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Review Article

A RaDiCAL gene hunt

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الملخص

في السنوات العديدة الماضية، شرعت الاتحادات للأمراض النادرة في استهداف اكتشاف الجينات المسببة للأمراض في الأمراض المندلية، باستخدام أساليب تسلسل الجيل القادم. وعلى الرغم من نجاح هذه المبادرات الواسعة التطبيق، لم يتعرف الباحثون على المسببات الجينية للكثير من الأمراض. يدرس "التعاون للأمراض النادرة لمواضع الصبغيات الجسدية" (راديكال) أندر الأمراض، التي قد لا يتوفر بها سوى مستلفت واحد، في سبيل التعرف على الجينات المفترَضة المسببة للأمراض. تستعرض هذه المقالة الكيفية التي تعامل بها التعاون للأمراض النادرة لمواضع الصبغيات الجسدية مع بعض التحديات لاستحداث وثائق الموافقة المسبقة المطلوبة للمشاركين الدوليين. كما أنها تأخذ في الاعتبار، الموضوع الناشئ "حق ألا يعلم" في تصميم الدراسة.

الكلمات المفتاحية: راديكال؛ الجينات؛ مستلفت؛ الأمراض المندلية؛ حق ألا يعلم

Abstract

In the past several years, rare disease consortia have embarked on the discovery of disease-causing genes for Mendelian diseases using next generation sequencing approaches. Despite the success of these large-scale initiatives, many diseases still have no identified genetic cause. The Rare Disease Collaboration for Autosomal Loci (RaDiCAL) studies the rarest diseases, where occasionally only a single proband is available to identify putative disease-causing genes. This article reviews how "RaDiCAL" addressed some of the challenges in generating informed consent documents for international participants and considers the emerging topic of the "right not to know" in study design.

Keywords: Genes; Mendelian diseases; Proband; RaDiCAL; Right not to know

Introduction

In the past two decades, the power and capabilities of DNA sequencing technologies have rapidly increased. As a result, there has been a flurry of gene discoveries for the molecular basis of a wide range of diseases. Advances in whole exome (WES) and whole genome sequencing (WGS), in particular, have made important impacts in the ability to diagnose Mendelian disorders, with major biological[1–3] and economic implications.[4] Publication on the identification of a genetic mutation causing a rare Mendelian disorder using whole exome sequencing were began in 2010.[5] Since then, next generation sequencing (NGS) approaches have eclipsed all previous methods, resulting in nearly three times as many gene discoveries than obtained from conventional approaches.[1] However, of the approximately 19,000 predicted protein-coding genes in the human genome, an impact on human biology has still not been determined for approximately 52% of genes.[1] Several large-scale efforts have been made to increase our understanding of the function of these protein-coding genes through the study of rare diseases. The Centers for Mendelian Genomics in the United States and Care 4 Rare (formerly FORGE) in Canada have concentrated

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their efforts on identifying genes that cause human diseases. In addition, a number of smaller disease-specific initiatives have been conducted with similar goals. However, many of these organized efforts have focused on phenotypes for which several patients have been identified or for which several family members have been affected. RaDiCAL (Rare Disease Collaboration for Autosomal Loci), based at McGill University, aims to identify the genetic variants responsible for putative autosomal recessive diseases, even if only a single proband is available.[6] The approach of RaDiCAL is to collect a single, clinically well-described proband for each autosomal recessive disease for which the gene is not yet known, with the ultimate goal of expeditiously constructing a morbid map.[6]

The motivations of RaDiCAL have previously been reported[6] and discussed in the context of collective innovation for global health.[7] Although the informed consent design for genomic studies has been widely deliberated in previous studies, a discussion of the RaDiCAL informed consent regime has not yet been reported. This paper highlights some of the discussion concerning international informed consent, including individual research results, incidental findings, the right not to know, and data sharing, revealing how RaDiCAL incorporated these discussion topics into its study design.

Informed consent

The informed consent document provides information to potential participants to enable autonomous decisions on whether these individuals would like to enrol in a study. Informed consent procedures should avoid deception and eliminate any potential form of coercion.[8] Furthermore, informed consent forms must be clear and concise; it is generally recommended that these forms are comprehensible to someone with an eighth grade reading level.[9] In addition to creating a comprehensive and easily understood document, studies that enrol patients worldwide have the added obstacle of generating documents that are appropriate for individuals from diverse cultural, linguistic, and socio-economic backgrounds.[10] Over the past decade, informed consent practices in genomic studies have been considered, focussing on the nature of the information to disclose, method of disclosure, how much the potential research participant should understand, and how explicit the consent should be.[11] This discussion has suggested the inclusion of core information elements during consent procurement based on key values that include respect for patients and patient family integrity and the right to enjoy the benefits of scientific advancement, altruism and solidarity.[12]

The motivation for RaDiCAL was to provide individuals diagnosed with rare monogenic diseases the option to attempt to discover the genetic cause of their disorder using next generation sequencing approaches.[6] For many patients with rare diseases, genomic research presents the only possibility of receiving information on the cause of their condition. Thus, it is important that the consent practices are well conceived from the conception of the study and do not present a hurdle that will restrict research on these diseases. The RaDiCAL information and consent forms were generated for a study population comprising individuals diagnosed with Mendelian disorders anywhere in the world, but for which the genetic basis is unknown (Appendix A). These forms were designed to be brief, but needed to encompass enough information for the individual to make a rational decision about participating in the study. The core elements in the RaDiCAL consent form include: the study procedures, reasonably anticipated benefits, data sharing, use of next generation sequencing techniques, return of results, return of incidental findings, right to withdraw, storage and safekeeping of participant DNA, potential risks, and contact personnel. These elements ensure that the individual has information on the goals of the study and its potential impact on the participant. These elements also describe how the genetic information will be stored, shared with others, and disclosed to the participant. The document enables continuing communication with the local physician if the participant requires more information throughout the duration of the study.

Return of individual research results

The return of results is one of the most important core elements of informed consent, particularly in the context of rare disease studies. The parents of children diagnosed with rare diseases indicate that the primary motivation for entering genomic studies to identify the genetic cause of disease is to learn the cause of their child's disorder.[13,14] Adult patients and parents of children with rare diseases often speak of diagnostic odysseys, in which years are spent visiting doctors in the hope of identifying a diagnosis for their disease. Many authors and normative documents have suggested that participants in genomic research should receive results from the studies in which they participate.[15,16] However, the results that should be returned and how these results should be returned is still under debate.

RaDiCAL returns results only when the study identifies the specific gene mutation causing the participant's phenotype. Only the results pertaining to the disease-causing variant are returned. Return of individual research results is facilitated through the patient's local physician, as these caregivers are most familiar with the clinical history and impact of the research results on the future healthcare of the patient. The physicians can ensure the dissemination of the findings and facilitate genetic counselling for the patient in the most appropriate manner. In addition, local physicians are also more likely to have a similar cultural and linguistic background as the patient, enabling easier communication with the study participant.

Incidental findings

Incidental findings are perhaps one of the most controversial and debated topics in genomic research on human diseases. The return of incidental findings has been extensively reported in the literature in both research and clinical contexts,[17] but the implications of these findings and the manner in which they are returned remains controversial. Scholars and expert committees have recommended addressing the return of incidental findings as part of the

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