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REVIEW

GENETIC COUNSELING IN THE AGE OF EPIGENETICS

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Summary

Genetic counseling is a complex, specialized activity that aids people understand and deal with their inherited diseases. Epigenetic modifications control gene silencing and activation and they can also be inherited. Depending on each person's familial history and type of disorder genetic counseling has to take into account both genetic and environmental factors. New testing possibilities and new information about gene interactions cannot alter the main goal of genetic counseling that is to help patients and their families to understand the cause of their illness and to deal with every aspect of it.
Key words: genetic counseling, epigenetics

Résumé

Le conseil génétique dans l'ère de l'épigénomique/l'épigénétique

La consultation génétique est une activité complexe et spécialisée qui aide les gens à comprendre et à savoir comment traiter leurs maladies héréditaires. Les modifications épigénétiques contrôlent le silençage génique et l'activation des gènes et cela peut, aussi, être hérité. En fonction de l'histoire familiale de chaque personne et du type du trouble génétique, la consultation doit tenir compte de deux facteurs: génétiques et environnementaux. Les nouvelles expérimentations et informations sur l'interaction des gènes ne peuvent pas modifier le principal but de la consultation, celui d'aider les patients et leurs familles à comprendre la cause de leur maladie et à traiter chaque aspect de celle-ci.
Mots clefs: conseil génétique, épigénétique

Introduction

Drawing and analyzing pedigrees, calculating the risk of appearance or reappearance of a disorder in a family and providing genetic counseling, are the particular moments of a genetic consultation, moments that are added to the usual steps followed by a physician when looking for a diagnosis or treatment for his/her patients. Discoveries and advances culminated in the last years with whole exome or genome sequencing, technology that changed expectations both for physicians and patients.

Defining Genetic Counseling

Genetic counseling was first defined in 1975 by the Committee on Genetic Counseling of the American Society of Human Genetics. A non-directive communication between counsellor and patient or couple, the genetic counseling is supposed to inform about the genetic mechanism of the disorder and the possible options to choose from, so that an informed decision according to own personal views and beliefs could be easier made by the counselees. (1) A genetic consultation is divided in at least two different sessions, so that the family history can be thoroughly remembered by the patient and recorded together with the signs and symptoms of the disorder, and so that a risk of occurrence or recurrence can be calculated and explained.

In 2006 a more comprehensive definition became necessary in the conditions of the advancing technologies and the expansion of the use of genetic information into different domains of human activity (from biology to social science, from medicine to psychology, etc.). Patients have to be informed about the available tests, their benefits and limitations, the personal and familial management of the disabilities caused by the presence of the disorder and the possible prevention of complications or even recurrence of the disease at other family members. The Genetic Counseling Definition Task Force of the National Society of Genetic Counsellors, who published the definition of

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genetic counseling after a three years analysis and debate, expresses as the main quality of this medical endeavor the need to help "people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease". (2) Nevertheless, subjects as disclosure of information about heterozygotes, carriers of disease genes, cultural and religious issues, as well as different other old or new bioethical controversies have to be carefully dealt with depending on the specific needs of those counselled. (3)

Issues to consider in genetic counseling

Although genetic counseling was first targeting individuals who had themselves or one or more family members with either a disorder caused by a chromosomal abnormality or an illness due to mutations in single genes, today the range of specialists who can refer their patients to such a medical procedure varies largely (from cardiologist to ophthalmologist; from endocrinologist to neurologist, etc.). (4) Whether general practitioners, family physicians or other specialists know to recognize a patient or couple that needs a genetic consultation, or whether they are certified genetic counsellors, can make a difference in the way they address an inherited disorder. Genomic testing being available today direct to consumer and world-wide, challenges genetic specialists to educate the public to know what analysis to choose and especially where to ask for an in depth explanation of the results, if necessary. Besides explaining the genetic mechanisms of inheritance and the origin of the specific test results, a cornerstone in developing a trustful relationship with the patients or couples is to allow and stimulate their questions, supporting them in their need for understanding their feelings and for overcoming uncertainty, anxiety, denial, anger, grief. (5, 6) Studies have shown that the major motivation to ask for whole genome sequencing is curiosity, either generally about science or specifically about genetics and the own gene profile. People are also motivated by their personal family history (if there was a disease present or suspected) and by the need to know and eventually inform their children and other relatives about the risk to develop a certain disease. (7) But genetic and genomic analysis cannot explain phenomena like epistasis, where nonallelic genes interact and condition the phenotypic expression of one another. The European Best Practice Guidelines for Quality Assurance, Provision and Use of Genome based Information and Technologies: the 2012 Declaration of Rome envisages the creation of "virtual twins", computational models that could increase the quality of healthcare services by following a person over time. Such a technology would use mathematical models to integrate data on the person's genotype and phenotype, algorithms to analyze information on the specific genome, proteome, epigenome, microbiome, exome, transcriptome, etc. reducing or eliminating the limitations of currently available investigations. Data on environmental conditions and risk factors that cause a disease as well as information on the specific response to therapeutic measures would also be registered. Easy to operate this could then become a useful tool for healthcare providers and patients. But can such computer programs replace human interaction and pertinently evaluate transgenerational and developmental data to patients' benefit? (8, 9) How would a couple evaluate the risk of an abnormal pregnancy in case of being heterozygotes for an autosomal recessive disorder? But, in fact do the mendelian probabilities of 25% for the autosomal recessive and the 50% for the autosomal dominant disorders still have a usefulness in explaining the occurrence and/or recurrence risk when epigenetic phenomena control the silencing or activating of genes?

Epigenetics and genetic counseling

Numerous more or less representative figures of public media have raised the notion of epigenetics to a different level compared to other genetic medical information, emphasizing that life is not strictly shaped by the content of active genes but merely by every - day life habits, beliefs and environment, meaning that we can shape our destiny. It is a well - established fact the interaction between genotype and environment in creating the phenotype and the subject is explained and discussed with the patients in case of common disorders that have a polygenic – multifactorial inheritance pattern or when the inheritance type is not straight forward from the information provided by the pedigree. The present knowledge on common diseases does not allow separating genetic and environmental factors and during a counseling session one cannot exactly quantify their individual contribution in building up the different traits of a person.

Epigenetics studies heritable changes of the phenotype (genes are expressed or not) without genotype (DNA sequence) modifications; it was proven that these changes can be influenced by several factors like age, the environment or lifestyle (diet, behavior, smoking), etc. Epigenetic mechanisms that can take place are: DNA methylation, histone tail modifications and non-coding RNA intervention. (10, 11) An extensive study analyzed 127 human tissues and cell types proving the plasticity of the epigenome. Using different types of assays this concerted multicenter action had as result the database Roadmap Epigenomics Project. It was made public especially for further research of the domain, but genetic counselors and other clinicians can use the information provided by the Roadmap Epigenomics Project to update their knowledge on gene regulation and the presence of epigenetic modifications. The reciprocal influence of DNA and epigenetic marks is not yet well explained, and also the role of epigeneticists in clinical settings is to be defined. (12, 13) All this new information and its continuously increasing amount calls for a better collaboration between professionals, from biostatisticians to primary care providers, from medical specialists to legislative government members. Any advice given during a genetic counseling session has to be well documented, updated and it should also be the result of a multidiscipline collaboration. (14, 15)

Conclusions

The need to integrate epigenomic data in patient's testing and advising has increased due to our present knowledge and technology. Expanding access to genetic information especially by its distribution through media can either help patients and their caregivers or not, depending on a lot of factors (type of disorder, patients' personality type and level of education, accessibility to testing, etc.). Even if findings in the field of epigenetics seem to have put a greater emphasis on the non-genetic environmental conditions that cause diseases, the histone changes, DNA methylation patterns and non-coding RNA synthesis are also inherited and can be discussed and explained during genetic counseling to help patients better cope with their disease.

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