EMBJ.ORG FOR YOUNG DOCTORS

EUROMEDITERRANEAN BIOMEDICAL JOURNAL
2018,13 (27) 118-119
(*FORMERLY: CAPSULA EBURNEA*)

Review

ROLES OF SINGLE-NUCLEOTIDE POLYMORPHISMS IN HEALTHY SUBJECTS AND DISEASE

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ARTICLE INFO

Article history:
Received 15 May 2018
Revised 30 August 2018
Accepted 19 October 2018

Keywords:
SNPs, disease-causing, genetic risk.

ABSTRACT

The application of sequencing technologies has steadily increased over the past few years. This has allowed an exponential amplification of the information available in genome databases. Therefore, more accurate data are now available to perform disease association studies. This brief communication aims to highlight the roles of single-nucleotide polymorphisms in the development of pathological phenotypes.

1. Aims

The application of sequencing technologies has steadily increased over the past few years. This has allowed an exponential amplification of the information available in genome databases. Therefore, more accurate data are now available to perform disease association studies. This brief communication aims to highlight the roles of single-nucleotide polymorphisms in the development of pathological phenotypes.

2. Single-Nucleotide Polymorphisms as useful tools in healthy subjects and human disease

Changes in nucleotide sequence of DNA can occur either spontaneously, as an adaptive response to evolutionary thrust, or be induced by chemical agents. One or more nucleotides can be involved. The prevalence of a specific variation in the population is used to distinguish between two classes of DNA alterations. Mutations are alterations of the nucleotide sequence affecting up to 1% of the general population; conversely, alterations with a frequency equal to or greater than 1% are defined as polymorphisms. While mutations usually lead to the development of pathological phenotypes, the effects of polymorphisms vary significantly. Single-Nucleotide Polymorphisms (SNPs), affecting single nucleotides, are the most diffuse variations and the main source of inter-individual diversity [1]. However, most SNPs fall within non-coding genome regions, thus making it difficult to predict of their effects. Genetic diseases comprise all pathological conditions arising from DNA mutations.

Single mutations affect a very low percentage of the population; the consequent pathological conditions are therefore defined as rare. Genetic diseases are usually monogenic and characterized by a Mendelian inheritance pattern. However, there are many factors that can influence the phenotype of mutation carriers. Most genetic disorders, instead, are characterized by incomplete penetrance and variable expressivity. These characteristics are also observed in subjects with the same mutation, resulting in varied spectra of phenotypical manifestations for the same disease. This phenomenon is easily discernible in Cerebral Cavernous Malformations (CCMs). CCM is a vascular disorder affecting microvessels in the brain. The affected capillaries appear dilated and tangled, leading to a high risk of intracerebral haemorrhage events. Lesions can arise sporadically or be inherited through an autosomal dominant pattern, leading to familial forms of the disease. Familial CCM is a monogenic condition and arises due to mutations in CCM1 (7q21.2), CCM2 (7p13) or CCM3 (3q26.1) genes [2]. A recent study conducted on a Greek family showed how carriers of the same mutations developed different phenotypes; in particular, differences between family members included both the number of lesions (detected by neuroradiological investigations) and clinical manifestations, as only one family member reported symptoms caused by CCM [3]. This phenomenon is probably linked to the existence of SNPs within both the known causative genes and unrelated genes. For example, in CCM, three SNPs in genes involved in oxidative stress response, glyoxalase I (GLO I) and paraoxonase I (PON I), have been found to be associated with disease onset and progression. These SNPs lead to missense substitutions [4]. However, several association studies have shown that SNPs can also take on a protective role.

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DOI: 10.3269/1970-5492.2018.13.27
 ISSN: 2279-7165 - Available on-line at www.embj.org

SNPs acting as modifiers in phenotypic manifestations can affect both coding sequences and regulation regions. In terms of gene promoters, changes in nucleotide sequence can affect transcription factors and miRNA binding sites, resulting in an altered gene expression [5]. Moreover, controversial roles have been reported for other SNPs, like in the case of Stargardt disease (STGD). STGD can be defined as a form of retinitis pigmentosa (RP). RP involves a large number of retinal dystrophies, characterized by rods and cones degeneration. STGD is a very heterogeneous disorder that develops at a young age; and three different forms of the disease have been reported. These show similar phenotypes despite being caused by different genes. Particularly, STGD1 arises due to mutations at the ABCA4 (1p13-p22) gene and is usually inherited as an autosomal recessive trait; however, rare dominant forms have also been reported. STGD3 is linked to ELOVL4 (6p14.1) gene mutations, and shows an autosomal dominant inheritance pattern. Mutations in PROM1 (4p15.32), instead, lead to STGD4; most PROM1 mutations act as dominant allele [6]. Among SNPs, rs3112831 (c.1268A>G) affects the ABCA4 gene and leads to the histidine → arginine missense substitution. This polymorphism was found to be associated with STGD1 development in a study conducted by Schulz [7]. However, molecular and pedigree analysis conducted on a family with natural history of STGD1 highlighted its potential protective role [8].

SNPs also play important roles in the development of multifactorial diseases, such as hypertension, obesity, chronic inflammatory bowel disorders, psychiatric illness, and autoimmune syndromes [9]. Moreover, in the recent years, researchers have been directing their attention towards the possibility to personalize pharmacological treatments in relation to individual allelic types. Many drugs, like enzymes or receptor inhibitors, might act differently depending on the three-dimensional structure of their targets, potentially meaning that SNPs causing missense variations could affect their efficacy. Likewise, adverse drug reactions may vary in relation to genotype [10]. In particular, personalized medicine is considered the most promising therapeutic strategy for both tumours and rare genetic diseases. Figure 1 summarizes the characteristics of SNPs and their roles in healthy subjects and genetic diseases.

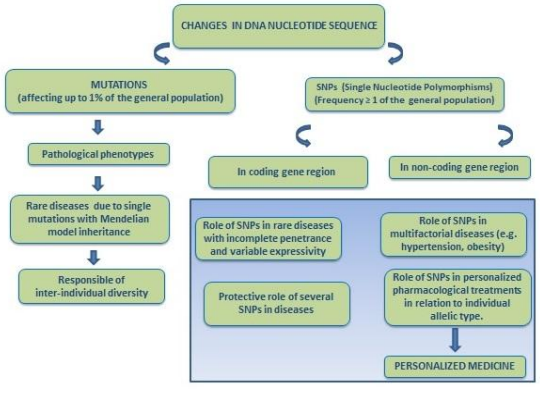

Figure 1 - Schematic illustration of the changes in DNA nucleotide sequence. The main features of mutations and Single-Nucleotide Polymorphisms (SNPs) are showed. The roles of SNPs in healthy subjects and genetic diseases are listed.

3. Conclusions

Following the sequencing of the human genome, advanced technologies, such as genomics and bioinformatics, have allowed us to set up SNP databases, providing valuable information on the pathogenesis of monogenic and multifactorial human diseases. SNP analysis has become a valuable tool, since it allows the assessment of the influence of SNPs on disease susceptibility and drug sensitivity/resistance. Another key factor of SNP analysis is the possibility to quantify the risk of developing a specific disease as early as possible and to facilitate the diagnosis, especially in cases where classic diagnostic tools are not sufficiently informative.

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