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Discussion

Communicating complex genomic information: A counselling approach derived from research experience with Autism Spectrum Disorder

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ABSTRACT

Individuals with Autism Spectrum Disorder (ASD) share characteristics (impairments in socialization and communication, and repetitive interests and behaviour), but differ in their developmental course, pattern of symptoms, and cognitive and language abilities. The development of standardized phenotyping has revealed ASD to clinically be vastly heterogeneous, ranging from milder presentations to more severe forms associated with profound intellectual disability. Some 100 genes have now been implicated in the etiology of ASD, and advances in genome-wide testing continue to yield new data at an unprecedented rate. As the translation of this data is incorporated into clinical care, genetic professionals/counsellors, as well as other health care providers, will benefit from guidelines and tools to effectively communicate such genomic information. Here, we present a model to facilitate communication regarding the complexities of ASD, where clinical and genetic heterogeneity, as well as overlapping neurological conditions are inherent. We outline an approach for counselling families about their genomic results grounded in our direct experience from counselling families participating in an ASD research study, and supported by rationale from the literature.

1. Introduction

Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in communication, reciprocal social interaction, and a tendency to engage in restricted and repetitive behaviours. An increase in the prevalence of ASD has been documented over the last few decades, with the most recent study in the United States reporting an incidence of 1 in 68 children [1]. ASD demonstrates heterogeneity with regard to (i) sex, with a 4:1 ratio of males over females [2], (ii) clinical expression, both between and within families (even identical twins), and (iii) genetic etiology, evident in the identification of hundreds of different genes contributing to ASD [3–5].

The inheritance of ASD is described to follow a multifactorial model in which both genetic and environmental factors, possibly acting in combination, have a role [6,7]. Data support a strong genetic basis for ASD, with estimates of heritability between ~50-90% [7–9]. Hundreds of genes have been implicated in the etiology of ASD [5,8,10–15]. Until recently, 10–15% of individuals with ASD have been found to have an identifiable genetic cause [4,16]. This includes individuals who have a single gene disorder (e.g. Fragile X syndrome, Rett syndrome) [17–20] and individuals with chromosome microdeletions/microduplications (e.g. 16p11.2 microdeletion) [11,21,22]. No single genetic cause accounts for more than 1% of ASD [4,23–26], and most individuals with an identifiable genetic cause have a syndromic form of ASD, which is associated with other physical and/or systemic features [16,27,28]. The majority of individuals who are diagnosed with ASD have non-syndromic/

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idiopathic ASD, the cause of which has been more difficult to elucidate [15,24].

Advances in next generation sequencing (NGS) technology, including whole exome and whole genome sequencing, have enabled us to identify an increasing number of genes that contribute to the etiology of idiopathic ASD [23,24,29–33]. In some instances a single (strong) genetic change (variant) is sufficient to cause ASD, however, in the majority of cases evidence suggests that ASD results from a combination of genetic variants including those of weaker effects, as well as other contributors, which we collectively refer to as environmental factors (i.e. anything non-genetic). The complexity of the genetic etiology of ASD is further confounded by the recent finding that within some families, siblings with ASD have different contributing genetic variants [23,29]. Moreover, many of the genetic variants associated with ASD have also been identified in individuals with other neurodevelopmental disorders, including intellectual disability (ID), obsessive compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD) and some psychiatric disorders (e.g. schizophrenia, bipolar disorder, depression), complicating our interpretation of the impact of these genetic variants on neurodevelopmental outcomes [10,34,35]. Additionally, comorbidity is common in ASD, in that individuals with ASD have other neurodevelopmental diagnoses (e.g. ID, OCD, ADHD) [3,36]. While furthering our knowledge regarding the genetic causes of ASD, genome sequencing data has also highlighted the need to further understand the many additional complex factors contributing to the genetic architecture of ASD [6,30,37–41].

The need to equip healthcare professionals with the knowledge and tools to effectively communicate complex genomic information is crucial and has been recognized [42–44]. As the use of NGS technology for the investigation of ASD moves from research into clinical care there will be increased demand to communicate genomic results to families and facilitate understanding of the significance of these results [45,46]. This task will fall to genetic professionals/counsellors and other health care providers in turn [47–49]. Guidelines and best practice reports on how to effectively communicate this information are limited. Existing literature centers on the consenting process for NGS and provides recommendations for topics to cover in the pre-test discussion [50]. Little is written about the post-test counselling approach, specifically regarding the challenges of how to present genomic results, how to explain their meaning, how to counsel about implications for patients and their families, and how to discuss the remaining uncertainty. Although the challenges have been recognized, no practical paradigms exist in the pediatric setting for communicating genomic data, especially for complex disorders like ASD.

Here, we present a model to facilitate communication regarding the complexities of ASD, where clinical and genetic heterogeneity, as well as overlapping neurological conditions are inherent. We outline an approach for counselling families about genomic results grounded in our experience from counselling families participating in an ASD research study with rationale from the literature. The resources and tools developed by our group, shared below, are tailored for ASD but can be adapted and applied to other neurodevelopmental conditions.

2. Conceptual model for the complexity of ASD

2.1. Complexity of ASD

ASD is a good paradigm to showcase the complexity of neurodevelopmental conditions. Not only do individuals with ASD present with a broad clinical spectrum, the genetic factors involved in ASD are varied and complex, with some variants being inherited and others occurring for the first time in the child with ASD (*de novo*). Non-syndromic forms of ASD are considered to have multifactorial inheritance, where genetic risk factors and environmental risk factors both may play a role. It is the additive effect of these factors which, upon reaching a critical threshold, lead to ASD [51].

2.2. Existing multifactorial-threshold models

The concept of multifactorial inheritance and threshold models is not unique to ASD or neurodevelopmental disorders. It applies to many complex conditions, including diabetes, cardiovascular disorders, and mental illness. A few conceptual models have been developed to help describe this complex inheritance pattern, including a jar model for mental illness [52] and balance scale model for common adult conditions like diabetes [53]. Both models depict the role of genetic and environmental factors in the contribution to risk, but have different emphasis. In the balance scale model, environmental/lifestyle factors contribute more strongly to risk and the idea that risk is not static is illustrated. Individuals have some control over their health and can make behavioural changes that impact their disease risk (i.e. exercising and dietary modifications can decrease risk, while smoking can increase risk) (Fig. 1). In the jar model (Fig. 2), the concept of

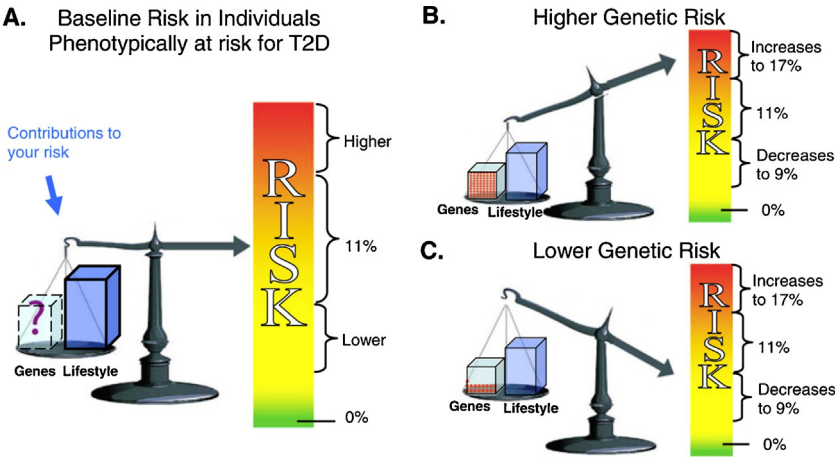

Fig. 1. Balance scale model for diabetes: [A] baseline risk for developing type 2 diabetes (T2D) [B] adjusted risk of 17% for those with a higher genetic risk [C] adjusted risk of 9% for those with a lower genetic risk [53].

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