% showed ROH of >10 Mb on a single chromosome suggestive of UPD.[18] However, the frequency of UPD in newborns is estimated to be quite rare, ~1 in 3500 births (0.029%).[19] Effects of UPD can vary based on whether the chromosome in question is imprinted (eg, chromosome 15 and Prader-Willi or Angelman syndrome)[8] or if the presence of 2 identical copies of a parental chromosome can unmask deleterious recessive alleles and lead to AR disorders (eg, neonatal diabetes mellitus and congenital hypothyroidism; *GLIS3* at 9p24.2).[6] Detection of these homozygous regions by CMA may lead to a recommendation of additional diagnostic confirmation by ES/GS[18,20] or molecular confirmation of putative UPD.[21] Results obtained may reveal a familial relationship or consanguinity between parents. The findings may provide evidence of abuse, especially if 1 parent is a minor at the time of conception, vulnerable, or intellectually disabled.[15,22] However, laboratories should consider the possibility of marriage between first cousins, which is legal in many states within the United States and practiced in many cultures.[23] It is estimated that approximately one-fifth of the global population resides in communities in which consanguineous matches are traditional and a cultural norm. Such populations include, but are not limited to, Middle Eastern, East Indian, and North African ancestry.[23-26]

Detection of Consanguinity

The clinical suspicion for an AR etiology should be high when evaluating a child referred to genetics with clinical signs and symptoms of an illness, born to healthy consanguineous parents.[27] Genomic regions that are IBD originate from a common ancestor, and the proportion of the genome that is autozygous correlates with parental relatedness. The average proportion of the autosomal genome that is IBD in offspring of related parents is given by the coefficient of inbreeding (F).[28] For example, on average, 6.25% (1/16th) of the genome in an offspring of first cousins (F = 1/16) is IBD. Given these percentages of IBD, the offspring of first-cousin (F = 1/16) and double-first-cousin (F = 1/8) mating will be identified by ROH in CMA and ES/GS testing. While the coefficient of inbreeding provides a theoretical value,[28] significant deviations from the expected values do occur.

Because smaller ROH (<3 Mb) spread throughout the genome are common even in outbred populations, laboratories typically set a size threshold of >3 to 5 Mb under which segments are not considered significant.[13,29,30] The size threshold may be platform-dependent; for example, it has been demonstrated that lower density microarrays may overestimate ROH,[18,31] so for lower density arrays a larger size threshold may be needed. Hypothetically, in the offspring of a second-cousin mating, an average of four 12.5 Mb ROH per genome will be present, although both the number and the size of homozygous segments can be highly variable.[28] When ROH involving multiple chromosomes is present, the percentage of the genome that is IBD can be estimated by the sum of the sizes of the homozygous segments divided by the total autosomal genomic length (approximately 2881 Mb for GRCh37/hg19). The sex chromosomes are typically excluded from the calculation as males have 1 X and 1 Y chromosome and therefore cannot have homozygosity at any locus outside of the pseudoautosomal regions. This calculation is likely an underestimation of the actual percentage of the genome that is IBD because only those segments of homozygosity meeting the size threshold set by the laboratory may be flagged for inclusion in the calculation.[13] This percentage can then be compared to the theoretical value derived from the coefficient of inbreeding for any given parental relationship.[28]

Because recombination during meiosis is a somewhat random process, the variation from the theoretical value increases with each meiosis,[25] such that in some cases, third cousins may share more DNA sequences than second cousins. Even among the progeny of first cousins, in whom the average percentage of the genome that is IBD is 6.25%, the standard deviation is 2.43%.[28] These expected percentages are based on a single common ancestor in an outbred population; however, multiple loops of consanguinity or multiple generations of breeding within a relatively closed community could complicate the estimation of the degree of relationship. These variations from the expected or theoretical values are more pronounced for more distantly related individuals and may be caused by stochastic events, multiple loops of consanguinity, small gene pools, and unknown family structures (adoptions, misattributed paternity, etc).[28] Certain populations that have gone through a population bottleneck, eg, Native American populations, typically have at least 1 large ROH due to this.[32] Because of these variables, the specific familial relationship or degree of relatedness between the parents cannot always be extrapolated from the percentage of the genome that is IBD. CMA analysis is not designed to be a paternity test nor should it be used to definitively assign a specific relationship between the parents of the proband.[1]

Concerns for abuse arise when IBD proportions suggest that the parents of the proband are first- or second-degree relatives, particularly when 1 parent is a minor at the time of conception, vulnerable, or intellectually disabled. Among the progeny of first-degree (F = 1/4; 0.25) and second-degree (F = 1/8; 0.125) relatives, the number of meioses separating the parents is sufficiently low, such that the standard deviation is relatively low. Therefore, when high percentages of the genome (≥10%) are IBD and several large segments of homozygosity are present, it is reasonable to suspect a close parental relationship.[1]

Detection of UPD

UPD occurs when both homologs of a chromosome are inherited from 1 parent, typically through defects in segregation of homologous chromosomes in meiosis via nondisjunction.[33] The inheritance of 2 homologous/nonidentical copies of a parental chromosome via nondisjunction in meiosis I leads to heterodisomy, whereas both nondisjunction in meiosis II and monosomy rescue can result in isodisomy.[8] The most common mechanism for UPD is trisomy rescue or reduction to disomy in a conceptus derived from a fertilization resulting in 3 copies of a given chromosome.[21] Although rare, monosomy rescue can occur in a conceptus with a monosomic chromosome after fertilization, which is increased to disomy by duplication.[16] UPD of chromosomes with clinical relevance include chromosomes 6, 7, 11, 14, 15, and 20, with imprinting or parent-of-origin effects leading to aberrant expression/repression of certain genes or genomic regions.[8]

UPD is suspected based on ROH detectable by various genomic technologies, including CMA and ES/GS.[8-12,21] Isodisomy is detected as a large ROH, typically on a single chromosome, including the pericentromeric region, and in some cases the entire chromosome.[16,34] In contrast, heterodisomy may be detected by 1 or more large ROH on a single chromosome that does not include the pericentromeric region.[16,34] However, because UPD is not always accompanied by large ROH, up to one-third of all UPD cases may be undetectable using CMA.[8,21] Recent literature has proposed reporting criteria for different genomic testing

platforms, including CMA[8,21,35] and ES/GS.[8] For postnatal CMA detection of UPD, Hoppman et al[21] proposed the following: telomeric ROH cutoffs of ≥5 Mb for any chromosome, with increased scrutiny for any possible telomeric ROH on imprinted chromosomes; ≥10 Mb for interstitial ROH on imprinted chromosomes; ≥15 Mb for interstitial ROH on nonimprinted chromosomes. Hoppman et al[21] did not propose cutoffs for multiple interstitial ROH on a single chromosome, which suggest UPD, but referred to Papenhausen et al[16] who proposed using an additive cutoff of >15 Mb for multiple interstitial ROH on 1 chromosome. For prenatal CMA testing, Wang et al[35] proposed the following: presence of ROH on a single, entire chromosome (isodisomy), and a single large (≥20 Mb) or multiple segments of ROH on a single chromosome (uniparental isodisomy and heterodisomy [iso/hetero UPD]). Del Gaudio et al[8] discussed UPD results via ES/GS in excess of 10 Mb and recommended that they be reported as nondiagnostic findings when such findings are consented to, with recommendations for confirmation by a clinically validated orthogonal genomic assay. In any instance of possible UPD result, follow-up testing is indicated to rule out false positives.[8]

Recommendations for Pretest Counseling

It is recommended that each patient/family undergoing CMA and ES/GS testing receive pretest counseling. The consenting process for CMA and other genomic testing should include the possibility of revealing ROH/consanguinity and/or UPD.

Recommendations for Reporting Findings of Consanguinity to the Ordering Clinician

It is important to recognize that detection of 1 or more ROH, in and of itself, is not diagnostic for a particular genetic disorder. However, the detection of segments that are homozygous does increase the likelihood that the proband has inherited 2 copies of a deleterious allele for an AR disorder. Clinicians may find utility in this knowledge if the patient's phenotype matches that of an AR disorder for which 1 or more candidate genes are located within 1 of these segments.[22,36] Because there is clinical utility in the detection of excessive homozygosity, even when the percentage of the genome that is IBD is quite low (<3%), many laboratories may choose to report this finding back to the ordering clinician to encourage consideration of recessive mechanisms and facilitate autozygosity mapping in ROH designated by the clinician that may be relevant to the proband's phenotype.[1] Laboratories should set a cutoff for the percentage of homozygosity that is reported as excess homozygosity detected. A cutoff of 2% to 3% of the autosomal genome for reporting ROH is recommended based on the progeny of second cousins, in whom the average percentage of the genome that is IBD is 1.56%, using segmental ROH cutoffs of >3 to 5 Mb to account for possible ethnicity-specific or isolated population loops of ancestral consanguinity.[30] Given that consanguineous matches occur frequently in many cultures,[30,32] the presence of excess homozygosity should not be the final diagnosis for the proband. Instead, the information may be used to help determine the most likely regions within the genome that harbor AR variants consistent with the proband's phenotype. Laboratories may choose to include a percentage or proportion of the genome that is homozygous in their reports. In general, caution should be exercised when using an automated calculation of the percentage of the genome that is IBD. Some analysis programs generate this calculation using all segments displaying ROH, regardless of size or mechanism, which can include deletions. This automated calculation is also typically inflated by small ROH that are more likely representative of regions of suppressed recombination or linkage disequilibrium (identity by state). Limiting this calculation to segments >3 to 5 Mb is more likely to result in the inclusion of segments that are truly IBD.[30] However, at the discretion of the laboratory director, regions below the cutoff may be reported for certain cases. In general, larger ROH may harbor diagnostic recessive variants.[6] Because there is typically little phenotypic information available to correlate between genes in putative homozygous regions and possible homozygous variants in fetal testing via prenatal CMA, a cutoff of ROH >5% of the autosomal genome in fetal testing is recommended. A >5% reporting threshold will be sufficient to cover most first-cousin (6.25% ± 2.43%) and closer matings[28] where the known risk of AR disorders starts to rise significantly.[13]

Special Considerations

The observation of a possible first- or second-degree parental relationship, particularly when 1 parent of the proband is known to be a minor at the time of conception, vulnerable, or intellectually disabled, raises a suspicion for abuse involving that parent. For pediatric specimens, laboratories do not typically have information regarding the parents' ages, intellectual status, or family structure; therefore, they do not have adequate information to communicate a suspicion for abuse to any authoritative agency. Thus, when the percentage of homozygosity reaches a level that could be consistent with a first- or second-degree parental relationship (>10% ROH with multiple ROH of >3–5 Mb or larger), laboratory reports should indicate that the results could be associated with possible consanguinity to ensure that the ordering clinician (geneticist or nongeneticist) understands the implications of the results. An example of suggested language is as follows[1]:

"Several large regions of homozygosity (_ Mb or larger) were detected, encompassing >_% of the genome. Although this result is not diagnostic of a specific condition, it raises the possibility of a recessive disorder with a causative gene located within one of these regions. Additionally, these

results could indicate a familial relationship (first or second degree) between this individual's parents. A genetics consultation is recommended."

Laboratories are encouraged to engage the ordering clinician when a first- or second-degree parental relationship is suspected based on the results of the analysis. The clinician is the most appropriate person to correlate laboratory results with family history and to investigate any concern for abuse. It is advised that each laboratory or hospital consult with its ethics review committee and legal counsel for policy development concerning the requirements for and manner of reporting.[1]

Given that the analysis of ROH can reveal possible incidents of incest, ethical and legal issues must be taken into consideration. Grote et al[37] addressed variable approaches to genetic counseling when addressing CMA findings of ROH associated with putative parental relatedness. Because the detection of ROH and possible UPD has clinical utility, the possibility of identifying ROH should be addressed as part of the standard of care within the informed consent process. Through this process, the proband's parents or guardians should be counseled on the possibility of findings such as ROH that suggest parental consanguinity. Although this may have medical implications (eg, raising the likelihood of an AR disease), it may also suggest an incestuous relationship. If the parent of the proband being tested was a minor at the time of conception, had diminished mental capacity themselves, or was otherwise considered vulnerable, then this may indicate criminal abuse. In such circumstances, there may be a legal obligation to report these findings to welfare agencies. There is no uniform law that dictates what must be reported, although the federal Child Abuse Prevention and Treatment Act does require each state to develop a system for mandatory reporting.[38] Because the relevant statutes are state-based, they vary as to who must report, when reporting must occur, and what exactly must be reported. However, if neither parent was a minor, intellectually disabled, or considered vulnerable, a finding of consanguinity in the proband is not to be considered reasonable evidence of abuse and not subject to mandatory disclosure. In addition, marriage between first cousins is legal in some states within the United States, and some ethnic groups have cultural norms of consanguinity, thus these possibilities must also be considered.[23]

Violations for failing to report also vary but can include criminal penalties.[39] Notably, a lack of certainty regarding the occurrence of incest will typically not excuse reporting obligations. In most states, a duty to report is triggered when there is a reasonable suspicion of incest.[40] In some states, mandatory reporters include anyone who has a reasonable suspicion that child abuse has occurred,[41] and other states list specific mandatory reporters, such as those engaged in the healing arts[42] or employees at universities or the hospitals themselves.[43]

Further, the mandatory disclosure is not expected to violate physician–patient confidentiality or the privacy rule of the Health Insurance Portability and Accountability Act because several courts have found that confidentiality must give way to the need to report.[44] Most state laws provide broad immunity from a civil suit for those who report in good faith.[45] Even so, mandatory reporters should reveal only the minimum amount of information to comply with the statute, so as to maximally protect patient confidentiality. All individuals with access to genetic information indicating suspected incest should consult their state's reporting requirements.

Although relaying sensitive information of this nature to patients and families is commonplace for medical geneticists and genetic counselors, they must be aware of the legal and ethical implications as well. Even in the absence of a legal duty to report potential abuse, there may be ethical obligations based on nonmaleficence or autonomy. The potential for criminal prosecution will complicate what is already a difficult conversation. It is often wise to include the institution's social worker to assist with the provision of follow-up social services as well as legal counsel to be sure that all legal requirements are accurately and completely followed. Laboratories with findings suggestive of incest should also consider how to best report this sensitive information to clinicians. In some cases, it might be necessary to use the word incest itself rather than potentially obfuscating this information in terms such as ROH or even consanguinity.

Conclusion

The ability to detect ROH is an important clinical tool, with clear utility in the context of the detection of AR conditions and UPD. A secondary consequence of this observation is the possible discovery of a consanguineous relationship between the proband's parents. This possibility should be a point of emphasis in pretest counseling. Although a specific relationship cannot be determined using currently available technologies, this information may be useful to the clinician caring for the patient and family. It is the responsibility of the clinician, not the laboratorian, to perform clinical correlation and investigate any concern for abuse. The laboratorian's duty is to effectively communicate the possibility of a familial relationship between the parents to the ordering clinician when a first- or second-degree relationship is suspected based on the results of the analysis. Laboratories are encouraged to develop a reporting policy in conjunction with their ethics review committee and legal counsel.[1]

Conflict of Interest

The authors declare no conflicts of interest.

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