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Genetic and Socio-Cultural Risk Contributions to Disease

Complex diseases: the relationship between genetic and sociocultural factors in the risk of disease*

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Resum. Les malalties complexes són causades per una combinació de factors genètics, ambientals i socioculturals, que interacciones entre si i amb el factor temps. Són molt comunes en la població i bona part també són cròniques, una combinació que comporta alts costos d'atenció sanitària. Però també són malalties que es poden prevenir, fet que també té moltes implicacions importants per als sistemes sanitaris. Els biomarcadors ens permeten integrar les dades clíniques, bioquímiques i genètiques per a calcular millor el risc d'una malaltia. A més, en molts casos, també sabem com controlar els factors socioculturals que contribueixen a la malaltia, com ara l'adopció d'una dieta i un estil de vida diferents. En aquest sentit, la medicina personalitzada convida els pacients a prendre accions clares per a millorar llur estat de salut, prevenir el desenvolupament d'una malaltia o reduir-ne la gravetat.

Paraules clau: medicina personalitzada · malalties complexes · factors de risc genètics · factors de risc socioculturals · biomarcadors · malaltia cardiovascular · Cardio inCode

Summary. Complex diseases are caused by a combination of genetic, environmental and sociocultural factors, interacting with one another and with the factor of time. They are very common among the population and most of them are also chronic, a combination that implies high healthcare costs. But they are also preventable, which likewise has many important implications for healthcare systems. Biomarkers allow us to integrate clinical, biochemical and genetic data to better calculate the risk of disease. Furthermore, in many cases we also know how to control the sociocultural factors contributing to the disease, such as adopting different diet and lifestyle choices. In this sense, personalised medicine allows and invites patients to take clear actions to improve their health status, prevent the development or reduce the severity of a disease.

Keywords: personalised medicine · complex diseases · genetic risk factors · sociocultural risk factors · biomarkers · cardiovascular disease · Cardio inCode

Complex diseases

If we talk about the relationship between genetics and sociocultural factors in determining the risk of developing a particular disease, what we are in fact talking about is complex diseases, in which the relationship between genetics and sociocultural factor is well established. Thus, in complex diseases, general socio-economic, cultural, and environmental conditions, such as agriculture, food production, education, work environment, unemployment, water and sanitation, healthcare services, and housing, interact with social and community networks, individual lifestyle factors, and a person's sex and age. According to several studies, the weight of both genetics and sociocultural factors in the risk of developing a complex disease is 40–60 % [X].

What are the characteristics of complex diseases? First of all, as their name states, they are complex, as several factors interact to promote these diseases in a particular person. Another characteristic of complex diseases is that they are very common among the population, and most of them are chronic diseases. The combination of common and chronic implies high healthcare costs. But, these complex diseases are also often preventable, which likewise has many important implications for healthcare systems.

In complex diseases, genes and/or our sociocultural or environmental factors may predispose a person, or not, to a particular disease. Furthermore, these factors interact not only with each other but also with another important aspect, which is time. A clear and classic example of the time-related development of a complex disease is atherosclerosis. If we look at the timeline of atherosclerosis development, we see that endothelial dysfunction progresses, sometimes as long

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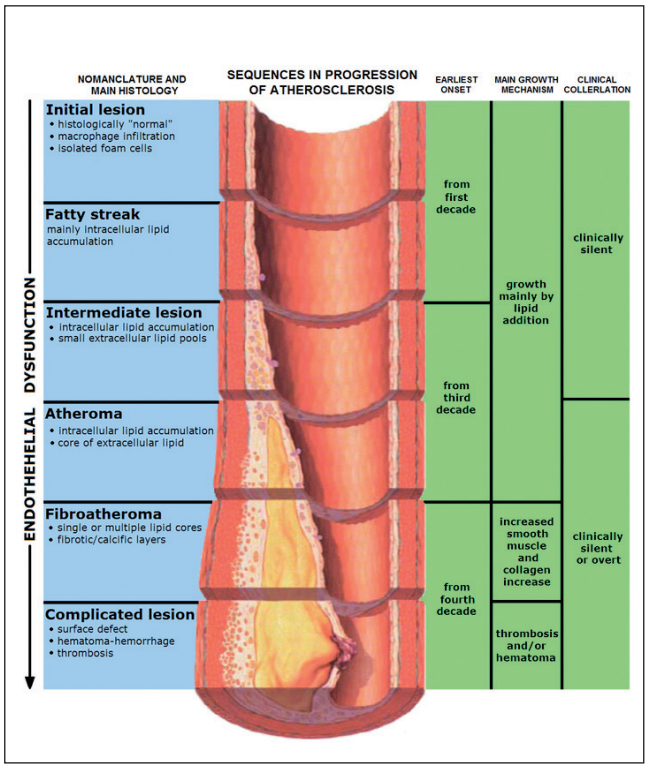

Fig 1. Stages of endothelial dysfunction in atherosclerosis. Source: Wikimedia Commons.

as four decades from the initial lesion until the atherosclerotic lesion. During this period, lipid accumulation in the arteries (foam cells, fatty streaks, intermediate lesions, atheroma) is eventually followed by the formation of fibrous plaques and complicated lesions (Fig. 1).

Accordingly, time is also a very important factor in the therapeutic equation, because it means that we have time to intervene, in this case, to prevent the development of atherosclerosis. Another important point is that because of the combination of genetic and sociocultural factors, the disease process can be very fast or very slow. For example, some people with an adverse combination of genes and sociocultural factors develop atherosclerosis and myocardial infarction by the age of forty-five whereas those with a protective combination develop atherosclerosis very late in life or not at all.

Although there might not be much we can do about the genetic contribution, in many cases we do know how to control the sociocultural factors, which is thus where our efforts should be concentrated. Sociocultural factors affect our exposure and vulnerability to disease because they include risk-taking behaviours. They are also important in gauging the effectiveness of health promotion efforts, including the access to, availability of, and quality of healthcare, and in the perceptions of and responses to health problems.

But, has acting on sociocultural factors ever proved to be efficacious? The answer is yes. Studies of the percentage decrease in deaths from coronary heart disease (CHD) attributed to treatment and to risk factor changes in different countries [1] have shown that, in most cases, altering sociocultural factors is highly relevant as it is associated with a two-fold higher reduction in CHD than obtained by treatment. The goal is to integrate sociocultural, biochemical, clinical and genetic factors in an algorithm that could quickly provide an estimate of the risk to develop a disease, and therefore identify preventative measures or therapeutic objectives for a particular person.

Throughout the 2012 EPTA meeting, it was often stated that we still know very little about our genes and the genome. While this is true, the following practical example shows that, despite these gaps in our knowledge, we can learn much from the information currently available to us. During a visit to Japan, I carried out a small experiment that, since I do not know how to read Japanese, would at least allow me to identify the Japanese characters for 'exit' and for 'toilet.' Relatively quickly, I was able to clearly establish a relationship between some particular characters and the exit and other particular characters and the toilet, without any problem and with a success rate of 100%.

The same type of experiment can be carried out with biomarkers. Thus, even though we do not understand the relationship between certain biomarkers and either disease or sociocultural factors, it does not prevent us from establishing a clear association between a particular marker and a particular disease/sociocultural factor and then validate it. Having done so, we will find that the knowledge, like the distinction between the toilet and the exit, is highly useful. And, analogous to gradually acquiring competence in a foreign language, as our understanding of the genome expands, we will eventually understand the reasons why those particular biomarkers are associated with a particular disease. But for the time being, in order to identify risk, we do not need to understand the whole story. Rather, we can use the aforementioned algorithms that combine different biomarker measurements to determine the risk that the individual in question will develop the disease under study.

Several speakers at this conference also mentioned the Personalized Medicine Coalition (PMC), which represents innovators, academics, industry, and patient and provider communities in the advancement and adoption of the concepts and products of personalised medicine. In the view of this organization, the future might be as follows:

An email alerts the physician about a new study demonstrating a connection between multiple rare mutations and the likelihood of developing type 2 diabetes. The physician then conducts a quick search of her patient database and finds some patients who are at risk in that according to their medical records they have pre-diabetic symptoms. The physician then sets up appointments with these patients to consider proactive treatment with drugs that can prevent disease onset. Those patients at risk but without pre-diabetic symptoms are sent a strong reminder and advice on diet and lifestyle choices they can adopt to avoid disease occurrence.

While for the PMC this is a view of the future, there are several current examples showing that this future is now. One thing that we should keep in mind, and which is illustrated by the PMC's vision, is that genetic and other personalised medicine tests should be channelled through physicians, and not offered openly to the general population. This can be regulat-

ed in the same way that the acquisition of antibiotics is regulated, by the requirement for a doctor's prescription. It is important to remember that genetic tests provide information that can be very useful, but it must be used specifically and the results evaluated by those with the skills to do so.

The case of Cardio inCode

To illustrate this point, I offer as an example one of the services that Gendiag (www.gendiag.com), the biotechnology company I work for, has developed. Cardio inCode® is a personalised medicine product that is already available to physicians. It is a cardiovascular risk assessment DNA-chip that has been designed to predict low-intermediate cardiovascular risk. By identifying gene polymorphisms related to cardiovascular disease phenotypes and their markers in 111 gene polymorphisms, it assesses an individual's risk of suffering from a cardiovascular event (angina, myocardial infarction, stroke, or peripheral arteriopathy) in the next 10 years. To calculate this risk, Cardio inCode incorporates clinical, biochemical, and genetic data into a validated risk algorithm. It also assesses the genetic predisposition to develop the classical cardiovascular risk factors. Finally, for the physician to provide advice to his or her patient, Cardio inCode's report also considers the sociocultural factors affecting that particular patient.

For all platforms in personalised medicine, it is important to obtain both clinical validation and analytical validation. Cardio inCode has been validated clinically in several studies. Specifically, clinical validation was aimed at establishing the association of disease biomarkers with the risk of the disease, and whether the approach used by Cardio inCode to calculate cardiovascular risk improves the predictive capability of the risk equations currently in use. The linear relationship between associated risk and the number of risk alleles was confirmed in two different large cohorts during clinical trials carried out by the Cardiovascular Group of the Municipal Institute for Medical Research of the Hospital del Mar and Gendiag [3,4].

To validate the biomarkers, the criteria of the American Heart Association for the evaluation of novel markers of cardiovascular risk were followed [2]:

1. Proof of concept: Do novel marker levels differ between subjects with and without outcome?
2. Prospective validation: Does the novel marker predict the development of future outcomes in a prospective cohort or nested case-cohort/case cohort study?
3. Incremental value: Does the novel marker add predictive information to established, standard risk markers?
4. Clinical utility: Does the novel risk marker change predicted risk sufficiently to change recommended therapy?
5. Clinical outcome: Does the use of the novel risk marker improve clinical outcomes, especially when tested in a randomised clinical trial?
6. Cost-effectiveness: Does use of the marker improve clinical outcomes sufficiently to justify the additional costs of testing and treatment?

The association of genetic markers with the disease is in the same range as that of currently used risk factors, such as cholesterol and high blood pressure, whose association with cardiovascular disease is well studied. From the results of Gendiag's studies, it was concluded that Cardio inCode provides more accurate information than obtained from the classical risk equations [3,4]. This allows for more effective preventive actions, a better definition of therapeutic objectives, and their improved achievement.

Personalised medicine allows and invites patients to take clear actions to improve their health status. Figure 2 shows an example of some of the sections of the report we provide to patients. It allows us to inform a patient about the risk of developing coronary heart disease (CHD) based on his or her genetic profile genes and relevant sociocultural factors, but also to teach the patient how, by following certain actions, the risk of cardiovascular disease can be very significantly reduced. Thus, personalised medicine allows the physician to invite the patient to collaborate in reducing disease risk.

A few decades ago, when we talked about cholesterol as a risk factor, we meant total cholesterol. But we now know that cholesterol is made up of different fractions, and that higher serum concentrations of LDL particles (low-density lipoproteins) and lower serum concentrations of functional HDL particles (high-density lipoproteins) are strongly associated with cardiovascular disease, because they promote atherosclerosis. By measuring cholesterol in blood and identifying the differences between LDL and HDL and their relationship to CHD, we have been able to develop more appropriate drugs for the prevention and treatment of atherosclerosis and CHD.

In personalised medicine, a commonly voiced concern is how insurance companies will use the information provided by a person's sequenced genome. But we forget that risk factors can be used in the same way. Should we be as concerned about our cholesterol measurements as we are about our genes? Cholesterol is a marker of risk: high serum cholesterol implies a higher risk of developing CHD. But most of us do not object to providing insurance companies with our cholesterol data. Yet the ethical concerns are essentially the same for cholesterol levels as for genetic markers. Furthermore, today, we do not have any problem in analyzing a person's cholesterol level, but in the early 1950s, when the Framingham Heart Study (www.framinghamheartstudy.org)—a long-term ongoing cardiovascular study on the residents of Framingham, Massachusetts—began to evaluate these cohorts, they too were measuring several factors whose full implications they could not yet understand. This is currently the case for genetic information, which we can relatively easily collect but only scarcely interpret.

Insights gained from experience

I would like to share some thoughts based on our experience in the development of personalised medicine products. First, with the aid of biomarkers—although we still do not understand how they work—we can integrate clinical, biochemical,

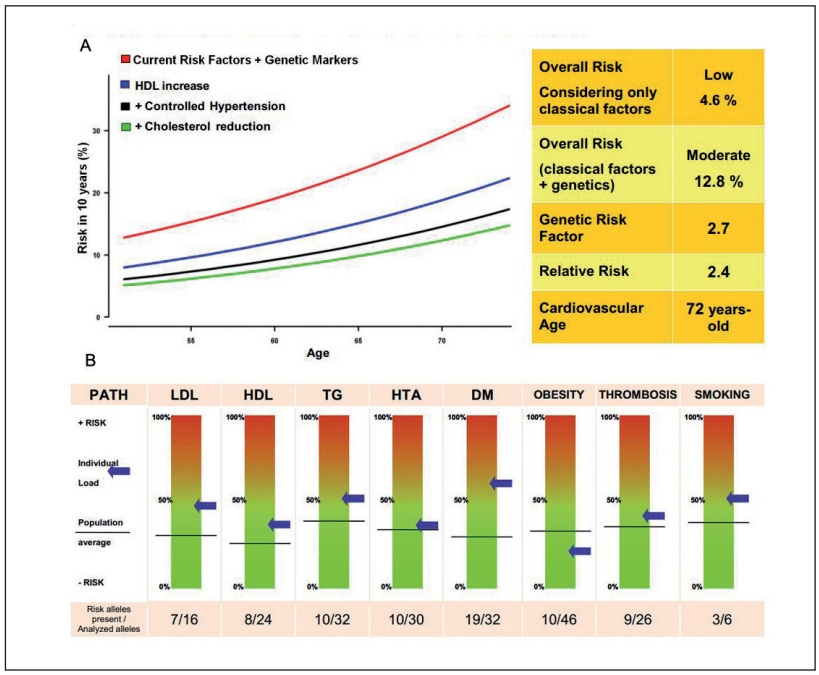

Fig. 2. (A) Results from genetic factors associated with cardiovascular risk. Probability of coronary event in the next 10 years based on REGIOR function. (B) Results from genetic markers associated with pathophysiological pathways.

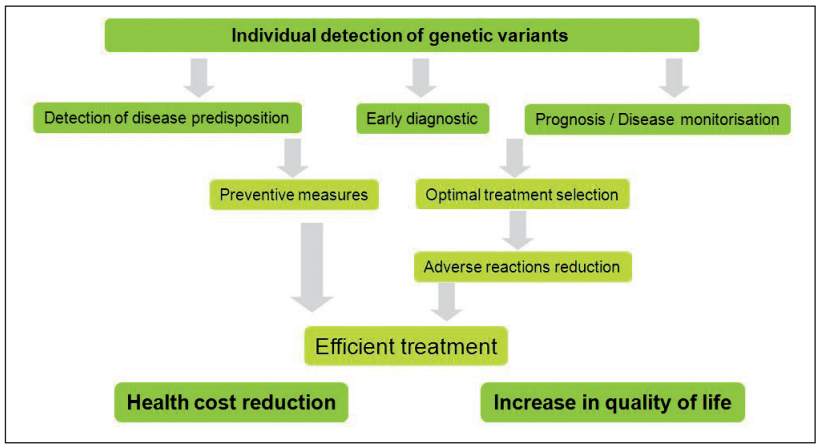

Fig. 3. Pioneering services in personalised medicine.

genetic, and lifestyle data to better calculate disease risk. With improved estimates, more efficacious therapeutic and preventative objectives can be established and achieved. We will thus be better able to prevent disease development and to reduce disease severity.

Second, other uses of personalised medicine are also possible, such as early diagnosis, prognosis, selection of best treatment, and patient follow-up. The field of personalised medicine is just beginning, so our capabilities in terms of prediction, diagnosis, and prognosis are limited. But as knowledge, technological development, and experience accumulate, so will our awareness of the potential of personalised medicine. Figure 3 shows schematically how the individualised detection of genetic variants can help us predict disease predisposition as well as its use in early diagnosis and prognosis. Ultimately, we will become more efficient in prevention and treatment, thus increasing patients' quality of life and reducing health costs.

Third, it is interesting to consider that the technology required for personalised medicine is in continuous development. Nowadays, there is intense competition between companies but also difficulties in developing and bringing to market in vitro diagnostics (IVD) products. Well developed laboratory developed tests (LDTs) should be admissible. In the end, there will most likely be two main, complementary products: point of care (POC) and next generation sequencing (NGS). But in my opinion, from a legislative point of view, NGS should become the gold standard.

Fourth, genetic tests should be used in clinical practice and they should be reimbursed, provided that the test has clinical and analytical validation and has been subject to rigorous cost-efficiency studies. Educational programs on personalised medicine should be initiated at all levels: aimed at the public, physicians, and politicians. In addition, cohort studies should be established and promoted in different countries. We have to be able to include samples and clinical data from different populations in order to better validate personalised medicine products, and to do so faster.

Finally, there is the need for the proper allocation of resources. In Europe, we have been very good at providing funding for *basic research*, conscious that it generates knowledge, wealth in the form of patents, and the overall development of society. But we have also started funding *translational medicine*, as it

facilitates the applicability of knowledge, increases the value of knowledge, and rewards public investments in R&D, in terms of small, medium, and large enterprises, employment, and a better public health system. The latter depends on adequate funding for the *application to society* of the products we have developed. It does not make sense to fund basic research and translational medicine if in the end we do not benefit, economically or in terms of improved health, from our investments. Resources set aside for personalised medicine applications will increase the overall efficiency of the system, provide patients with better treatment, improve the quality of life of the population, reduce the wasteful exposure of patients to ineffective treatments, reduce treatment side effects, delay the development of chronic diseases, emphasise prevention over treatment, and provide resources to stakeholders in the value chain. To achieve these goals requires fairly distributed resources, both from funding agencies, proving funds for clinical analysis of the new personalised medicine tools, and from governmental bodies, to finance the purchase of these technologies so that they become adopted by the health system.

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