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EDITORIAL

Current state of cardiovascular genomics in Colombia

La actualidad de la genómica clínica en el área cardiovascular en Colombia

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Clinical genomics has advanced exponentially worldwide during the last decade due to innovation in sequencing techniques, which has made procedures increasingly faster and more economical. The current scenario is one in which the physician has the latest generation diagnostic aids in molecular and sequencing techniques at his/her disposal. What follows is a brief review of diagnostic aids based on genetic knowledge of the patient, and their current status in the Colombian market.

Prior to new generation sequencing technologies, the alternative for obtaining a patient's genetic information was traditional sequencing methods, based on Sanger's technology. In order to obtain the sequence of a specific gene, the target gene of interest was first selected. The physician had to have an idea of which of these genes could be involved in his/her patient's disease, a decision which can be relatively complex to make. Sequencing of any gene can be cumbersome due to the large difference in size and number of exons among genes, which is relevant for understanding the way in which genes are sequenced using traditional methods. For genetic studies of one gene, first, all coding parts of the gene are amplified, using the PCR (polymerase chain reaction) technique. For example, the SCN5A gene has 28 exons with an approximate size of 80 kb. This entails many PCR amplification cycles, where each exon must be amplified independently, thus increasing costs and labor time of molecular biology personnel. In cases in which sequencing of a single gene has clinical validity, taking SCN5A as an example, the complexity of the laboratory processes pales in comparison to the great benefit for the patients of knowing the possible genetic cause of their disease or cardiovascular event. However, since cardiovascular conditions are not classical Mendelian diseases, in most cases it is impossible to make an easy decision regarding which specific gene to study.

The era of new generation sequencing expanded a bit more the genetic tests that can be run simultaneously. Sequencing of panels of genes associated with certain diseases may be more useful when making decisions, compared with the information provided by the sequencing of a single gene. There are many gene panels on the market, which in the case of cardiovascular diseases may range from a dozen to several hundred genes. Many of these are commercial kits with a fixed list of genes to be sequenced. The availability of these panels varies in the reference laboratories, depending on the sequencing technology implemented. In economic terms, they can be a bit more expensive than single gene sequencing, but the clinical usefulness increases with the amount of information obtained. The literature has shown that in certain cases the gene involved in the pathology is not included in the complete lists available for study in these panels, due to the fact that the human genome is still being studied, and the association of genes with diseases has not yet concluded.

In addition, there are other panels which are very effective and useful. These do not sequence genes associated with diseases, but rather focus on genes whose

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functions are related to metabolism and drug interactions. These tests are known as pharmacogenomic tests, which provide information regarding how a patient will react to taking a medication: whether favorably, as a non-responder, or dose-dependent. In the cardiovascular field, there are many medications which are included in these tests, among which are antiarrhythmics, anticoagulants, antianginals, antiplatelets, beta-blockers, calcium channel blockers, phosphodiesterase inhibitors, and statins.

These results, together with genomic tests of genes associated with diseases, lead to an understanding of the reasons why specific patients do not respond adequately to certain treatments. An example of this would be those who do not respond to cholesterol medications, for whom there can be various scenarios:

1. The patients have gene mutations associated directly with body processes which process cholesterol, such as the LDL and Apo B genes. These patients do not respond to the medication since their genetics do not allow the regulation of cholesterol levels.
2. The patients do not have mutations in the genes associated with body processes, but they do have mutations in the cytochrome P450 genes involved in drug metabolism, causing an inadequate response to treatment.
3. The patients have a combination of mutations 1 and 2. In this case, there is much evidence to consider new generation medications which may be more effective, but the genetic causes of high cholesterol levels affect the results.

Furthermore, what should be done when studying orphan cardiovascular diseases which do not have enough clinical genomics studies, and for which there are no available gene panels to aid in diagnosis? The most inclusive test today with clinical usefulness is whole exome sequencing. This technique is based on sequencing all the coding regions of the human genome. At last report, the human genome codes for approximately 20,000 genes. This complete picture provides greater clarity on how the body as a whole maintains a functional balance through its protein structures, which allows the physician to treat his/her patient with precise and personalized medicine.

The implementation of whole exome sequencing provides, in a relatively economical fashion, all the genetic information which will code for proteins whose functions will be involved in the maintenance, performance and healthy functioning of the human body. Being the most inclusive does not mean that it is the most employed test. Many physicians still order single gene sequencing tests.

Perhaps the myth regarding how expensive panel or whole exome tests can be, or the lack of coverage under the compulsory health plan, may be the reasons why single gene tests are still ordered. On the other hand, there is a great cost-benefit in sequencing all an individual's genes, *versus* one gene at a time. With regard to costs, single gene sequencing can cost approximately one to three million pesos, and more in some cases. The cost of exome sequencing is close to six million pesos. To simplify the comparison, let us suppose that the same user has the SCN5A sequencing done for two million pesos. If we compare the cost-benefit of obtaining information on one gene for two million pesos, and a complete exome for six million pesos, the sequencing of each gene using the exome (taking into account that the human genome has approximately 20,000 genes) would be 300 pesos. This cost-benefit exercise clarifies that whole exome sequencing continues to be a better option when genetic tests are needed. As far as coverage by POS [compulsory health insurance coverage], in 2015, the Ministry of Health and Social Protection issued resolution 5592, where the Health Benefits Plan was comprehensively updated, funded by the Captitation Payment Unit of the General Health Social Security System. Codes 90.8.4.02 to 90.8.4.39 mention system coverage for molecular/genetic/genomic tests. In particular, codes 90.8.4.12 (molecular study of diseases), 90.8.4.19 (mitochondrial DNA genetic studies), 90.8.4.20 (molecular gene studies), 90.8.4.22 (molecular exon studies), and 90.8.4.24 (molecular study of mutations), fit within the interpretation that the whole exome sequencing could be implemented for these tests.

In conclusion, the use of whole exome sequencing is a test that may have sufficient clinical validity when issuing a complete diagnosis. The potential benefits for the patients outweigh the risks. The presence of pathogenic genomic variants does not mean a 100% probability of developing some medical problem, since other still undescribed factors may exist. For many diseases which may be treatable, this information will allow the patient and physician to implement timely prevention processes.