

COMMENTARY

Ethical issues raised by common copy number variants and single nucleotide polymorphisms of certain and uncertain significance in general medical practice

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Abstract

The ethical issues surrounding genotyping for single nucleotide polymorphisms (SNPs) or for copy number variation (CNV) are very different. SNP genotyping can focus on ancestry, risk probability, single gene diagnosis, pharmacogenetics, and carrier testing, and the combination of these in a single test can present difficulties. The interpretation of such tests, inconsistencies between laboratories, and access to genotype information for future reference need to be considered, as well as the value of genotypes of known clinical significance compared with those that provide modest risk modifications with limited potential to take medically useful steps. For CNV genotyping, the major concerns relate to CNVs of uncertain significance and to those with incomplete penetrance. Such CNVs present acute difficulties in counseling symptomatic and asymptomatic individuals and have substantial potential for stigmatization of both groups, as well as raising difficulties when detected in prenatal diagnosis. Improved prenatal diagnosis of many disorders provided by array tests compared with the traditional karyotype probably outweighs the uncertainties for families who would terminate pregnancies with findings associated with severe disabilities. There are substantive concerns about offering SNP or CNV genotyping direct to consumers without a physician or counselor to provide guidance for interpretation of the results.

Introduction

The ethical challenges currently presented by testing for single nucleotide polymorphisms (SNPs) and copy number

variants (CNVs) in medical practice are sufficiently different to require separate discussions. The nature of any uncertain significance is somewhat different for SNPs and CNVs. In addition, SNPs can be divided into those known to be associated with single gene disorders and those that can provide risk modification for common diseases.

SNP testing

The technologies used to analyze SNPs are not intended to discover new point mutations, but rather to detect ancient genotypes carried by thousands of people (for example, apolipoprotein E4, Online Inheritance in Man (OMIM) ID 104310) and sickle cell mutation (OMIM-603903); they also can detect recurrent new mutations (for example, achondroplasia, OMIM-100800). Numerous laboratories are offering SNP testing for ancestry or disease risks, separately or in combination. These include 23andMe [1], deCODE [2], Pathway Genomics [3], and Navigenics [4]. The Department of Molecular and Human Genetics at Baylor College of Medicine [5] and some of these providers offer testing focused on less common mutations that establish a diagnosis of a single gene disorder. At least two laboratories are offering expanded carrier testing for recessive disease risks to prospective parents; these are 23andMe and Counsyl [6]. Many laboratories are offering pharmacogenetic testing, which determines a wide range of genotypes. Laboratories vary widely with respect to the combinations of genotypes they focus on, out of ancestry, risk probability, single gene diagnosis, pharmacogenetics, and carrier testing. It is very difficult to compare the offerings of different laboratories using their websites, because they generally do not provide complete information on exactly which SNPs are scored.

Clinical utility of SNP genotyping

There is a gradation of clinical utility of SNP genotyping, starting with SNPs actually conferring a diagnosis of a single gene disorder. Examples of such disorders that

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have relatively high frequency include factor V Leiden (OMIM-188055), hemochromatosis (OMIM-235200), and α 1-antitrypsin deficiency (OMIM-107400). Other disorders are less common, and therefore technically not frequent enough to qualify as common polymorphisms, but are still not rare; these include recurrent or widely distributed mutations causing hereditary non-polyposis colon cancer (HNPCC, Lynch syndrome (OMIM-120435), *Li-Fraumeni syndrome* (OMIM-151623), breast and ovarian cancer caused by *BRCA1* or *BRCA2* mutations (OMIM-113705 and OMIM-600185), and heterozygous familial hypercholesterolemia (OMIM-143890). Also of high utility is testing for recessive mutations that confer carrier status and for which there is the risk of having an affected child if a reproductive partner is also a carrier for the same locus; examples would be disorders such as Tay Sachs disease (OMIM-272800), cystic fibrosis (CF, OMIM-219700), or sickle cell anemia.

Of intermediate utility would be SNP genotypes that do not represent a single gene disorder but that confer risk modification of substantial magnitude; examples would be the APOE4 genotype and risk of Alzheimer's disease (OMIM-104310) and genotypes related to risk of age-related macular degeneration (OMIM-603075). Then there are very common SNP genotypes of less utility that confer very modest risk modification for common disorders, such as type 2 diabetes mellitus [7]. SNPs used to determine ancestry have little medical utility. Finally, the vast majority of SNPs on many widely used commercial arrays have absolutely no known medical utility. Each of these categories raises distinct ethical issues.

General ethical issues in SNP testing

One ethical and medical question is whether combining SNPs of the five types mentioned above, in the same test, is appropriate. Ancestry testing is largely for curiosity and perhaps recreational interest. Although ancestry can influence medical decisions and testing for single gene disorders and carrier testing, there is no evidence that ancestry testing by SNPs has greater medical value than the information available from history and physical examination. Testing for risk modification has some medical value, although most of the SNPs used in this way could be considered to be of limited clinical utility. Risk modifications of less than two-fold would rarely be medically actionable, although a small increased risk of type 2 diabetes or hypertension might motivate a patient to pursue an exercise program and control weight more than they might otherwise. The testing offered by some providers combines ancestry and disease risk modification, although the two can often be ordered separately. The coverage for mutations that establish a single gene disorder varies widely among providers. Although it is technically feasible to combine any of these forms of

testing with reproductive carrier testing, it is probably best to keep this form of testing separate, as most but not all providers are doing at present.

There is a potential conflict when laboratories fail or refuse to provide detailed information about precise genotypes being tested. They may consider this information proprietary. The US National Institutes of Health has just announced the intent to create a Genetic Testing Registry, an 'online resource that will provide a centralized location for test developers and manufacturers to voluntarily submit test information such as indications for use, validity data, and evidence of the test's usefulness' [8]. Given that this initiative is voluntary, it may or may not improve information sharing.

One of the most debated ethical questions at present is the offering of direct-to-consumer testing. The availability of such services through 2003 was reported [9]. The American College of Medical Genetics issued a statement in 2004 opposing direct-to-consumer testing [10]. The European Society of Human Genetics has published a discussion from a November 2009 meeting [11]. Other recent discussions are available [12,13], and one publication describes differences in reports when the same samples were submitted to 23andMe and Navigenics [14]. Some forms of direct-to-consumer medical testing are widely accepted, as exemplified by home pregnancy testing. However, when broad testing panels include genotypes with substantial risks, such as APOE4 for Alzheimer's, mutations in mismatch repair genes for HNPCC, and *BRCA1/BRCA2* mutations for breast cancer, the involvement of counselors or physicians is essential, and simply having counselors available at the discretion of the person being tested is not sufficient. Presumably requiring that only physicians or counselors could communicate results would be one alternative.

Testing for genotypes underlying a single gene disorder

For genotypes conferring a diagnosis of a single gene disorder, such as factor V Leiden or hemochromatosis, the risk-benefit ratios are among the most favorable, but even here there are concerns that such testing is not cost effective, is not evidence based and may lead to stigmatization or undue anxiety [15,16]. Assuming low-cost and high-throughput genotyping and good physician and patient education, this form of testing carries relatively few ethical concerns in my view. If physician and patient education are lacking, inappropriate outcomes or management may result.

Evidence-based practice should dictate any change in management based on genotype. With proper physician and patient comprehension, there are potential clinical benefits and relatively little downside to knowing that an individual is at increased risk of thrombosis related to factor V Leiden, emphysema related to α 1-antitrypsin

deficiency, or death related to hemochromatosis. Just as physicians have routinely incorporated factors such as obesity, blood pressure, and low-density lipoprotein cholesterol into management decisions, the physician of the 21st century should incorporate genotype into management decisions. The potential clinical benefits for the less common but quite serious genotypes for HNPCC, heterozygous familial hypercholesterolemia, and BRCA1/BRCA2 are perhaps even more compelling. One can make a strong argument that premature mortality and morbidity can be avoided by proper monitoring and intervention for these disorders. From an ethical perspective, there may be a growing responsibility for physicians to offer these forms of testing.

For carrier testing for recessive mutations, there is well-established precedent and published evidence [17] that carrier testing for disorders such as Tay Sachs disease, thalassemia, CF, and sickle cell anemia can reduce the frequency of these disorders among births. Medical practice guidelines in many countries strongly suggest that couples should be offered carrier testing for specific diseases. The primary ethical issues for carrier testing relate to religious and other guiding principles as to which reproductive behaviors are acceptable and appropriate. The primary approach used to avoid the birth of affected children has been prenatal diagnosis and termination of affected pregnancies, although other approaches such as genotyping to identify and avoid 'risky matches' have been used. Abortion based on fetal genotype is possible, but is ethically unacceptable to many individuals and is illegal in many parts of the world. For couples at 1 in 4 risk (such as when both carry a CF mutation) or 1 in 2 risk (such as an HNPCC mutation) of having an affected offspring, preimplantation genetic diagnosis may be a very attractive option that would have wider but not complete acceptance ethically, although high costs and risks of twin and higher multiple pregnancies are still a concern with this approach.

If one accepts that offering carrier testing for some disorders (for example, Tay Sachs disease) is good medical practice, then testing for other disorders of similar severity (such as Hurler mucopolysaccharidosis) would seem ethically desirable. Testing for all known recessive mutations for individual loci is theoretically possible, and sensitivity for detection of carriers will improve over time. Counsyl claims that its testing is 'shown to be more than 99.9% accurate for more than 100 serious genetic diseases' on its website as of April 2010 [6]. Although this may be true for detection of a specific genotype, it is not true if (as readers might assume) accuracy is defined as ability to distinguish carriers and non-carriers reliably. The ability to detect carriers varies by locus, but no ethical principle argues against testing if only a proportion of carrier couples are detected so long

as proper education and counseling explain this limitation.

There are major ethical controversies in deciding whether carrier testing for less severe disorders such as recessive deafness is appropriate or not. Individuals and societies are probably rather divided on whether it is ethical to terminate a pregnancy because of the presence of a connexin 26 genotype (OMIM-121011) causing deafness. At present or in the future in the US medicolegal context, the availability of carrier testing and prenatal diagnosis for some forms of deafness could lead to an obligation to inform couples of this [18]. Perhaps it is reassuring that, to my knowledge, couples and those offering testing have not found the phenotype of colorblindness (for example) suitable for carrier or prenatal testing. In this case, a large fraction of individuals and societies might find such testing to be ethically unacceptable.

CNV testing

Although point mutations and CNVs can give rise to the same phenotype (for example, neurofibromatosis, OMIM-162200), generally the ethical issues surrounding CNVs are very different from those related to SNPs. Much of the knowledge of the medical relevance of CNVs to disease is very recent and sometimes alarmingly incomplete. Although deletion CNVs causing DiGeorge syndrome, Williams syndrome, and many other syndromes have been known for decades, the importance of other CNVs, such as deletions and duplications of chromosome 16p11.2 and duplications of the Williams syndrome region was discovered just in the past few years [19]. Testing in medical practice began as a method to identify an etiology, often but not always *de novo*, in children with mental retardation (intellectual disability), birth defects, and other developmental disabilities. To the extent that such CNVs are *de novo* and have 100% penetrance for a severe phenotype, analysis provides the medical benefits of knowing the etiology of that phenotype, and the data allow much improved genetic counseling of families, although there is rarely any genotype-specific treatment as yet. The ethical difficulties are limited in such cases. Much greater ethical difficulties arise when penetrance is incomplete (not everyone with the genotype has an abnormal phenotype); when there is variable expression (those with the genotype and an abnormal phenotype vary widely as to the nature and/or severity of their phenotype); or when there is great uncertainty as to whether there is any phenotypic risk whatsoever for a given CNV.

Issues raised by CNVs with incomplete penetrance

A likely example of incomplete penetrance is deletion of chromosome 15q13.3. Many children with this CNV

have developmental disabilities, and they often meet criteria for a diagnosis of autism. This deletion is also associated with schizophrenia, bipolar disorder, epilepsy, and perhaps antisocial behaviors [20,21]. However, it is not rare [20] to find a parent with the deletion who is considered by themselves, their family, and their physicians to be normal. This would seem to represent lack of penetrance. Let us suppose for the sake of discussion that 70% of individuals with this duplication have clear developmental disabilities, that 15% are near normal but have mild disabilities that generally would be seen as within the range of what is 'normal' in the population, and that 15% are completely normal with no phenotypic effect from the genotype. Imagine that a parent had some learning difficulties in school, or that the IQ of such apparently unaffected individuals with the deletion was statistically significantly lower than for their non-deletion siblings, but the majority of the IQs are still within the normal range. Imagine that this parent and their partner go to the internet and read about the circumstances posed here. There certainly are societal challenges. Is it ethical or unethical to explain all this on a public website? Will parents with borderline phenotypes be harmed, traumatized, or stigmatized? Will they see themselves differently and will their partner see them differently? Could family members with the deletion genotype but a completely normal phenotype be stigmatized?

Issues raised by CNVs of uncertain significance

Another situation arises when CNVs of uncertain significance occur with typical frequencies of 1 in 50 to 1 in 500 in the general population. These CNVs are usually first observed in patients with developmental disabilities because this is the population being tested. These initial observations often result in publications of one or a few patients suggesting that the CNV might cause the disability phenotype in the patients. However, these CNVs could be completely benign, with the association with a phenotype being entirely coincidental. Alternatively, even if a normal parent has the CNV, there could be incomplete penetrance, and the CNV may be the cause of the phenotype in the child. What should the laboratory report to the physician and what should the physician tell the family? Should the information be withheld by the laboratory or the physician because the genotype is of uncertain significance? It may be preferable to explain the findings and all the uncertainties and to keep the family well informed as new information accumulates over the next year or two or more. However, this may be very time consuming and may result in undue anxiety or distress for the family.

The detection of a CNV with known pathological effects but known incomplete penetrance or of a CNV of

very uncertain significance is particularly difficult when the test is performed for prenatal diagnosis. Array methodology has already largely replaced karyotype methods for diagnosis of pediatric disabilities [22], and a similar transition is expected for prenatal testing, but a CNV of uncertain phenotypic significance presents greater ethical difficulties in the prenatal setting. Our experience has been that findings of troublesome uncertain significance occur in about 1% of routine prenatal samples [23]. Families seem not to be excessively distressed by findings of uncertain significance and generally are quite comfortable if the finding is present in a normal parent, although this does not guarantee that the CNV is benign. *De novo* CNVs appropriately raise greater concern, but these still may be benign. In the prenatal setting, these 1% of cases are often discussed by a group of experts before information is shared with the family. Decisions of families are heavily influenced by their previous willingness to accept any increased risk and by their attitudes regarding abortion. I have not observed pregnancy terminations in instances in which my colleagues and I felt that the statistical risk of a disability phenotype was real but relatively low. I believe that the improved prenatal diagnosis of many disorders provided by array tests compared with the traditional karyotype outweighs the uncertainties for families who would terminate pregnancies with findings firmly associated with severe disabilities.

One relatively new ethical difficulty arises when SNP arrays are used to evaluate children with disabilities; and it is likely that combined SNP and copy number arrays will be more widely used going forward. These arrays can easily identify blocks of absence of heterozygosity that occur on the basis of uniparental disomy or consanguinity. This can be helpful in diagnosing uniparental disomy causing disorders such as Prader-Willi and Angelman syndromes and in identifying candidate gene regions for disease in children born of first cousin and similar matings. However, the occurrence of incest, as in the mating of a parent and child or between siblings, is immediately obvious because about one-quarter of the genome shows absence of heterozygosity because of identity by descent (ALB, unpublished observations). There is limited information as to the frequency with which developmental disabilities are caused by incestuous matings, but the frequency of intellectual disability is high in such offspring [24]. Now, with SNP arrays, such cases of incest will be readily identified with a test that will be widely applied for evaluation of children with disabilities; no parental sample is required for a near certain recognition that a child was born from an incestuous mating. This may often involve sexual abuse of young children in the home. If one parent is below a certain age, child abuse laws may require reporting to

authorities. If both the parents are legal adults, it is not clear whether the physician would be legally obliged to report the finding to authorities.

Governmental regulation

There are two areas in which the role of government comes up for genetic testing: gene patents, and regulation of laboratories and testing. Is it ethical, legal, or desirable to allow gene patents that can limit the availability of testing or increase the cost? Policies related to diagnostic gene patents vary widely around the world. Gene patents have been issued in the US, although a recent court decision struck down some *BRCA1* and *BRCA2* patents. The final word on gene patents in the US is likely to await a Supreme Court decision. The European Patent Office revoked diagnostic patents for *BRCA1* and *BRCA2* in 2004.

On the matter of regulating genetic testing, the US Food and Drug Administration (FDA) has asserted its authority and intent to regulate such testing, but most SNP and CNV testing is not FDA approved at present. Again, policies vary widely across the world, with most regulatory efforts in their infancy. The FDA has begun specifying that certain pharmacogenetic testing is desirable or perhaps mandatory prior to prescribing some medications, and this approach is likely to expand and be used in many countries.

One final question is whether regulations should require that the requesting physician or the patient must have access to all the CNV or SNP genotype data. For CNVs, it is probably common at present that two different genetic laboratories might detect the same CNV, and one laboratory would report it back to the physician as being of uncertain significance whereas the second laboratory might not report the finding at all. Alternatively, two laboratories might report a CNV but provide somewhat different interpretations as to whether the CNV is pathogenic or not. For SNP genotypes, different interpretations have been reported from different laboratories, as noted above [14]. In addition, it is possible that the interpretation provided for a specific SNP genotype in 2010 might be very different from that given in 2015. Although a case can be made for having genotypic data become part of the (hopefully electronic) medical record, this is not common at present. This also raises the question of whether the physician or patient should have the ability to obtain a second opinion regarding the interpretation of the data. One attractive option would be to have a group of professionals that might be called 'genomicists' who would provide a second interpretation analogous to that which a radiologist or pathologist might provide today for a magnetic resonance image or a histology slide, respectively.

Abbreviations

CF, cystic fibrosis; CNV, copy number variant; HNPCC, hereditary non-polyposis colon cancer; FDA, Food and Drug Administration; SNP, single nucleotide polymorphism.

Competing interests

The author is Professor and Chair of the Department of Molecular and Human Genetics at Baylor College of Medicine, which offers extensive genetic laboratory testing including use of SNP arrays and CNV arrays, and the Department derives revenue from this activity.

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