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Expanding Genomic Sequencing and Incomplete Penetrance

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Abstract

Background: Genetic data have the potential to impact patient care significantly. In primary care and in the intensive care unit, patients are undergoing genetic testing. Genetics is also transforming cancer care and undiagnosed diseases. Optimal personalized medicine relies on the understanding of disease penetrance. Here this article examines the complexity of penetrance.

Methods: This article assesses how variable penetrance can be seen with many diseases, including those of different modes of inheritance, and how genomic testing is being applied effectively for many diseases. The article also identifies challenges in the field, including the interpretation of gene variants.

Results: Utilizing advancing bioinformatics and detailed phenotypic assessment, we can increase the yield of genomic testing, particularly for highly penetrant conditions. The technologies are useful and applicable to different medical situations.

Conclusions: There are now effective genome diagnostics for many diseases, however the best personalized application of these data still requires skilled interpretation.

Summary for the Table of Contents

Genomic sequencing is rapidly impacting diagnostics and research, however disease penetrance remains a challenge.

Keywords

Genetic testing; Penetrance; Genomic; Pediatric; Adult-onset

Introduction

The potential for genomic technologies to detect those at risk for disease is tremendous, yet reduced (or incomplete) penetrance presents a challenge for providers and patients. When a medically-important gene variant is found, but symptoms are not present, there is often

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uncertainty about when or if symptoms will develop. Genome-scale testing is available more broadly these days, however the most effective clinical applications of testing rely on our understanding of penetrance. Diagnostic genetic testing and genetic screening may require customization by disease in order to optimize clinical utility and minimize uncertainty. This article assesses factors influencing penetrance. How do they impact clinical testing? Can we apply genomics early in a patient's medical care?

Heritable Disease and Penetrance

Reduced penetrance can be seen in any mode of inheritance--autosomal dominant, autosomal recessive, or X-linked. Let us consider autosomal dominant conditions first. While some dominant conditions manifest at an early age, many dominantly-inherited conditions have a delayed onset of symptoms or age-dependent penetrance. Since testing for many conditions early in life was not possible in the past but is increasingly possible now, it is important that we consider penetrance. Cancer predisposition conditions, select cardiac conditions, and a list of corresponding genes for these conditions, have been recommended as reportable secondary findings in clinical genomic sequencing[1]. As more sequencing is done, we will detect individuals at risk for these conditions early in life. This may be advantageous because a family history of early-age/multiple cancers[2] is often not present in individuals with a cancer-predisposing gene variant and broad testing could find those at risk despite the family history[3]. Tailored cancer surveillance screening for these individuals could lead to early disease detection. We aim to optimally implement and interpret the genetics so we can apply genetic technologies in the most effective manner for each individual or population[4,5]. Dominant family pedigrees are well-recognized, but X-linked pedigrees are important to consider as well. Many X-linked conditions can have variable penetrance also. These conditions are classically known to manifest in males[6], but symptoms can range widely in females. Females may be asymptomatic carriers, or they may be significantly affected by an X-linked condition[7]. Some females carrying pathogenic variants in the ornithine transcarbamylase gene, *OTC*, can present with episodic hyperammonemia, whereas others do not, and diagnosis and management of disease can dramatically affect clinical outcomes[8,9]. Although mitigation of symptoms may be due to X-chromosome dosage or due to the influence of other genes, environmental factors--such as dietary intake, surgical or metabolic stress--may also play a role.

Recessive conditions can also have variable penetrance. For example, hereditary hemochromatosis, due to disease-associated variants in *HFE*, is an important example. Although iron-overload is an issue for adults primarily, recent studies have found that iron studies in children with *HFE* mutations are subtly different, suggesting a lifetime of cumulative effects that can influence penetrance. Not all mutation-harboring individuals, however, will develop iron-overload or organ system manifestations. Identification of individuals at risk for disease by genetics could have future management implications. For example, genetic results could influence management of iron supplementation or influence iron level monitoring[10]. Indeed multiple genes seem to have an effect on iron levels, and these should be considered as candidates that influence disease penetrance[11].

Genetic Testing in Practice

With more genetic testing being employed in pediatrics, parents are being asked to make genetic testing decisions affecting their own children. Providers may respect the decision-making autonomy for parents, but this does not necessarily take into account the autonomy of the child, who may be too young to understand a testing decision[12]. This potential loss of autonomy may be balanced by beneficence–that is, the potential to detect or prevent disease early in life. The medical conditions to target in testing may need to be significant, treatable or better-managed with early detection. On the other hand, for low-penetrance susceptibility loci or common variants, it is unclear how medically actionable these typically are[13,14], compared to highly-penetrant variants.

Effective genetic testing and counseling rely on our understanding of gene-disease relationship. Disease-associated genes and clinical phenotypes are numerous and important for differential diagnosis. Perhaps equally important are the different effects of genomic variants. Indeed, several groups are systematically annotating known gene-disease pairs and individual variant pathogenicity[15] as the number of Mendelian disease genes reaches several thousand[16]. Even with previously-annotated disease gene variants, it is hard to predict the precise natural history of disease. The diagnosis of a genetic condition for a patient may still result in altered, and hopefully improved, health management. Assessment of clinical utility of genetic diagnoses may require further patient, provider, and stakeholder engagement. Consortia including CSER2 (Clinical Sequencing Effectiveness Research) and others are trying to address these important challenges[17].

Understanding Gene Variants

Different variants in a disease-associated gene could have disparate effects that perturb penetrance. For some genes, variants are well annotated, while for others, variants are sparse. Loss of function variants are easier to interpret[18], while amino-acid substituting variants are harder to interpret given the variable effect on function. New methods and tools are being developed to help with gene and variant level interpretation using sequencing data from the population[19–21]. Population data from ExAC, gnomAD, NHLBI TOPMed and other population-based sequence data are important resources for this process. For example, certain genes demonstrate intolerance to loss of function variants, and population exome data, from thousands of individuals sequenced in research studies, led to these findings. Recently, missense depleted regions (MDRs) in genes have been identified[21], and these are highly-conserved coding gene regions that are unlikely to be changed without phenotypic consequences. Highly-penetrant genetic conditions corresponding to MDRs are likely to be diagnostically useful, and these genes may need to be prioritized in early screening applications. As further individuals from diverse populations undergo sequencing and detailed phenotyping, we should also develop a better understanding of disease penetrance. Further focus on highly-penetrant mutations may also be important, however the effect of a single mutation may not be immediately obvious if other mitigating genetic factors are also important. For example, in recessive conditions, each potentially pathogenic variant by itself may confer an effect on dosage, and therefore the specific combinations of different variants would be important to consider in disease severity or penetrance.

With broader genetic testing available, patients and practitioners are increasingly recognizing the potential limitations of genetic tests. Multigene testing may increase the chance of pathogenic variant detection, but testing may also result in variants of uncertain significance (VUS), which are often interpreted by practitioners in various ways. Attempts should be made to resolve VUS by further testing of family, further assessment of interpretation criteria[22], or phenotyping and followup over time. The interpretation of results is likely as important as the sequencing technology itself. Genetic variant interpretation is challenging[23], and further integrative studies combining clinical and laboratory efforts are needed.

Challenges in Genetic Disease Screening

As an example, genetic fatty acid oxidation problems can be flagged by abnormal carnitine/acylcarnitine levels currently used in newborn screening (or used in metabolic-condition testing). *SLC22A5* is the primary free carnitine transporter, and pathogenic variants in *SLC22A5* lead to systemic primary carnitine deficiency. A low free carnitine (C0) level, a hallmark of primary carnitine transporter defect, can also result from prematurity, medications[24,25] or other metabolic disorders, making such biochemical newborn screening results less specific for primary carnitine deficiency. *SLC22A5* deficiency is a treatable genetic condition. Genomic sequencing could play an important role in diagnosing recessive fatty acid oxidation conditions, such as this primary transporter defect, however direct sequencing of *SLC22A5* alone identified only one mutation per individual in õne-third of patients in a study[26]. Genomic sequencing could potentially permit pathway analysis detecting multiple variants in a biochemical pathway that could in combination yield phenotypic effects[27,28]. An example is a variant in *SLC16A9*, another transporter, which may affect C0 levels as suggested by a genome-wide study for variants affecting metabolic traits[29]. The known disease-associated gene *SLC22A5* does not determine C0 levels alone.

Newborn screen false negative results for carnitine deficiency may result since newborn carnitine levels are influenced by maternal carnitine status. Since carnitine levels decrease after birth, the newborn screening sample may reflect maternal sufficient carnitine levels and could mask an underlying carnitine deficiency in the newborn. On the other hand, mothers who are carnitine-deficient may have newborns who test falsely positive for a genetic disease on biochemical screening, as the newborn may only appear deficient prior to significant dietary intake. Additionally, genomic sequencing could define the newborn genotype, providing information to minimize newborns that test falsely positive and falsely negative by biochemistry in newborn screening[30,31]. Sequencing could help identify neonates born to mothers with carnitine deficiency, although this is beyond the traditional scope of newborn screening. Genomic sequencing could allow for improved diagnosis of newborns and help prevent potential consequences of carnitine depletion, such as hypoglycemia, cardiomyopathy, and hepatic complications. Although carnitine conditions may have reduced penetrance, the genetic results could have clear benefits, if used appropriately. Carnitine transporter defects also have some predilection to affect newborns of Asian descent[32], although it affects others as well. Screening in Asian countries support the prevalence data from Asian Americans in California[33]. Caucasian newborns who are screen positive for medium chain acylcarnitines (medium chain acyl-CoA dehydrogenase

deficiency, MCAD) often have a common *ACADM* variant, while other newborns of other ancestries may have different variants. We may need to take into account ancestry or other potential covariates for a full understanding of penetrance. Interestingly, X-linked adrenoleukodystrophy demonstrates a great degree of clinical variability, and current newborn screening efforts for this condition will be of tremendous interest.

In many instances gene dosage will affect disease penetrance. Variant effects on dosage and the symptomatic dosage threshold will vary from condition to condition. To predict with confidence how variants lead to effects, we need to have a deep understanding of genetics and associated human disease. *De novo* dominant conditions are rapidly being recognized using exome and genome sequencing. It is becoming clear that there are numerous, highly-penetrant conditions that cannot be predicted by current carrier screening. Effective management for these genetic conditions is also challenging; often only a handful of patients are initially known. By connecting patients and the medical community, we can promote a better understanding of genetic conditions[16] and the factors that underlie variability. We can indeed prevent potential medical complications of genetic conditions if we approach these challenges together.

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Abbreviations:

MDR	missense depleted region
C0	free carnitine

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