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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 المفترضة 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 their efforts on identifying genes that cause human diseases.

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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

research plan and consent process.[16,18,19] When identified, the incidental findings have typically been reviewed on a case-by-case basis by researchers and expert committees to determine the best course for the return of these findings to the participant.[20] Challenges in the identification of incidental findings have been acknowledged, such as the lack of validation of the variants in the clinical context[21] and uncertainty about the penetrance of variants, which can create potential for over-treatment and unwarranted anxiety for the participant.[22]

Incidental findings have traditionally been defined as "results that arise that are outside the original purpose for which the test or procedure was conducted".[19] RaDiCAL defines incidental findings, according to the Canadian Tri Council Policy Statement, as unanticipated discoveries made during the course of research that are outside the scope of the study.[23] Despite recent positions aimed more specifically at the clinical setting,[24] the recommendations for the research community have affirmed that researchers do not have a duty to "hunt" for incidental findings.[16,19] RaDiCAL does not screen or search for any genes outside the scope of identifying the gene causing the patient's disorder. However, for clinically significant, preventable, or immediately treatable findings not related to the disorder being studied and discovered through the search for disease-causing genetic variants (i.e., the gene variant is present in the final filtered list of variants screened manually through a literature search), adult participants have the option of choosing to be contacted. RaDiCAL returns incidental findings in this manner, reflecting the idea that individuals are interested in identifying the cause of their illness, and not the unanticipated findings for which they did not visit their physician. However, a person may be interested in learning about genetic findings that may have a clinical impact or that could be treated immediately, and thus the option is provided to receive those findings. In cases involving children, parents cannot opt out of clinically significant, preventable or immediately treatable incidental findings in their children. These findings, when identified, are forwarded to the child's physician, consistent with parents having a right to make health decisions in their child's best interest, except under life-threatening circumstances.[16,25]

Right not to know

The right not to know is increasingly included in debates on the return of genomic research results. The right not to know is the individual's right to refuse knowledge of the information that pertains to him or her. In medical research, the right not to know typically refers to the refusal of medical information affecting the person's lifestyle or quality of life. On the basis of autonomy, the right not to know in medical ethics can be viewed as a correspondent to the right to know, in that respecting the right to have access to medical information is complementary to respecting the right to choose to not know this information. The sheer amount and individualized nature of the information generated from NGS have revealed important ethical concerns when dealing with participants and their genomic findings. Discussions on how this information affects research participants have typically focused on how to return the results back to participants and what type of information should be included, rather than whether these participants should have a right to refuse this information entirely.[26]

Genomic research studies can be divided into those that examine disorders hypothesized as monogenic and aim to identify the single gene mutation causing the participant's disorder, such as RaDiCAL, and studies that examine the associations of genetic variants in diseases that may be caused by many different genes and can also have environmental contributions. Identifying the genetic cause of a disease provides an explanation for the cause of the patient's disorder, whereas identifying the association of a genetic variant with a disease identifies the potential for increased disease risk, but does not identify the primary cause of the disorder. The distinction between these two types of studies is important with respect to the return of results. In the former, the implicit motivation for the study is to identify the genetic cause of the participant's disease, and thus the individual almost always has an interest in knowing the results. The inherent interest of studies to identify the genetic cause of the participant's disease does not provide an option for the participant *not* to know the result. In studies where genomic associations with phenotypes are identified, the main purpose of the study is to learn about the disease itself, and not the cause of disease in each participant. The lack of inherent motivation for the identification of genetic causes of diseases for the participant provides the option to include the right not to know one's results in the informed consent document.

Studies, such as Centres for Mendelian Genomics, Care 4 Rare and RaDiCAL, are aimed at identifying the genetic variants that cause rare diseases in humans. These studies enrol patients as participants to identify the cause of the patient's disease, and thus provide the participant with the results of the study. Although guidelines on the return of results are increasingly including the right not to know,[16] the differentiation between studies aiming to identify a monogenic cause of disease versus studies to identify genetic variant associations with disease is typically not included. Because of the inherent goal of RaDiCAL to identify the genetic cause of the participant's disorder, including the right not to know in RaDiCAL's policy for the return of results would impair the core purpose of the initiative. Other NGS studies do not have this implicit goal because the data generated from the participants' genetic material is used to generate novel associations of genetic variants with complex diseases that may have several predisposing factors. These studies include the participant's right not to know their genomic information in their informed consent documents.

Although RaDiCAL does not provide an option not to receive results, if the cause of the disease is identified, the right not to know incidental findings is respected, and adult participants can choose not to receive these results. Given the uncertainty of the significance of the incidental findings identified in research, reflecting differences in research testing standards from those of a clinical laboratory,[18] the unknown penetrance in the general population of many pathogenic variants,[24] and the potential for psychological harm and anxiety in the individual,[27] it is reasonable that the right not to know one's incidental findings is respected in

genomic research. Arguments based on autonomy, privacy, and right to an open future are also among those cited to defend the right not to know the incidental findings.[22] However, in RaDiCAL, the right not to know clinically significant, preventable or immediately treatable incidental findings only pertains to the adult population. The parents of minors participating in a study do not have the opt-out option for receiving findings of highly penetrant variants that are medically actionable during childhood.

Data sharing

Rare disease aetiology is remarkably aided by data sharing, as patient samples for each disease are scarce. However, researchers can occasionally be hesitant in sharing information until enough findings are obtained for publication.[28] The aim of RaDiCAL is to disseminate genomic findings within the research community, whether through publications or online databases, to identify disease-causing variants as quickly as possible. Laboratories worldwide are now capable of easily performing candidate gene sequencing. However, the challenge is to have a candidate gene to test. Thus, the speed of data dissemination is imperative for identifying candidate genes that can be tested in patients around the world identified with similar phenotype profiles. The patient data collected through RaDiCAL, but not biological samples, can be shared with other researchers through a controlled access database. At conception of RaDiCAL in 2011, it was not clear how candidate variants could be quickly shared with the research community to facilitate the rapid identification of patients with similar phenotypes and the same genotype. Platforms have recently emerged that enable the secure sharing of genomic sequencing data with the corresponding patient phenotypes. When it is not possible to identify the disease causing gene in a single patient, platforms such as PhenoTips[29] and GeneMatcher[30] are effective tools to share coded sequencing and phenotype data between researchers to identify several patients with similar phenotypes and mutations in the same gene.

Conclusion

The fast-paced discovery of genetic causes of Mendelian diseases has generated significant benefits to patients suffering from these disorders and highlighted a number of important ethical issues. RaDiCAL aims to ensure that the rarest of rare Mendelian disorders, for which there is potentially only a single proband, are not overlooked in the whirlwind of studies collecting many patients to identify the genetic causes of diseases. This initiative generated international consent forms with core elements to ensure that bioethics principles are respected for study participants worldwide and to maintain its basis of providing individuals with rare Mendelian disorders an opportunity to identify the genetic cause of their disease.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jtumed.2016.11.007.

Conflict of interest

The authors have no conflict of interest to declare.

Authors' contributions

MP drafted and revised the manuscript. MZ conceived the project and revised the manuscript. DSR conceived the project and revised the manuscript. All of the authors approved the final version of the manuscript for publication.

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