Low-penetrance genes: the democratization of cancer genetics

THE LOTTERY OF GENETICS: THE BIG PRIZE AND THE REIMBURSEMENT

We are what we are. A few of us have been very unlucky and have received a number of «bad» genes from our progenitors. But, what is the actual frequency of these gene lesions that so clearly determine that a disease will develop? In the case of cancer, the strong familiar linkage affects only around 10% of the population with neoplasms that we see in our hospitals. What is going on with the remaining 90% of patients? What is happening with the vast majority of the cancer population? Environment is certainly one reason, but genetics is also another. However, this is not the beautiful genetics with large genealogical trees and markers heavily associated with the disease that we read in the textbooks. Instead of this idealistic scenario, we are going to find that small and subtle changes in numerous genes involved in many cellular pathways are going to be key in determining our predisposition to cancer. We will call these genes involved in individual susceptibility to cancer without strong familial linkage the low-penetrance genes or the tumor modifier genes. The accompanying review from doctors Fernández-Piqueras and Santos¹ provides a good introduction to this subject.

In recent years, researchers around the world, taking the approach of comparing cancer study cancer cases versus controls, have begun to identify certain germline variants and polymorphisms in numerous genes that are associated with the presence of cancer. From colon to breast, from lung to endometrium, from head and neck to stomach, no tumor type has escaped^{2,5} (examples in the following review). What should define these changes in these genes? They should be changes that lead to some reduction of the activity of the protein they code for (but which is the cut-off point? 10%, 25%, 50%?), they should be present in a significant proportion of the population, and some plausible biological mechanism should be at least proposed. Most of these low-penetrance genes are first sought using a candidate gene approach, but we have to be more imaginative in the future. Mouse models are perfect systems to explore and finding new

tumor-modifiers, as described in the following review. Such work requires a combination of basic scientists and human molecular geneticists, a teamwork that is provided for example in the laboratories of doctors Alan Balmain and Bruce Ponder in the United Kingdom. These joint approaches are essential if we wish to find the real low-penetrance genes for all forms of human cancer.

KNOWING HOW YOU ARE MAY HELP YOU TO COMBAT THE DISEASE

The reality is, of course, more complex than the user-friendly picture I have described above. First, a single low-penetrance gene, by its own definition, is not going to be enough. We should describe for each tumor type the combination of genotypes (the haplotype) that confers the different susceptibilities to the malignancies. Second, some genetic variants may confer you «protection» against certain diseases and thus they have been selected through evolution. This is an area almost completely unexplored. Third, some germline variants in certain genes can be associated with the activity of other genes that are the real cancer culprit. For example we have found that polymorphic variants of methyl-group metabolism genes modulate the aberrant DNA methylation pattern present in human cancer⁶. Finally, low-penetrance genes are more than «cold» indicators of cancer risk. They can suggest strategies to us for prevention and therapy. For example, a person with a specific genotype that confers a reduced capacity for catabolizing a particular chemical compound should be made aware of the need to avoid all exposure to that agent. Likewise, a cancer patient who has a germline variant in a DNA repair enzyme involved in correcting the lesions induced for a particular alkylating chemotherapeutic agent, may be, in function of the drug dose, more chemosensitive or have more toxicities to that agent. Nobody escapes from the temptation to try to prevent cancer and predict responses to pharmaceutical agents (the pharmacogenomics). Doctor Craig Venter himself, the driving force behind the privately funded

Fig. 1. Low-penetrance genes in the cross-road of cancer risk, personalized treatment and individual cancer prevention.

effort to sequence the human genome, logically took the advantage of the knowledge that he had a genotype that predisposes him to lipid-related vascular diseases, by starting to take a hypolipemiant. None of us escapes from genetics, but we can modify our environment.

THE FUTURE BEHIND THE CORNER

One day, not very far away, we will be able to read our genome just as we now read the morning newspaper. Each nucleotide will make sense. By then, the tiny pieces of the huge puzzle of the low-penetrance genes will fit together neatly (fig. 1). We will have identified not only the set of genes that defines the risk of each cancer, but also those determining the propensity for suffering other human diseases. This information should be the basis for good things. We must avoid and fight against all types of public and private discriminations based in our different haplotypes. This is key issue in the case of the polymorphisms-associated with disease because each ethnicity has its own frequency distribution of these genetic changes⁷. The studies needed to unravel the major low-penetrance genes in human cancer have also to be complemented with wide-ranging epidemiological studies that will allow us to understand the cross-talk between genetics and human behavior. Such knowledge will be helpful not only for defining

cancer risk and preventing the development of the disease, but also for accomplish the long-desired goal of the personalized treatment of cancer patients.

References

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