Detection and Reporting of Homozygosity Associated with Consanguinity in the Clinical Laboratory

Kristen Lipscomb Sund^a Catherine Weaver Rehder^b

^aCincinnati Children's Hospital Medical Center, Cincinnati, Ohio, and ^bDuke University Health System, Durham, N.C., USA

Key Words

Consanguinity · Homozygosity · SNP microarray · ROH · Clinical laboratory · Detection · Reporting practice

Abstract

The detection of consanguinity by the presence of multiple regions of homozygosity (ROH) is not an uncommon occurrence in clinical laboratories performing SNP microarray analysis. Reporting practices amongst laboratories are highly variable, due in part to differences in testing platforms, threshold parameters, language utilized, and laboratory policies. While guidance documents have provided a framework for detection and reporting practices, and will doubtless serve to harmonize the field, there are still many facets of the testing that remain at the discretion of the performing laboratory. Clinician and patient education remain a high priority. In the clinical laboratory, these homozygous segments are often examined to identify genes associated with a phenotype that matches that of the proband and autosomal recessive inheritance. While the detection of these ROH is possible with whole genome sequencing, it currently requires special algorithms be utilized, an uncommon practice in most clinical laboratories currently performing this type of testing.

© 2014 S. Karger AG, Basel

Introduction

While cytogenomic microarray platforms were initially designed to detect only genomic imbalances using bacterial artificial chromosome (BAC) probes or oligonucleotide probes, many platforms utilized in today's clinical cytogenetic and molecular laboratories are also designed to genotype single nucleotide polymorphisms (SNPs). These polymorphisms may be genotyped or simply examined for homozygosity or heterozygosity. Segments showing continuous homozygosity with no intervening heterozygosity, termed 'regions of homozygosity' (ROH) or sometimes 'runs of homozygosity', may represent uniparental disomy (UPD), ancestral homozygosity due to linkage disequilibrium, or regions inherited from a more recent common ancestor that are identical by descent (IBD). The segments are sometimes termed 'long contiguous stretches of homozygosity' (LCSH) or regions of 'loss of heterozygosity' (LOH) or 'absence of heterozygosity' (AOH). In this context, these latter two terms are less appropriate, as LOH implies that heterozygosity, while once present, has been lost, a common occurrence in acquired malignancies, and AOH is also inclusive of deletions in which heterozygosity is not possible. While many terms have been used in the literature, LCSH and ROH are the most appropriate for constitutional analyses.

Fig. 1. ROH detected by SNP microarray analysis (Affymetrix Cytoscan HD) in a male child who was the offspring of a brother-sister mating. Each block on the right of the chromosome represents a genomic region at least 3 Mb in size. The laboratory-reported autosomal Froh was >21%.

In the context of constitutional testing, the presence of multiple large homozygous segments involving multiple chromosomes indicates that the patient is the offspring of related parents (fig. 1). Some clinical laboratories sum the ROH to obtain a quantitative measurement of the relatedness of the patient's biological parents. This figure can be represented as the total homozygous length in megabases (Mb), or the total can be divided by the size of the genome or autosome to give a percentage of the genome/autosome which is homozygous (Froh). These calculated percentages can be compared to the theoretical inbreeding coefficients to estimate the degree of a biological relationship, e.g. first-degree relatives such as father and daughter or third-degree relatives such as first cousins (table 1). The accurate sizing of these homozygous segments is critical as many laboratories include the genomic coordinates of the segments and/or the percentage (Froh) on clinical reports. High Froh values can trigger the suspicion of abuse; therefore, close attention should be paid to factors which could inflate Froh. Common causes of such inflation include true biological phenomena, such as multiple loops of consanguinity or small gene pools, and technical or artifactual causes, such as probe density or threshold values chosen by the laboratory. ROH are also often closely interrogated for candidate genes which match the patient's phenotype, such that inaccurate sizing could extend a patient's diagnostic odyssey. In this review, we aim to describe the detection of these segments, the reporting

approaches utilized by clinical laboratories, the published reporting guidelines, and the unique challenges this type of testing can pose.

Detection of Homozygosity by SNP Microarrays

Multiple genomic microarray platforms exist which utilize a combination of copy number probes and SNP genotyping probes, so-called SNP arrays. In the vast majority of clinical tests, the SNP probes are not individually genotyped, but instead the genome is examined for ROH based on the SNP genotyping results. For each SNP, one allele is arbitrarily assigned as 'A' and the other is arbitrarily assigned as 'B'. Homozygous SNPs are either 'AA' or 'BB', and heterozygous SNPs are 'AB' (fig. 2). Kearney et al. [1] reviewed the formulas used by the different software programs to assign zygosity, i.e. homozygous or heterozygous, to each probe. Platforms can vary in the placement and density of these SNP probes. Platforms with a lower density of SNP probes can overestimate the number and size of homozygous segments in the genome which can inflate the percentage of the genome that is homozygous, and lead to the investigation of erroneous regions when attempting homozygosity mapping [2]. Software programs can return all ROH regardless of size, or a threshold value can be set, over which regions are automatically flagged by the software. Froh calculated from all ROH regardless of size can increase

Fig. 2. **a** Allele plot from an Affymetrix Cytoscan HD array visualized with the Chromosome Analysis Suite software (ChAS 1.0) depicting homozygous (AA and BB) SNPs and heterozygous (AB) SNPs. **b** Allele plot showing a 28-Mb terminal block of homozygosity.

the percentage of homozygosity 10-fold over values obtained using 3 Mb as a threshold value [Rehder, unpubl. data]. Percentages can also be returned based on autosomal ROH or total genomic ROH.

Calculation of Homozygosity by SNP Microarray

A number of earlier studies have described methods for calculating Froh based on SNP array data [1, 3, 4]. These authors calculate Froh by summing the total ROH in the autosome and dividing by the total number of base pairs in the relevant genome build. Despite some consistency in these approaches, there are many details that are left to the interpretation of the clinical laboratory and lead to variability in both the numerator and the denominator of the calculation.

The numerator of Froh is a sum of all ROH in the genome. Though this seems straightforward, several things should be considered when generating this number for purposes of comparison to the theoretical inbreeding coefficient. First, laboratories must determine a threshold value above which a segment of homozygosity is considered significantly large enough to represent inheritance from a close common ancestor. In a report on their web-based program used to mine ROH for genes of interest and phenotypic correlation, Wierenga et al. [5] reported

Table 1. Theoretical percentages of homozygosity and confidence intervals as calculated by Sund et al. [4] for given parental relationships, in a presumed outbred population

Degree of parental relationship	Theoretical Froh (offspring)	Confidence interval
First degree		
Parent/child, full siblings	25%	21.3–28.7%
Second degree		
Half siblings, uncle/niece	12.5%	9.7–15.3%
Third degree		
First cousins	6.25%	4.6–8.3%
Fourth degree		
First cousins once removed	3.125%	2.6–4.2%
Fifth degree		
Second cousins	1.5625%	0.5–1.6%

Examples, but not an exhaustive list, of each degree of relationship are given.

variance in total ROH based on different size thresholds (1 vs. 8 Mb). The difference between the two values is striking, and in some cases the total ROH more than doubles when the threshold is changed from ROH >8 Mb to ROH >1 Mb, illustrating the importance of threshold determination. Even within outbred populations, ancestral

ROH (i.e. due to linkage disequilibrium/low levels of recombination) is common [3, 6–8]. Though ancestral ROH are often small in size (<1–5 Mb), this is not always the case [3, 7, 9]. While some ancestral ROH are similar across many diverse ethnic groups, some are specific to more recently divergent populations [7, 8]. Clinical laboratories typically set a cutoff value designed to minimize the contribution of ancestral ROH to the total percentage of homozygosity, limiting the calculation to larger segments inherited from a more recent common ancestor, which would have been subject to less selective pressure.

The concept of population-specific threshold values has also been suggested [10]. The sizes of ancestral ROH have been shown to display consistent geographical patterns corresponding to population migrations, with the largest segments being observed in populations with the greatest distance from Africa [11]. Using a population-specific threshold would minimize the inflation of ROH due to ancestral linkage disequilibrium and maximize the likelihood that the reported segments represent those inherited from a more recent common ancestor, making the identification of a rare disease-causing autosomal recessive mutation more likely. The practicality of using population-specific values is considered challenging and not easily incorporated in the clinical laboratory setting [12].

Laboratories must also decide whether to use all segments (autosomal and sex chromosome) or to restrict the analysis to autosomal segments. Many studies exclude the X chromosome in their calculation of genome-wide homozygosity [1, 3]. In a discussion of clinical calculations, Kearney et al. [1] stated that X chromosome homozygosity is excluded because males are always hemizygous and the female X chromosome often has inflated homozygosity due to limited recombination. However, Sund et al. [4] calculated homozygosity with and without the X chromosome on a small number of patients. This study concluded that although it makes sense to exclude the X chromosome from the calculation, it can be helpful to observe the patterns of homozygosity on the X chromosome for further validation of suspected degrees of relationship.

Another consideration in the calculation of both the numerator and the denominator is the version of the microarray platform used. Genome coverage and spacing of SNPs should be considered, as they can vary dramatically between microarray platforms. Importantly, the calculation of the total base pairs in the genome for the denominator should be based on the same genome version as the microarray. Second, on most microarrays, SNP coverage of centromeres and telomeres is often sparse.

For this reason some studies have excluded these regions from both the numerator and the denominator in this calculation [3, 4]. SNP spacing throughout the genome is also an important consideration, as low SNP coverage will lead to inflated homozygosity values [2].

Guidelines for Reporting Suspected Consanguinity

Shortly after the advent of this technology, it became evident that guidelines were needed to help direct the reporting of suspected consanguinity after clinical genomic microarray testing [13, 14]. The American College of Medical Genetics and Genomics (ACMG) issued a guidance document in 2013 which focused on detection and downstream communications with ordering clinicians [12]. These guidelines as well as other publications have addressed the essential role of pre-test counseling for patients and their families ensuring that families understand that SNP microarray testing can reveal consanguinity [15, 16]. The ACMG guidelines also recommend that each laboratory should establish a size threshold for inclusion of ROH in genomic calculations, suggesting 2–5 Mb as a potential threshold, excluding the X chromosome. The authors [12] suggest that while reporting a percentage of the genome that is homozygous has utility, laboratories should not speculate on a specific relationship between the parents. Comparison of the calculated values to theoretical values can be useful, but multiple factors can cause deviation from the expected values: multiple loops of consanguinity, a limited gene pool, unknown relationships, and random events [12, 17]. Sund et al. [4] compared the percent homozygosity calculated from SNP microarray testing to the theoretical percentages predicted from the mating of individuals of patient-reported relationships. Nine of 43 individuals had significantly higher or lower percentages of homozygosity than would be expected based on the 95% confidence interval. The authors of that study calculated a confidence interval around the theoretical percentage of homozygosity; however, approximately 25% of patients had percentages of homozygosity which fell between the confidence intervals and were considered to have parents with uncertain degrees of relationship (table 1).

The ACMG guidelines also recommend that when a possible first- or second-degree relationship is observed (ROH totaling $\geq 10\%$ of the genome using a threshold of 2–5 Mb or larger), laboratories should include language in the report, indicating a close relationship between the parents such that clinicians could be alerted to the pos-

sibility of abuse of the mother. The primary responsibility of the laboratory is accurate and effective communication of results, such that clinicians may be as informed as possible when caring for their patients [12].

Utility of Autozygosity Mapping/Causative Recessive Gene Identification

Autozygosity mapping refers to the practice of examining segments which are IBD within a proband or within a sibship of similarly affected individuals to identify a causative gene with an autosomal recessive inheritance pattern. This type of analysis is commonly performed in the context of novel gene discovery research. However, it can also be performed for cases of consanguinity detected in the clinical laboratory. The chances of identifying a causative gene are greatest when specific phenotypic information is provided to the laboratory and the differential diagnosis is relatively narrow. Communication between the ordering clinician and the laboratory can often be key. Several studies have demonstrated the utility of this type of analysis in the clinical laboratory [1, 4, 5, 18, 19]. Many other laboratories have unpublished cases for which this type of analysis was productive; however, it is not clear if a majority of clinical laboratories actively engage in this practice, which can be time consuming. A commonly used web-based tool allows users to input phenotypic information and the genomic ROH to potentially identify causative genes [5]. One estimate suggests that autozygosity mapping can lead to the identification of a causative gene with subsequent sequence identification in 10% of cases in the clinical laboratory [1].

Current Practices of Clinical Laboratories

Prior to the publication of the aforementioned ACMG guidelines [12], there was little direction for laboratories attempting to interpret and deliver results of homozygosity, so each laboratory proceeded at their own discretion. A survey was administered during that time to ascertain the practices of these clinical laboratories regarding the reporting of homozygosity [20]. Those practices are summarized here with respect to the main ideas discussed in the ACMG guidelines. It is unclear how these practices will change in light of the new document, but the survey concluded that there has historically been a good deal of variability in laboratory calculations and reporting of homozygosity.

In the survey administered by Grote et al. [20], laboratories reported varying approaches related to size thresholds used in the ROH calculation. Multiple laboratories used a pre-determined size threshold without consideration for the number of ROH found throughout the genome (the most common size threshold was >10 Mb, followed by >5 Mb; one laboratory used >8 Mb). Another approach depended on the presence of more than one ROH of a pre-determined size (>3 Mb) to indicate IBD, followed by a smaller size threshold (>1 Mb) for the Froh calculation documented in the clinical report. None of the laboratories reported a size threshold >10 Mb. Based on the results of this study, it appears that the size threshold used in the numerator of the ROH calculation in most clinical laboratories varies between 1 and 10 Mb. Laboratories were split on the issue of whether or not to include the X chromosome in the calculation of Froh. Six laboratories reported including the entire genome, while 8 used only the autosome.

The reportability of homozygosity detected on microarray is reflected in the generation of nomenclature by the International System for Human Cytogenetic Nomenclature [21, 22]. This nomenclature references the genome build utilized and the genomic coordinates of the ROH; size can be inferred. Therefore, it is no surprise that the majority of laboratories surveyed by Grote et al. [20] have been reporting size, location, and number of ROH. The ACMG guidelines do not specifically address whether or not laboratory reports should include the genomic coordinates of the homozygous segments meeting the reporting criteria of the laboratory; however, inclusion of the individual segments in the clinical report facilitates any downstream autozygosity mapping efforts.

The largest observed difference between clinical laboratories prior to the ACMG guidelines was the decision about whether or not to include the percent homozygosity in the report. Just over half of the responding laboratories included this number in the report [20]. The ACMG guidelines stated that 'labs may choose to include a percent homozygosity in the report', and provided language to use in such reporting [14]. Though this is hardly a mandate to include percent homozygosity, it does represent a slight majority of the laboratories in the survey, and the guidelines may lead to an increase in the number of laboratories that include percent homozygosity in their reports. While the ACMG guidelines use 10% as the threshold value above which clinical reports should indicate a possible first- or second-degree relationship, most surveyed laboratories quoted >20% as indicative of incest. Less than one third of the

surveyed laboratories used a threshold of 12.5%, the coefficient of inbreeding for second-degree relatives [15].

The size and location of ROH identified in a patient is important information that, when analyzed with the proper tools, can aid in the identification of a candidate gene that causes an abnormal phenotype. It is the interpretation of the total number of ROH and the percent homozygosity that can be used to speculate on the possibility of parental relatedness. For example, laboratories identifying a single large ROH thought to indicate UPD universally reported this interpretation [20]. Consistent with the number of laboratories that reported percent homozygosity, just over half of laboratories surveyed included an interpretation of parental relatedness in their report. Only two laboratories specified the degree of the suspected relationship, including the possibility of incest. Though the ACMG guidelines suggested laboratories may wish to include percent homozygosity, they discouraged the speculation of a specific relationship [14]. It is important to remember that Froh is just an estimate, and when comparing this number to theoretical percentages, there are often significant deviations as delineated previously [12, 20].

Disclosing Results of Homozygosity to Patients

Though the laboratory plays a key role in detecting and reporting homozygosity, the interpretation and return of results of homozygosity to the patient is a clinician role. The laboratory may suspect that the patient is the offspring of two very closely related individuals, but, in general, does not have information about the family structure, the age of the mother at the time of conception or the intellectual status of the mother. The key role of the laboratory is to ensure that physicians *understand* AND can *communicate* reported homozygosity and the implications. As SNP microarray is still a relatively new technology, clinician interpretation of these results and patient care related to results of homozygosity are quite variable. Clinician follow-up for results of homozygosity was the focus of the survey by Grote et al. [15]. The study assessed clinician comfort level in receiving/reporting results of homozygosity, pre- and post-test counseling for microarray results of homozygosity, patient reactions to results of homozygosity, and physician understanding of laws related to the duty to report incest. The majority of clinicians who responded to the survey were genetic counselors, but clinical geneticists were also included.

Clinician Comfort Level with Interpretation and Reporting of Genome-Wide Results of Homozygosity

In today's global world, it is common for physicians to see patients of many different races, ethnicities, and nationalities. As consanguinity is common in many parts of the world [23, 24], it is not surprising that more than half of the respondents to Grote et al.'s survey [15] state that they were very comfortable when receiving microarray results of homozygosity that suggested parental consanguinity. However, the survey also showed that 64.3% of respondents were very uncomfortable when microarray testing revealed the possibility of a parental incestuous relationship. A number of clinicians stated that this discomfort was in large part caused by their own uncertainty regarding the accuracy of microarray testing to reliably predict a parental relationship. Microarrays are considered a frontline test for individuals with developmental disabilities or congenital anomalies [25]; this suggests that the technology is highly reliable. However, the technology is limited by our ability to accurately interpret the data. Above, we discussed laboratory variability in reporting and emphasized that percent homozygosity is an estimate. This is compounded by the fact that even the most accurate calculations can produce a Froh that significantly deviates from the expected inbreeding coefficient [12, 20]. For this reason, it is no surprise that clinicians struggle with questions about the accuracy of a predicted parental relationship. There is no question that further molecular studies are needed to improve our ability to accurately interpret parental relatedness categories based on size and patterns of ROH. However, we suggest that the technical data obtained from microarray is sound, as it is being widely used for diagnostic purposes. A small number of clinicians stated that they were uncomfortable with the result because they were not aware SNP microarrays could detect such information, emphasizing the need for continuing education of clinicians in the face of rapidly advancing laboratory testing strategies.

Pre- and Post-Test Counseling for Homozygosity

The survey by Grote et al. [15] evaluated the content of pre- and post-test patient counseling when microarray was ordered. Of those genetics clinicians who ordered SNP microarray, only about one quarter discussed the ability of microarray testing to detect a biological relationship between the parents with their patients prior to testing. In general, this subgroup of clinicians was more comfortable disclosing microarray results that suggested

consanguinity. Other clinicians described feelings of discomfort when disclosing such results because they were unprepared to deal with the incidental finding or did not know how to accurately interpret the data. In a small number of cases clinicians were uncomfortable because they either chose not to or were told not to disclose the interpretation of this finding. Though it would be ideal for all patients to have pre-test counseling prior to microarray testing, this is not realistic. Many of these tests are ordered by non-geneticist in-patient providers who may lack the background or opportunity to discuss these issues with parents. Clinicians should be prepared to review the purpose of the test and the possibility of incidental findings prior to disclosing results.

Only about half of clinicians reported discussing interpretations of parental relatedness or UPD with their patients [15]. Most of these clinicians reported that their first step following the receipt of a result of homozygosity was to review the patients' pedigrees. A recent study [20] showed that there are often discrepancies between the calculated percent homozygosity and the clinical documentation of family history. The study concluded that these discrepancies may be due to multiple generations of consanguinity leading to an inflated percent homozygosity, a distant parental relationship that was unknown to the family, or a close parental relationship that the family did not wish to disclose. These types of discrepancies demonstrate the reasoning behind the ACMG recommendation to *not* speculate on a specific degree of relationship in a report [14].

To assess clinical follow-up of laboratory results suggesting homozygosity, Grote et al. [15] asked genetics professionals to describe their personal experience returning a result of homozygosity. These informative examples illustrated several themes that describe clinician and patient response to results of homozygosity. A minority of clinicians approached legal and/or ethical committees for advice on the type of information to return. In some cases, the results were returned to a non-biological guardian and counseling was more straightforward. In those cases where results were returned to biologic parents, some parents acknowledged a biological relationship, some continued to deny a parental biological relationship, and some had a cultural explanation for the parental relationship.

Clinician Duty to Report

In practice, most clinicians who order microarray testing do not set out to determine the degree of a parental relationship, but total ROH should be reported on micro-

array because it can aid in the diagnosis of a patient [5, 20]. In Grote et al.'s survey [15], 36% of clinicians surveyed reported that they have received a microarray result that indicated parental incest. Although the majority of health-care providers (78.6%) expressed familiarity with the duty to report child abuse, and almost half (47.7%) were familiar with laws to report statutory rape, only 20.2% said they were extremely or moderately familiar with their duty to report incest. This ambiguity may arise in large part due to differences in laws by state but also because clinicians may be separating the duty to report incest from their duty to report abuse or statutory rape, when they are actually very similar. The duty to report should be considered if one of the parents is underage, mentally or physically impaired, or if the clinician feels that the patient is at risk for abuse. These mandatory reporting requirements do not apply to consensual incestuous relationships. While they may be prohibited by state statutes, the affirmative duty to report only applies to cases involving minors or impaired individuals [authors, pers. commun. with the National Council of State Legislatures].

Homozygosity in the Genomics Era

Multiple whole exome/whole genome sequencing studies have already reported using homozygosity to screen for the causative variants in single gene and multigenic disorders [18, 26–28]. It is clear that results of homozygosity can be useful in filtering genome data for single gene disorders and for complex traits. However, it is not clear that filtered exome results in a clinical setting, by themselves, will lead to the same ethical issues regarding reporting that are experienced with genomic microarrays. While analysis pipelines may have the capability to identify ROH, many clinical laboratories are only looking at filtered data that is relevant to the patient phenotype. Even if there are multiple homozygous recessive variants in a row, many of them may be filtered out because they do not meet minor allele frequency criteria, or they are not believed to be pathogenic. Only those that seem significant to the patient phenotype will survive the filtering process. The variants alone are unlikely to lead to a strong suspicion of parental relatedness, unless the data is purposefully analyzed from a broader perspective. Several algorithms have been developed to specifically examine whole genome sequencing data from a broader perspective to detect IBD segments [29]. Because genotyping errors are much more common in sequencing data as compared to SNP array data, these algorithms must take these errors, which could cause false

positive or false negative results, into account. Whole exome data differs from whole genome data in that only small portions of the genome are interrogated with large gaps between sequenced regions, so these algorithms are more challenging to develop; however they have been used for autozygosity mapping in the research setting [30].

Concluding Remarks

The past ten years have witnessed the widespread adoption of SNP microarray testing for the assessment of genomic copy number imbalances in clinical labora-

tories. Although the detection of ROH was perhaps initially considered an incidental finding, today, it is a valuable component of the clinical laboratory toolbox. UPD, consanguinity, and isolated ROH can all be detected using many commercially available platforms. Whole genome and whole exome sequencing have the same capacity to detect these phenomena. While there is some variability in laboratory technical and reporting practices, guidance has been issued by the ACMG to better harmonize these standards [12]. As the adoption of this technology continues to expand, education of clinical providers and patients remains an essential need.

References

- Kearney HM, Kearney JB, Conlin LK: Diagnostic implications of excessive homozygosity detected by SNP-based microarrays: consanguinity, uniparental disomy, and recessive single-gene mutations. *Clin Lab Med* 2011;31:595–613, ix.
- Mason-Suares H, et al: Density matters: comparison of array platforms for detection of copy-number variation and copy-neutral abnormalities. *Genet Med* 2013;15:706–712.
- McQuillan R, et al: Runs of homozygosity in European populations. *Am J Hum Genet* 2008;83:359–372.
- Sund KL, et al: Regions of homozygosity identified by SNP microarray analysis aid in the diagnosis of autosomal recessive disease and incidentally detect parental blood relationships. *Genet Med* 2013;15:70–78.
- Wierenga KJ, et al: A clinical evaluation tool for SNP arrays, especially for autosomal recessive conditions in offspring of consanguineous parents. *Genet Med* 2013;15:354–360.
- Broman KW, Weber JL: Long homozygous chromosomal segments in reference families from the centre d'Etude du polymorphisme humain. *Am J Hum Genet* 1999;65:1493–1500.
- Gibson J, Morton NE, Collins A: Extended tracts of homozygosity in outbred human populations. *Hum Mol Genet* 2006;15:789–795.
- Li LH, et al: Long contiguous stretches of homozygosity in the human genome. *Hum Mutat* 2006;27:1115–1121.
- Kirin M, et al: Genomic runs of homozygosity record population history and consanguinity. *PLoS One* 2010;5:e13996.
- Rosenberg NA, et al: Runs of homozygosity and parental relatedness. *Genet Med* 2013;15:753–754.
- Pemberton TJ, et al: Genomic patterns of homozygosity in worldwide human populations. *Am J Hum Genet* 2012;91:275–292.
- Rehder CW, et al: American College of Medical Genetics and Genomics: standards and guidelines for documenting suspected consanguinity as an incidental finding of genomic testing. *Genet Med* 2013;15:150–152.
- Beaudet AL: Ethical issues raised by common copy number variants and single nucleotide polymorphisms of certain and uncertain significance in general medical practice. *Genome Med* 2010;2:42.
- Schaaf CP, et al: Identification of incestuous parental relationships by SNP-based DNA microarrays. *Lancet* 2011;377:555–556.
- Grote L, et al: Variable approaches to genetic counseling for microarray regions of homozygosity associated with parental relatedness. *Am J Med Genet A* 2014;164A:87–98.
- Tarini BA, et al: The perils of SNP microarray testing: uncovering unexpected consanguinity. *Pediatr Neurol* 2013;49:50–53.
- Carothers AD, et al: Estimating human inbreeding coefficients: comparison of genealogical and marker heterozygosity approaches. *Ann Hum Genet* 2006;70(Pt 5):666–676.
- Alkuraya FS: Homozygosity mapping: one more tool in the clinical geneticist's toolbox. *Genet Med* 2010;12:236–239.
- Alkuraya FS: Autozygome decoded. *Genet Med* 2010;12:765–771.
- Grote L, et al: Variability in laboratory reporting practices for regions of homozygosity indicating parental relatedness as identified by SNP microarray testing. *Genet Med* 2012;14:971–976.
- International Standing Committee on Human Cytogenetic Nomenclature, et al: ISCN 2009: An International System for Human Cytogenetic Nomenclature (2009). Basel, Karger, 2009, p 127.
- International Standing Committee on Human Cytogenetic Nomenclature, et al: ISCN 2013: An International System for Human Cytogenetic Nomenclature (2013). Basel, Karger, 2013, p 127.
- Bittles A: Consanguinity and its relevance to clinical genetics. *Clin Genet* 2001;60:89–98.
- Modell B, Darr A: Science and society: genetic counselling and customary consanguineous marriage. *Nat Rev Genet* 2002;3:225–229.
- Miller DT, et al: Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. *Am J Hum Genet* 2010;86:749–764.
- Chahrour MH, et al: Whole-exome sequencing and homozygosity analysis implicate depolarization-regulated neuronal genes in autism. *PLoS Genet* 2012;8:e1002635.
- Rodelsperger C, et al: Identity-by-descent filtering of exome sequence data for disease-gene identification in autosomal recessive disorders. *Bioinformatics* 2011;27:829–836.
- Walsh T, et al: Whole exome sequencing and homozygosity mapping identify mutation in the cell polarity protein GPSM2 as the cause of nonsyndromic hearing loss DFNB82. *Am J Hum Genet* 2010;87:90–94.
- Browning SR, Browning BL: Identity-by-descent-based heritability analysis in the Northern Finland Birth Cohort. *Hum Genet* 2013;132:129–138.
- Carr IM, et al: Autozygosity mapping with exome sequence data. *Hum Mutat* 2013;34:50–56.