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Allele Expression and Personalized Medicine: New Thoughts

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Abstract

Personalized medicine is a medical technique that stratified patients and look at their genetic make-up for optimal therapy. It will allow for a more accurate diagnosis, recommend preventive measures and optimal treatments for each patient. Many field of sciences involved with personal medicine, among are: pharmacogenomics, immunotherapy, cancer genomics, chemogenomics (pharmacy), pathology and molecular genetics. Allele action, expression and sequencing are the most important part for development optimal strategy for the benefit of patients and better health care. New thoughts and suggestions were discussed, which can be considered as important issues for better personalized medicine.

Keywords: Personalized medicine; Allele expression; Diseases; Health care

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Personalized Medicine

Personalized medicine is called precision medicine or genomic medicine. It emphasizes the way an individual's genetic make-up influences disease risk, metabolic rate and other factors of the health profile. It is one of the most terms dealing with directing healthcare through customization it to an individual's genetic profile. Furthermore, it is a new medical technique which has the ability to look at a patient on an individual basis. It will allow for a more accurate diagnosis and recommend preventive measures and exactly dose or optimal treatment for each patient. It can also categorize patients into various groups, to create a more unified practices, approaches, treatments, more efficient drug development and optimal therapies based on their diagnostic testing and predicted response of disease [1-3].

Pharmacogenomics

It is well known that medications saved millions of lives. Specific drug may work efficiently for particular patient but may not work for someone else. Furthermore, certain drug may cause severe side effect for one patient but not for others. Genetic make-up, age, lifestyle and health condition all influence drugs response. The different response of patient genetic make-up to medication is recently investigated by many researchers. Pharmacogenomics is the main field of personalized medicine as it individualizes and customizes health care with treatments tailored to each individual patient in every way possible. Molecular diagnostics evolved into a tool that could be used for therapeutic decision making in the treatment of specific disease states, such as KRAS for colorectal cancer, EGFR for lung cancer, Her2/Neu and BRAF for breast cancer and melanoma, respectively. In parallel, research has revealed a better understanding of how human metabolize and respond to medications used to treat diseases, depression and/or chronic pain. Recently, investigations on applied knowledge of genetics from the analysis of a patient's DNA to clinical pharmacogenomics have shown how the body alters a drug once administered, how a drug impacts the diseases in the body and to predict the most favorable drug response for that individual. In addition, it considers these results within the context of other factors such as environmental and dietary factors with the goal of selecting the most appropriate and effective therapy and to eliminate unnecessary medications and dangerous adverse events [4]. Pharmacogenomics is the study of how a person's unique genetic make-up (genome) influences patient's response to drugs. Currently, more than 100 drugs have label information regarding pharmacogenomic biomarkers, of which some measurable or identifiable segment of genetic information that can be used to direct the use of a drug. Moreover, each gene expression synthesized a certain protein in the cell. A particular protein may have a big role in drug therapy as it may act in transport, breaking down, to be a target of the drug and may have a role in series of biochemical reactions. When a group of people share a common genomes and a common drugs response, such as: A severe side effects,

need a specific dose to achieve a therapeutic effect or no benefit from the treatment. This kind of information is currently used to improve the selection and dosage of drugs to treat a wide range of conditions, including cancer, cardiovascular disease and arthritis. In cancer treatments, considerations should be taken to the stage of cancer and progression which may influence prescribing decisions as well as the genome profile of the patient. There are many causes of cancer, but most cancers are associated with damaged of allele on the DNA that allows uncontrolled growth of cells. The pharmacogenomic and personalized medicine are techniques that would be based mainly on molecular pathology specially genome sequencing, which can identify mutations in DNA that influence diseases ranging from cystic fibrosis to cancer. Similarly, RNA sequencing can also involve with certain diseases. The genetic make-up of patients play large role in how well they respond to a certain treatment, and therefore, genetic make-up determine more precise and optimal drug treatment. The genetic make-up of patients play large role in how well they respond to a certain treatment, and therefore, genetic make-up determine more precise and optimal drug treatment they should be received. The promise of personalized medicine therapy with the right drug at the right dose in the right patient is a description of how personalized medicine will affect the future of treatments [5-7].

Immunotherapy

There have been tremendous successful stories in cancer therapy and life-saving potential of immunotherapy. In this treatment strategy, a patient's own immune system plays role in control and, in some cases, even cures the cancer. It was reported that immunotherapy response doesn't work for everyone. The problem is how to identify with high precision which patients are likely to benefit from immunotherapy approach and who does not respond. Recent research results indicated which people with cancer would benefit from immunotherapy. The tumors with defects affecting the "mismatch repair" pathway were more likely to benefit from an immunotherapy drug. If a tumor is deficient in mismatch repair, it contains many more DNA mutations than other tumors, thus it turns out immunotherapy appears to be most effective against tumors. Personalized medicine can also help in preventive care. It was reported that many women were genotyped for certain mutations in the BRCA1 and BRCA2 gene if they are predisposed because of a family history of breast cancer or ovarian cancer [8-10].

Cancer Genomics

Recently cancer research has discovered many genetic varieties of types of cancer that appear the same in traditional pathology. There has also been increasing awareness of tumor heterogeneity, or genetic diversity within a single tumor. These discoveries may suggest the possibility of finding drugs that have not given good results when applied to many of cases may yet be successful with particular genetic profiles. Cancer genomics is the application of genomics and personalized medicine to cancer research and treatment. It is one of the most promising biological issues in medicine particularly because of its implications in drug therapy. Furthermore, sequencing techniques are used to characterize genes/alleles associated with cancer to better understanding disease pathology and improve drug processing and development. Studies showed that mutations were found within a genome, knowing the details of their DNA sequences can reduce the impact or delay the onset of certain diseases and will allow better guided decisions in determining the source of the disease and thus treating it or preventing its progression [3,11].

Allele Action and Expression

It was well known that an allele is a variant form of a given gene. Sometimes, different alleles can result in different observable phenotype. However, most genetic variations result in little or no observable variation. Most multi-cellular organisms have two sets of chromosomes (diploid). Gene interactions between the two alleles at a specific locus can be described as dominant or recessive. When allele pairs are the same, they are homozygous. When the alleles of a pair are heterozygous, the phenotype of one trait may be dominant and the other recessive (complete dominance) when the dominant allele is expressed and the recessive allele is masked. In heterozygous where neither allele is dominant but both are functioning and completely expressed in the phenotype of individuals; the alleles are considered to be co-dominant. When one allele in not completely dominant over the other, the allele is said to express incomplete dominance. However, many traits showed polygenic inheritance (many genes involved in expressing the trait or phenotype). Results of recent research indicated that most if not all gene loci are highly polymorphic, with multiple alleles, whose frequencies vary from locus to locus and from population to population. Allelic variation at a locus is measurable as the number of alleles (polymorphism) present. A null allele is a gene variant that lacks the gene's normal function because it either is not expressed or the expressed protein is inactive. Nevertheless, one gene (or locus) can have multiple effects or phenotypes (pleiotropy). For example, albino individuals lack pigment in their skin and hair and also have crossed eyes at a higher frequency than pigmented. Sometimes one gene can affect the expression of another gene (epistasis: interaction among genes/alleles of different loci). A good example of epistasis is inheritance of coat color in some mammals. On the other hand, polygenic inheritance (quantitative genetics) indicates when a character (single trait) is controlled by many loci (genes), which they may found on different chromosomes. In this case, character showed continuum (gradient) distribution in a population and as the number of loci (genes) involved increases, the differences between the various genotypes become more subtle and the distribution fits the normal distribution curve. Examples of polygenic inheritance in humans include height and growth (as quantitative traits). At the population level, however, many allele forms are possible, and that many traits are determined by multiple loci (genes) [12,13]. In most cases, both alleles of a gene are transcribed (bi-allelic expression), in contrast to bi-allelic expression, monoallelic expression occurs when only one allele is transcribed. Gene expression is termed "monoallelic" when only one of the two copies of a gene is active,

while the other is silent. It's possible in certain genetic disorders that do not show standard Mendelian patterns of inheritance [14]. Allelic specific gene expression or allelic imbalance appears to be an important factor in human phenotypic variability causing the development of diseases. A study was performed in which genotyping was coupled with an analysis of Allelic specific gene expression by screening 11,500 single nucleotide polymorphisms (SNPs) to identify differential allelic expression. It was found that (57%) SNPs had differential allelic expression. Furthermore, certain genes display allelic variation in gene expression which may be linked to common human disorders. Variation in gene expression may result from changes in the sequence SNPs. A recent research indicated that this phenomenon is widespread through the genome and tissues. Such changes may explain up to 25 to 35% of the between individual differences in allelic gene expression. Hence, identification and characterization of Allelic specific gene expression will help us to appreciate the extent of functionally important regulatory variation. This may be enabling to focus on candidate allele variation in expression and common diseases [15]. Nowadays allele specific expression is using RNA sequencing across multiple single nucleotide variation loci to investigate allele expression. Furthermore, a new technique was developed called a meta-analysis based allele-specific expression detection and was applied to a panel of cancer cell lines and paired tumor-normal tissue samples in cancer [16]. Transcriptional activity at the different alleles of a gene in a non-haploid genome can differ considerably. Whole genome DNA sequencing allows identification of single nucleotide mutations or polymorphisms in the entire human genome, while messenger RNA sequencing (RNA-Seq) enables quantitative analysis of gene/allele expression and sequencing then construct maps of functional genome [17].

New Thoughts of Allele Expression

Medical scientists are optimistic in advances in technology of personalized medicine since it accelerated the pace of discovery and lowered the cost. Scientists moved from that of single reference genome to sequence the hundred genomes of many individuals in all their variations. Nowadays, individual patients as well as sometimes healthy people too can have their personal genomes scanned or fully sequenced. This knowledge about the basic elements of human genomes and their differences is vital to the concept of personalized medicine. It's changing the field of medicine. It's important to remember that genes do provide information that can lead to make more informed decisions about human health and healthcare. Knowing genome or the molecular basis of a disease can be an important evidence for doctors seeking the most optimistic and favorable treatment plan. In the case of cancer, genetic tests could lead to successful drug treatment rather than radical surgery. As researchers and scientists are aware of development optimal strategy for the next generation of genomic-sequencing tools to the benefit of patients and for better health care, some thoughts and suggestions are presented below, which can be considered for the future investigations in personalized medicine. These thoughts and suggestions are:

1. Not all polymorphic alleles of the same locus (gene) act, interact and express with cytoplasm microelements (drugs, chemicals, amino acids, fatty acids, oils, various minerals, sugar, and synthesized proteins) same way in each cell. These different variant alleles may result in different observable phenotype. Nevertheless, many allele variants result in little or no observable variation. Different alleles of the same locus (gene) may act, interact, respond and express, in different ways to different microelements independently in each cell or few cells or specific tissue/organ. Furthermore, researched and scientists who deal with personalized medicine should consider the interaction between drugs, contaminated food with pesticides, risk environmental factors (smoke, pollution, radiation) with human DNA/genome or even at allele level for the variation in expression of polymorphic alleles.
2. If mutation occurs for specific allele for patient under therapy during mitosis due to interaction with cytoplasm microelements, psychological or emotional issues, this may needs to check genome continuously or periodically, as this may change allele(s) sequence, which effect genetic code (transcription and translation, alter protein sequence and biosynthesis). This mutated allele may consequently play role in different physiological activity of new protein and cause abnormal function of the cell(s), new disease and/or disorder. This may make the personalized medicine inefficient, and/or may make it little bit difficult to deal with.
3. Polymorphic alleles of the same locus (gene) may each express at specific time independently. This can be seen in a locus (or may be several loci) responsible of black hair in skin, where few alleles become inactive at specific time (specific age), consequently hair start to become grey or white in certain skin cell(s). Then ultimately, nearly all black hair becomes white in advanced age (this may take months or years). By the way this is not a case of codominate. It seems that each cell has its own allele form (sequence); each has its own specific age to be expressed and become inactive. Nevertheless, this may due to interaction between genotype and cytoplasm microelements (non-genetic factors), which may play role in each allele expression. Moreover, this phenomenon may also depend on the level (amount) of cytoplasm microelements or the time required for the expression of allele. Furthermore, although each specific allele exists in each cell in the body, not all alleles express themselves, where in many part of the body they do not express.
4. Blood profile (level of cholesterol, triglycerides, sugar, uric acid, water content, clinicopathological and immunohistochemical biomarkers), blood pressure, heart beat, depression, sadness verses happiness (laughing) should be considered for patients under personalized treatment, as these factors may play role in the expression of alleles and consequently effect the personalized therapy. Investigations on the homeostasis (repeatability, stability, variation and fluctuation) of these factors are vital issues in the therapy plan.
5. Cells may show selective power of up taking microelements including water from circulating blood, this will give a chance to

any allele to interact with the microelements to be expressed its self. Therefore, microelements as well as water content of blood are vital materials to be investigated by researchers dealing with personalized medicine. Nevertheless, oxygen is the most important factor for metabolism for all living cells. Therefore, fresh air and sun light may play big role in patients' therapy. Investigations on the effects of these vital factors on allele's expression may be important in personalized medicine. Considerations of the listed above thoughts and suggestions should be investigated thoroughly for the benefit of the patient under personalized therapy? Thus, we confirm the say that not one size fits all.

References

1 (2015) Stratified personalized medicine: A new direction for placing the patient at the centre of healthcare and health education (Technical report). Acad Med Sci.

2 (2014) The case for personalized medicine. Personalized Medicine Coalition.

3 (2014) Personalized Medicine. The Promise. Personalized Medicine Coalition.

4 Saldivar JS, Taylor D, Sugarman EA, Cullors A, Garces JA (2016) Initial assessment of the benefits of implementing pharmacogenetics into the medical management of patients in a long-term care facility. Pharmgenomics Pers Med 9: 1–6.

5 Battle A, Mostafavi S, Zhu X, Potash JB, Myrna M , et al. (2014) Characterizing the genetic basis of transcriptome diversity through RNA-sequencing of 922 individuals. Genome Res 24: 1424.

6 (2014) What is pharmacogenomics? National Institutes of Health (NIH).

7 Mancinelli L, Cronin M, Sadée W (2000) Pharmacogenomics: The promise of personalized medicine. AAPS Pharm Sci 2: 29-41.

8 Collins F (2017) Precision oncology: Gene changes predict immunotherapy.

9 Le DT, Durham JN, Smith KN, Wang H, Bartlett BR, et al. (2017) Mismatch-repair deficiency predicts response of solid tumors to PD-1 blockade. Science 357: 409-413.

10 (2014) Fact Sheet: BRCA1 and BRCA2: Cancer and genetic testing. National Cancer Institute (NCI).

11 Huser V, Sincan M, Cimino JJ (2014) Developing genomic knowledge bases and databases to support clinical management: Current perspectives. Pharmgenomics Pers Med 7: 275–283.

12 Yan H, Yuan W, Velculescu VE, Vogelstein B, Kinzler KW (2002) Allelic variation in human gene expression. Science 297: 1143.

13 Pembrey M (2012) An introduction to the genetics and epigenetics of human disease. Progress Educational Trust.

14 Singer-Sam J (2010) Monoallelic expression. Nat Educ 3: 1.

15 Palacios R, Gazave E, Goñi J, Piedrafita G, Fernando O, et al. (2009) Allele-specific gene expression is widespread across the genome and biological processes. PLoS ONE 4: 4150.

16 Mayba O, Gilbert HN, Liu J, Haverty PM, Jhunjhunwala S (2014) MBASED: Allele-specific expression detection in cancer tissues and cell lines. Genome Biol 15: 405.

17 Rozowsky J, Abyzov A, Wang J, Alves P, Raha D, et al. (2011) AlleleSeq: Analysis of allele-specific expression and binding in a network framework. Mol Syst Biol 7: 522.