The Collaborative Effort of Genetics and Medicine:

Can targeted genetic testing aid in early disease detection and improve patient outcomes?

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ABSTRACT

Increasing attention on preventative medicine promises to remodel healthcare by using proactive approaches designed to avert and avoid potential diseases from being introduced to the patient. Genetic screening is a subset of health program measures that is purposely designed to be offered to asymptomatic individuals to provide a promising form of early treatment. While many diseases are multifactorial in nature, early detection of the disorder can aid in tailoring effective medical interventions to the patient. This article will discuss implementing early genetic screening with the aim of promoting greater collaboration between the fields of genetics and medicine.

RÉSUMÉ

L'attention croissante portée à la médecine préventive promet de remodeler les soins de santé en utilisant des approches proactives conçues pour éviter et prévenir l'introduction de maladies potentielles chez les patients. Le dépistage génétique est un sous-ensemble de mesures des programmes de santé qui est délibérément conçu pour être proposé aux personnes asymptomatiques afin d'offrir une forme prometteuse de traitement précoce. Bien que de nombreuses maladies soient de nature multifactorielle, une détection précoce peut aider à adapter des interventions médicales efficaces aux patients. Cet article traite de la mise en œuvre du dépistage génétique précoce dans le but de promouvoir une plus grande collaboration entre les domaines de la génétique et de la médecine.

1. INTRODUCTION

In today's healthcare, there seems to be an emphasis on curative medicine. For this approach, a prior diagnosis is required before an appropriate intervention is prescribed in an attempt to restore and maintain the patient's health (1). Preventative medicine, however, uses methods to lower the risks of the patient acquiring the disease. Genetic screening is a type of health program that can be systematically offered to asymptomatic individuals with the aim of identifying and providing those with high risk of a disease with preventative interventions or early treatments

(1). This type of screening refers to medical tests that detect aberrations in chromosomes, proteins and genes, confirming or ruling out hereditary illnesses. Most diseases manifest from a combination of genetic, environmental, and lifestyle factors. Multifactorial or complex conditions with genetic susceptibility such as diabetes, rheumatoid arthritis, and mental illnesses are conditions which are partially caused by multiple low penetrance genes with various behavioural and environmental factors (1). Penetrance refers to the proportion of individuals carrying a certain variant of a gene that also demonstrate clinical expression of the related trait. There are many types of genetic screens, but not all of them bear the same predictive value. Some tests have a high predictive value, while other tests are associated with a high degree of ambiguity. This article aims to present different ways by which genetic screening can aid in early detection of illnesses such as diabetes, rheumatoid arthritis, and mental health disorders. We also present the challenges and the benefits of utilizing genetic screening as a preventative tool for these conditions.

2. DIABETES

Diabetes has been recognized as a grave medical condition for over 2000 years, but only recently, two types have been made distinct due to their unique modes of development (2). While both conditions are characterized by an elevated level of serum glucose, type II diabetes (T2D) is caused by a decreased sensitivity of receptors on the body's cells, and type I diabetes is an autoimmune disease leading to a complete loss of the insulin-producing β-cells in the pancreatic islets (2).

A) Heritability

Research has previously shown a strong hereditary component in T2D, although additional factors play a role (2). The multifactorial nature of the disease has often been an impediment for geneticists and physicians to effectively diagnose patients. However, it is estimated that T2D has a heritability value of 20% - 80% (3). This evidence was concluded using population sampling, twin-based, and family studies (3,4). The risk of developing T2D is 40% when just one of the individual's parents has the disease, and this increases to 70% when both parents do. People with no primary family history of T2D are about three times less likely to develop the disease later in their lives (3). Intriguingly, these observations point to the strong genetic component that may be involved in the development of T2D. For instance, candidate gene studies were used on genes previously known to have been involved in the secretion of insulin (3). Researchers have found that the PPARG, peroxisome proliferator-activated receptor gamma, is a profound candidate for determining T2D intermediate phenotypes in overweight patients (3). While PPARG is known for encoding the molecular target of thiazolidinediones (an old class of anti-diabetic medications), two variants of PPARG, particularly PPARG Pro12Ala and PPARGC1A Gly482Ser (C1A;Coactivator-1-alpha) polymorphisms, are associated with developing T2D mellitus due to gene-gene interactions (3). As another example, IRS-1 and IRS-2 genes encode peptides that play an important role in insulin signal transduction (3,4). Polymorphisms in these genes have been found to be associated with decreased insulin sensitivity in some individuals (3,4).

B) Challenges and Benefits

The field of medicine meets multiple challenges in the prevention of T2D, as the disease can often develop at a very early age (1). Through proper genetic screening, a physician may take measures to slow the progression of the disease. Given that diabetes is dependent on a number of factors, a physician are to review the patient's background with regard to their proper physical growth, activity level, language skills, cognitive development, social development, and emotional development, in order to properly assess the condition (1). With the implementation of genetic screening as a preventative measure in healthcare systems, the root cause of numerous complex disorders can be determined more efficiently and may in fact even accelerate the diagnostic procedure, bettering the healthcare provided to the patient and reducing financial costs in the long run. The physician may be able to educate the family of children diagnosed with T2D about offering healthy nutrition and promoting physical activity (1). While the early detection of the disease can induce an unpleasant emotional burden on family members, it may also prevent future complications, such as the need for insulin injections. The physician who works together with a geneticist may be able to suggest a diet that is individualized for the patient (1). For many patients, this may involve a more natural plant-based diet, but for others, alterative regimens might be superior. In addition, the parents may enroll their children in more activities that would keep them active and decrease the

further development of diabetes, by avoiding weight gain, which is also strongly correlated with the disease (1).

3. RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a medical condition characterized by swelling, pain and stiffness of joints (7). If left untreated, deformities and damage may occur due to the progression of the symptoms. While the ultimate cause of RA is unknown, researchers have found evidence for an association between family history and acquisition of the disease (7). Malfunction with gene expression is associated with the autoimmune attack of healthy lining of the joints. Treatment is used to relieve pain and swelling, slow down or stop joint damage, help lower the number of flare-ups, and improve the ability to perform daily activities (7).

A) Heritability

RA is a progressive disease that worsens with age (10). The heritability of RA has been estimated to approximately 60 %, while the contribution of cell-surface proteins responsible for regulating the immune system of the body, Human Leukocyte Antigen (HLA), would be heritable by 11–37 % (8,9). In a cohort of 91 monozygotic twin pairs, increased concordance for RA was observed suggesting a hereditary aspect to the condition (9). In addition, a 5-fold increased risk for RA concordance was seen in twins who were "homozygous" for the shared epitope, compared with those negative for the same (9).

B) Challenges and Benefits

While a genetic component is present, a multitude of other factors might be responsible for the accelerated degeneration of joints. Factors such as injury, abnormal metabolism, infections and immune system dysfunction, can potentially all play significant roles in the aggravation of rheumatoid arthritis in addition to the original genetic malfunction (10). Moreover, characteristics such as age, sex, weight, and occupation may also have an influence on the individual's condition.

Patients with a family history of rheumatoid arthritis who have implemented preventative measures in their lifestyle would benefit more from the physician's approach and recommendations (10). For instance, using a holistic approach, a physician may recommend a patient that is employed at a job requiring strenuous physical activity to look for an alternative occupation in order to prevent progression or even initial exacerbation of symptoms. Another example may involve an individualized diet rich in ingredients that lower inflammation, including fish, nuts, seeds, fruits, and vegetables, prior to the development of any symptoms at all (10). Omega 3 fatty acids, exclusively found in fish and nuts, have been shown to have a crucial role in the regulation of inflammation, which is considered to be one of the major causes of arthritis symptoms (10). Furthermore, while physical activity is almost always promoted as a mainstream method of acquiring good health, some exercises and types of workout regimens can, in fact, worsen the symptoms of arthritis by placing high pressures on joints (10). A preventative genetic screening could enable the physician to suggest specific exercises that are easier on bones and joints, such as swimming (10).

4. MENTAL HEALTH DISORDERS

Advancements in technology have created astonishing opportunities for diagnostics and personalized therapy, altering the practice of medicine, particularly in relation to mental health (11). It has been postulated that, in some cases, mental illnesses could have a genetic component (12). Both Mendelian and non-Mendelian disease inheritance patterns have been mathematically modelled and clear correlations were found between genetics and mental health disorders. Among numerous research studies performed in the past few years, one experimental investigation has demonstrated the significance of using genetically reprogrammed cells to unveil potential new therapeutic agents to treat bipolar disorder. The difficulties in understanding the underlying mechanisms of bipolar disorder arises from its varying array of symptoms and the inability to implement suitable animal models (13).

Mertens and colleagues have made progress using a biologically accurate model, known as induced pluripotent stem cell (iPSC) technology, to better understand the pathophysiology of bipolar disorder (13). Human induced pluripotent stem cells are derived from blood or skin cells and have been reprogrammed back into their pluripotent state in order to generate an unlimited source of all types of human cells, enabling therapeutic advancements (13). The research team found that bipolar neurons are hyperactive and represent notable transcriptional differences when

compared to the normally functioning neurons (control group) (13).

Cells derived from lithium-responsive patients were shown to respond to lithium in vitro by not only decreasing their cellular activity to control levels, but also partially correcting the transcriptional modifications associated with bipolar neurons (13). This trend was not observed in non-lithium-responsive cells (13). This correlation between in vitro and human phenotypes indicates that neuronal hyperactivity of iPSC-derived neurons might potentially be an endophenotype of bipolar disorder, which could be utilized to analyze the underlying disease mechanism of bipolar disorder and explore future therapeutic solutions for such complex disorders (13).

A) Ethical Consideration: Challenges

While genetic screening can demonstrate a promising role in terms of providing a vital source of information about the individual, a large component of medicine involves applying the ethics of beneficence and non-maleficence (11). To do no harm to a patient comes first in the mind of a physician. If a physician finds a medical history record of mental illnesses, he or she ought to consider the benefits and the disadvantages of requesting a genetic screen (11). Although genetic components are critical in the onset of a disease, many additional factors will either suppress or trigger the activation of the gene. Although the physician should ensure the patient understands that there is more to them than just the genetic aspect, informing patients about a high susceptibility of developing mental disorders may be unsettling.

B) Ethical Consideration: Benefits

On the other hand, a genetic screen may help prevent the onset of illness in some cases. Early detection of a genetic predisposition to a mental health disorder could enable the physician's work with the family to take precautionary measures that could benefit them in the long run (11). Examples of precautionary measures include involving children in multiple social groups, addressing concerns as soon as they arise, showing love and acceptance from an early age, showing interest for their activities and opinions, and teaching them how to set realistic goals. While these precautionary measures could be discussed with any families, there should be greater emphasis with families of children with greater predispositions to mental illnesses. Additionally, the family could help foster a more inclusive and affectionate environment to minimize stress (11). The family can do so by means such as offering additional protection or providing more attentive care in times of pressure. In addition, family members can also explore topics that stimulate learning about the illness, avoidance of stigmatizing language, joining a stigma-fighting mental health organization and fostering a strong peer support system (11). The benefits of informing the targeted individual about a predisposition to mental illnesses can in many ways prevent additional complications. Notably, genetic screening can exclude disorders imitating psychiatric conditions, which can lead to a faster and more precise diagnosis.

5. IMPLEMENTATION CHALLENGES

It is critical to point out that a great effort has been put toward combining the advanced strategies from the field of genetics with the practice of medicine for the improvement of healthcare (5,6). Genetic screenings have been rising as the advancement of technology has enabled the healthcare industry to seek more progressive and affordable means (5). Deciding on whom to perform the tests is an ongoing dilemma (6). Considering the vast array of socioeconomic statuses among the Canadian population and the struggle produced by the limited governmental funding, not all individuals will have insurance coverage or the means to pay themselves (5). In addition, running genetic screening on every single person would be very inconvenient and difficult to implement.

In rural areas for instance, there are limited medical resources that are accessible to healthcare professionals. Preventative medicine could be considered a long-term solution to resolve this issue since it can maximize the impact of financial resources for rural communities. Given the limited resources available, one could acknowledge that there might be a tendency to prioritize the resources toward achieving an immediate medical care available for rural patients in the form of curative medicine rather than preventative medicine. In a study comparing rural and urban differences in access to preventative healthcare among publicly insured populations, rural enrollees were more likely to report no past year preventative care compared to the urban group (14). Although it might impose a challenging transition for rural communities to adapt to such changes, it could ultimately benefit rural populations.

While in rural areas there may not be geneticists available, sputum vials could be easily shipped to nearby centres, enabling results to be properly analyzed and reported back to community physicians. This impediment leads to an alternative option which may be to use genetic techniques, such as hereditary family trees, to target those who are more susceptible (6).

If a child has a family history which includes a hereditary condition, it should prompt the physician to refer the presupposed patient, to a geneticist specialist. Increased awareness of the patient's family history may provide great benefits in the long run (6). While exercise and proper diet may be recommended by physicians to a child with risk of diabetes, a personalized approach may add value to the treatment plan. For example, a physician may recommend against a keto diet which may place the child's blood level into an acidic state. Combined with a risk factor for diabetes, a state of ketoacidosis could place an additional stress onto the child's body. Incorporating a genetic screen alongside a thorough family history, would give health providers a unique advantage to aid in picking up clues that otherwise would have been unknown. While both genetics and medicine can individually provide invaluable knowledge, only through their collaboration can the greatest benefits be achieved (6).

6 . CONCLUSION

Although a large emphasis in today's healthcare is directed on curative medicine, an increasing focus on preventative medicine could truly revolutionize the practice of medicine. While the majority of diseases are multifactorial, caused by genetic, environmental, and lifestyle factors, an early detection can help tailor medical interventions to the patient. A patient-centred approach to the practice of medicine ensures cost efficient and more effective treatment, which benefit the patient and minimizes the use of limited resources. The prevention of diabetes, rheumatoid arthritis, and mental illnesses are just a few examples of preventative medicine in practice. In conclusion, the many implications of genetic screening in preventative medicine should motivate additional research, which could further reveal many undiscovered advantages.

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