

## The Human Genome Project

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### INTRODUCTION

Although there were some events which preceded it, the launching of the idea of sequencing the whole human genome can be situated in an article of the Nobel Prize Renato Dulbecco<sup>1</sup>, published in the magazine *Science*, March 1986, where he explained that the struggle to eradicate cancer would have been effective only if carried out with this tool. Between 1986 and 1990 the Department of Energy (DOE) and the National Institutes of Health (NIH) of the United States organized, first separately and then jointly, the launch of what finally was known as Human Genome Project (HGP). The project, officially commenced in October 1990, was expected to last 15 years, while it has been brought forward to the year 2003<sup>2</sup>. The public consortium management of the Human Genome Project was entrusted to James Watson, who was in charge up until 1993, being replaced since then by Francis Collins. Although American laboratories were responsible of most part of the execution, the project had international character in the beginning, with the participation of centres in United Kingdom, France, Germany, Japan and China. As a whole, twenty investigation centres in six countries carried out the work, sharing the chromosomes to be sequenced. In the United Kingdom, the *Sanger Centre*, the main public Molecular Biology laboratory, took charge of it and its financing was carried out by *Wellcome*, the medical Foundation with the most important assets of financial resources in the world, and an active that ascended to more than 20,000 million dollars in 1992<sup>3</sup>. In 1998, the private company *Celera Genomics*, dependent on the *PE Corporation*, whose president, molecular biologist Craig Venter, had previously worked in the public consortium of the Human Genome Project, publicly announced that it was going to try the whole sequencing of the Human Genome using a new strategy. This new strategy, called shotgun, consists in cutting the genome into over 50 million pieces, subjecting them to an automatic sequencing and rebuilding the whole through a computer programme of great capacity for calculation. After a lot of competition with exchange of mutual accusations between the public consortium and *Celera Genomics*, they reached a draft agreement to jointly announce

the accomplishment of the project, event that took place on June 26<sup>th</sup>, 2000, at the White House<sup>4</sup>, with the presence, among others, of Francis Collins, Craig Venter and Bill Clinton, at that time the President of the United States of America.

To understand the scientific importance of the project, it must be remembered that the genetic information of the cells is contained in the DNA molecules which are part of the chromosomes, threadlike structures placed in the cells nucleus. Chromosomes are visible under the microscope during the cell division. Each chromosome has just one DNA molecule, which can contain several thousand of genes. DNA is made up of two long linear chains rolled up like a spiral, popularly known as double helix. The links of the DNA chains are formed by relatively small molecules called nucleotides, whose only variable part, the nitrogenous base, distinguished them. As there are four different nitrogenous bases, adenine, guanine, cytosine and thymine, respectively represented by the letters A, G, C and T, there are four different kinds of nucleotides in the DNA, designated by the letter of the corresponding nitrogenous base.

The genetic information is expressed by the order in which the nucleotides are placed along the DNA chain. This arrangement is called sequence. The sequence of nucleotides supplies the pattern of information for the cell to manufacture proteins, the molecules in charge of most of the cellular activity included in the carrying out of the metabolic reactions that allow the normal operation of the cells and, by extension, of the whole organism. Although there are some exceptions to this definition, we can consider a gene as a fragment of DNA which contains the information for the manufacture of a protein (or of part of a protein). Every gene has from a few hundreds to thousands or even hundreds of thousands of nucleotides. Since every chromosome has thousands of genes, the total length of the human chromosome is of several millions of nucleotides, being chromosome 1 the longest with over 263 million nucleotides of length (approximately the 8.3 per cent of the genome).

The Human Genome Project had the aim to sequence the whole genome, that is, to determine the sequence of the approximately 3,200 million

nucleotides which constitute the DNA of the 23 human chromosomes (24 if we separately consider the sexual chromosomes X and Y).

Although, as we have pointed out above, the accomplishment of the project was officially announced in June 2000, it has not definitely been completed yet. What has been presented consists in a draft document that approximately covers the 95 per cent of the genome, with a level of sequencing errors still too high to be considered reliable. The definitive conclusion of the project, as for the sequencing, is planned for the year 2003. Besides, today, almost two years since that presentation, the location of many genes is still uncertain and we do not know for sure how many human genes there are, varying the last estimates between thirty and forty thousand (31,000 in the case of the HGP and 39,000 in the one of *Celera Genomics*), but at the moment being not very much precise.

#### **ECONOMIC AND MEDICAL MOTIVATIONS IN THE HUMAN GENOME PROJECT**

Such ambitious project, scientifically and financially speaking, like the Human Genome Project, counts on good and powerful reasons that justify its starting point. For the approval of the necessary assignments of public funds by the corresponding organizations (over 3,000 million dollars altogether according to Walter Gilbert's initial estimate<sup>5</sup>) it was very important that the social usefulness of the project, in terms of medical applications, was acknowledged not only by the political responsible but also by the public opinion.

The first justification offered by R. Dulbecco was, as we have pointed out, the necessity of an effective strategy for cancer eradication. However, this cause turned out to be insufficient in the light of the reviews formulated by some prestigious researchers and from the reservations arisen from some political responsible. Very soon, the proclaimed aim of the project extended to the possibility of combating not only other genetic diseases but also the whole of diseases which afflict humanity<sup>6</sup>. James Watson, describing his point of view in 1985 wrote in a very clear way: "For the following months my initial mistrust vanished and I wanted to start the project as soon as possible. By then, I considered that this one had two main objectives. It was obvious that the first reason, and the easiest to sell to the public, would be its capacity of accelerating enormously the rate of finding the genes which cause diseases"<sup>7</sup>. Although, as I would try to argue afterwards, the

medical reasons were not, in my opinion, the main motives for the starting point of the project, we must not believe that these have been used as simple propaganda to facilitate its public success. The therapeutic applications and even more the diagnostic ones, although not immediately referred to the first ones, will be important in the future and can be source, at the same time, of important economic benefits. Besides, the ideology of the genetic determinism is very successful in the heart of the scientific community, particularly among the molecular biologists. This ideology, which implies a tendency to consider the genes as the main agents of the human behaviour, also touches the biomedical field, to the extent of considering that all human illnesses can be reduced to their genetic determinants. In this sense, the Nobel Prize Paul Berg has once declared (and he has not been the only one to express himself in this sense): "They can be sitting here for an hour and they will not make me reach the conclusion that any disease they are thinking about is not a genetic one"<sup>8</sup>. This point of view implied the acceptance of putting in close correlation the sequencing of the genome to the therapeutic applications it can let, although these applications can be situated in a horizon so far away in time. The implicit argument is that if all the illness have a genetic origin, their effective eradication can only come from the knowledge of genes and, in the last resort, from the gene therapy that this knowledge can permit.

The medical justifications were completed with others of scientific order, like the possibility of spectacularly increasing the knowledge of our organism functions at a genetic level and getting to the roots of many genes interactions, not very well known; a detailed knowledge of the evolutionary history of humanity or an advance in the comprehension of the genetic base of the physiological or the behavioural difference among individuals<sup>9</sup>.

However, in spite of the importance that can be given to the ideology of genetic determinism, it is difficult to accept that the belief in the therapeutic possibilities or others justifications of scientific nature were really the main motivations of the Human Genome Project launching; especially when it was clear that the practical applications of medical type derived from the knowledge of the genome could take long enough in time, perhaps years or even decades, before being effective. Beyond the future applications, some of them potentially very important, it seems that considerations of economic nature have been the most relevant ones in the launching and the subsequent

development of the project. Firstly, from the first years of its launching requests for patents of DNA fragments started to be submitted, not only of genes, partially or totally sequenced. In 1991, when Craig Venter was working for the public Human Genome Project, he completed the expressed sequence tags (EST) technique<sup>10</sup>. With this technique, Venter described in few months thousands of EST obtained from different human tissues. On June 20<sup>th</sup> 1991, the NIH presented a patent request for a first lot of 347 EST. The head of the Office of Technology Transfer at NIH, Reid Adler, justified this initiative saying: "Our main objective is getting the development of the products. The fact of having the patent will reinforce our capacity of transferring this technology to the rest of the companies. These companies would not spend the necessary money to develop it without the protection given by the patent"<sup>11</sup>. 2,421 new EST were added to the request in the early 1992. After an intense legal battle the request was rejected because they were dealing with genetic sequences of unknown function and the NIH withdrew the request in the end. However, the policy of patenting human genes has taken its normal course not only in the USA but also in Europe, the requests coming both from public and private organizations.

A second important element in the economic motivations of the Human Genome Project is constituted by the implication of researchers as shareholders or executives of biotechnological companies. The geneticist Richard Lewontin has declared that "no prominent molecular biologist of my acquaintance is without a financial stake in the biotechnology business"<sup>12</sup>. The economic implication in important pharmaceutical and biotechnological companies was one of the reasons that led James Watson to tender his resignation as head of the Human Genome Project, due to the conflict of interests that this implication could provoke<sup>13</sup>. Finally, we have to consider the interests of the biotechnological private companies. Although their direct implication in the large-scale sequencing of the genome did not take place until the formation of *Celera Genomics* in 1998, since 1992 there were already companies specifically devoted to the sequencing of the DNA from the different organisms, including the human DNA. The most important of them was *The Institute for Genomic Research* (TIGR), founded by Craig Venter in 1992, after his resignation as a researcher for the NIH. Since the early 90s the isolation and sequencing of human genes capable of being used for the adjustment of diagnostic experiments or for obtaining drugs were also interesting for several companies, among which

the *Human Genome Sciences* (HGS) stood out, associated with a TIGR for the commercial exploitation of the sequencing data obtained by this institute<sup>14</sup>. But even a long time before, with the first steps in genetic engineering in the 70s, some companies had been conscious of the economic potential of biotechnology<sup>15</sup>. To understand the growing economic importance of biotechnology in the Economy as a whole, we have to take into account the following data from the United States which have been collected by Emilio Muñoz: "At the moment there are 1,100 companies devoted to the manufacture of medicines through recombinant techniques, to which we have to add over 700 corporations interested in the sector. On the whole, these companies employ more than 100,000 people and represent a stock market value near 50,000 million dollars"<sup>16</sup>.

If there could be doubts about the importance of the economic interests in the initial motivations of the Human Genome Project, there is no doubt about the importance of these interests in its realization and in the perspectives of development in the years to come. The most significant case is, clearly, the creation of *Celera Genomics* and its project of sequencing in competition with the public consortium, officially ended with a shared success. But other pharmaceutical giants started collaborating with specialized smaller companies to use their genetic data with a view to final adjustments and marketing of new drugs. Among others, *SmithKline Beecham* has collaborated with *Human Genome Sciences*, *Eli Lilly* with *Millennium Pharmaceuticals* and *Pfizer* with *Incyte Genomics*<sup>17</sup>. This last one has taken advantage of the public data of the HGP and of free access to the *GenBank*, in order to complete an important genes catalogue and to patent their possible use in the end. Up to now it has already got more than 500 patents and has requested approximately other 7,000 more<sup>18</sup>.

#### MEDICAL APPLICATIONS AND ASSOCIATED PROBLEMS

We shall consider now the present and future medical applications that can be derived from the knowledge of the genome. Although a critic look about the origin and development of the Human Genome Project make us accept as fundamentally correct the assessment that the main causes for its carrying out were mainly economic, this fact should not lead us not to consider the possible medical applications that the accomplishment of the genome sequencing is going to contribute in the future. Although we too believe that these hypothetical

applications could have been exaggerated to facilitate a greater social acceptance, at least in relation to its therapeutic possibilities in the short term, there must be real potentialities for therapeutic effectiveness in the medium term. If something is expected to be sold because of its practical usefulness and it really lacks it, it is difficult that such a market strategy can work effectively, although it is protected by an ideological wrapping about the importance of genes on health. Indeed, the Human Genome Project has got important medical potentialities which must be considered, although, as we will see, they also have problematic aspects. These applications can be classified in diagnostic and therapeutic, being the latter ones direct (like the gene therapy) and indirect (like the obtaining of new drugs). Diagnostic applications are the ones that have taken great steps forward nowadays and will take in the near future. More than 5,000 different genetic disorders have been recorded<sup>19</sup>. More than 1,000 genes and mutations responsible for diseases are known; and this knowledge can allow the development of a diagnostic test to know if a certain person, or an embryo, in case the technique of the preimplantation diagnosis is used, carries it. More than 740 genetic tests have been developed according to NIH data<sup>20</sup>. Even before the whole sequencing of the genome was realized several diagnostic tests for some diseases associated to particular genes had been adjusted as fast as these genes were isolated and sequenced.

The carrying out of genetic illnesses diagnoses is an advance derived from the knowledge of the genome and it is very positive, in itself, from the biomedical point of view. However, there are a series of problems associated with these genetic diagnoses which should be remembered; problems aggravated by the fact that these tests are commercialised by private companies which are obviously hoping to benefit from the economic investments carried out. A problem of general nature is that some of the diseases for which there is a diagnosis have no effective cure yet, not even a palliative therapy, and this makes the genetic diagnosis's usefulness to be seriously called into question. It can even happen that the diagnosis can be made several years before the appearance of the disease, raising doubts about the cases in which this type of diagnosis must be carried out. The most well-known example is the Huntington's disease; a dominant mortal illness, it appears when the bearer is in between a bit less than forty and a bit more than fifty years old, depending on the number of the CAG sequence repetitions the responsible gene has got, the more repetitions the

more probabilities of an earlier appearance of the disease<sup>21</sup>.

The bigger and bigger distance between the existence of tests for genetic diagnoses and the existence of therapies is due to the fact that the isolation of the gene which causes a disease does not necessarily imply a knowledge of the physiological mechanism by means of which the protein, encoded by that gene, acts in the organism. In some cases the identification of the gene produces important clues about this function, but in many others cases it does not. Besides, as well shall discuss in the following chapter, at the moment much more difficulties than the ones expected have been found in the gene therapy advances. This every time bigger distance between diagnosis and therapy can maybe reduced in years to come with the development of biochips<sup>22</sup> or DNA microarrays. With this technology we will not only be able to analyse thousands of genes with diagnostic purposes at the same time (searching for the alleles responsible for the diseases), but we will also be able to detect the expression or even the level of activity of the genes<sup>23</sup>. They could also be used to study the differential answer of the individuals genetic profiles to several drugs or to discriminate the particular causal agent of the different conditions with the same symptoms. These two latter applications could have direct therapeutic consequences on the short term (some of them are now investigated) because they will be used to select those drugs more suitable both for each individual patient and for each specific pathological agent. In the monogenic diseases, which follow a Mendelian inheritance standard, the diagnosis could be established with absolute certainty (if discounted the false positives). Although they are very numerous (there are more than 4,000 catalogued), the incidence of each of these illness over the population is very low. For example, the cystic fibrosis, which is the more common monogenic lethal disease in the Caucasian populations, has an approximated prevalence of one out of 2,500 born alive individual in the native populations of the Western Europe<sup>24</sup>. Others are rather stranger. Duchenne muscular dystrophy, a mortal disease X-linked, shows a prevalence in men of one out of 5,000 births in the industrialized countries<sup>25</sup> and the fragile X Syndrome, another disease which is X-linked, of one out of 4,000 births in men and of one every 8,000 in women<sup>26</sup>. Much less frequent are still the phenylketonuria (one out of 16,000 births) or the cystinosis (one out of 40,000<sup>27</sup>).

By contrast, multifactorial diseases present a much greater incidence. Their global prevalence is

of between 26 and 32 sick people every 1,000 inhabitants<sup>28</sup>. Multifactorial diseases are diabetes mellitus, arteriosclerosis, epilepsy, hypertension or cancer. The appearance of the disease depends on the whole by the influence of the genetic factors (normally several genes, that is why this kind of inheritance is also known as polygenic inheritance) and of environmental factors. In these cases the presence of genes associated with the disease is not enough evident to determine whether it will develop. The only thing that the diagnosis can tell is the predisposition to the disease, expressed like a probability. The following example, taken by B. Jordan, clearly illustrates this question:

There are numerous examples of genetic predisposition, to cancer, diabetes, hypertension..., that are translated only into an increase in the risk of the disease. A person "prone to colon cancer will run a risk, for example, of 10 per cent of suffering it during their existence, instead of the 0.5 per cent for the whole of the population; we will say that the *relative risk* associated to their inheritance is of 20. Elevated risk in relative value; however, it is true that the 90 per cent of the prone group will never be affected by this cancer.<sup>29</sup>

As we can deduce from the above quotation, a high or very high relative risk associated to the genes does not prevent the low probability of suffering the disease. This fact limits in a very important way the usefulness of the diagnostic tests of multifactorial diseases. This limit is not determined by faults in the technological development of the tests but by the multifactorial nature of these diseases. The direct association among genes and diseases that can be established for many monogenic conditions disappears in the multifactorial ones due to the fact that the presence of the gene object of the diagnosis is not enough for the disease to develop. On the contrary, it happens that this presence is not always necessary for the disease to appear, even in the case of illnesses in which the bearer of the genes associated to it has a very high probability of getting ill. The reasons of this scant predictive power of the genetic tests in multifactorial diseases lie in the environmental factors which can play a very important part in the appearance of the illness.

The case of breast cancer is a good example. In relation to the genes *brca-1* and *brca-2*, associated to hereditary breast cancer, between the 40 and 50 per cent of women bearer of mutations for both genes develop cancer during their lives<sup>30</sup>, a high percentage in comparison with what happens with other genes associated with other types of cancer or with other

multifactorial diseases. However, despite this high probability, it represents only the 16 per cent of the hereditary breast cancer cases<sup>31</sup> and only the 5 per cent on the whole of breast cancer cases<sup>32</sup>; the 95 per cent of women suffering breast cancer do not have the *brca* mutated genes.

These data advise us to use the diagnostic tests for these genes on women with family antecedents, in which case they can indicate the presence of hereditary breast cancer. Besides, they reveal that a strategy against breast cancer based on the execution of a genetic screening over all the population not only lacks sense, since it would leave without a diagnosis the 95 per cent of the cases in which the disease would be produced, but it also could be counterproductive: if the test turns out to be negative the women, confident in the test itself, tend to ignore the preventive measures advisable not to suffer the disease.

However, the strategy of the companies *Myriad Genetics* and *Oncormed* (the first one has patented the gene *brca-1* and the second one has marketed the diagnostic test for this gene) is precisely to extend the use of the test to all the adult feminine population looking for the support from the medical group<sup>33</sup>. The reason to adopt this line of action is simply to look for a potential market as wide as possible, what is easily understandable if we take into account that the individual cost of the test is 3,000 dollars<sup>34</sup>. Only in 1997, more than 180,000 North American women underwent this test.

The case of breast cancer is only one example of the growing pressure that biotechnology industry exerts to make a massive screening of an every time bigger number of multifactorial diseases. What was faced, at the very beginning, to the medical ground has started to be applied in the labour market and in insurances too; but the last objective is to extend it to the whole population, with the only, although not recognised, real motive of increasing the volume of potential users of these tests because of the economic benefits derived from it.

The companies with interests in this sector always put forward the reason that the tests generalization do have positive effects, since if a person knows his or her genetic susceptibility to suffer a disease in combination to other environmental factors, he or she can adopt a healthier lifestyle, and avoiding the exposition to these factors will significantly reduce the probabilities of suffering it. Although this reasoning could seem common sense, things are not always like this really.

In order for these arguments to be credible,

epidemiological studies should be carried out, along with the investigation destined to the knowledge of the genes, to know which environmental factors increase the probability of suffering a particular multifactorial disease. In the absence of this knowledge, people could difficultly adopt the appropriate changes in their lifestyle. But the truth is that this kind of studies are hardly financed, as it has been clearly pointed out by Sánchez Monserrate: "To get an idea of the difference that exists between the money destined for epidemiologic studies with respect to the rest, suffice it to say, for example, that in 1974, the rate of grants given by the NCI (*National Cancer Institute*) only had a page about epidemiologic projects among the 307 pages of subsidized projects about cancer"<sup>35</sup>. In the case of cancer these data are specially flamboyant if we take into account that the environmental factors are responsible for between the 70 and 90 per cent of all the cases of cancer. Among these factors several pollutant agents, radiation, tobacco and substances present in the diet can be included<sup>36</sup>. The combined influence of the commercial interests and the dominant genetic determinism makes that, in practice, multifactorial diseases are considered as if they were only genetic<sup>37</sup>. Their diagnosis tends to erroneously receive the same consideration as the one in the monogenic diseases. The treatments for these diseases are more and more focussed on the molecular aspects related to the action of the genes, relegating in the background the investigation on environmental factors, which could significantly reduce the incidence on these diseases. The culmination of the Human Genome project will favour this tendency to be accentuated in the future, as we get to know all the human genes and their variants associated with the different diseases.

### CONCLUSION

The carrying out of the Human Genome Project has paved the way to an in-depth study of the human genes operation and their influence on many monogenic and multifactorial diseases. Its accomplishment allows the development of more and more tests about genetic diagnosis and therapies and new drugs can be investigated to combat many diseases more effectively.

However, from the beginning of the genome sequencing launching, biotechnological companies have been accentuated their presence in all the fields of investigation related to the genome. Their economic interests are more and more conditioning the practical applications of these investigations. In the medical

field these interests do not follow the same direction of the whole society's necessities and they favour a problematic use of the genetic tests and the treatments associated with them. From this point of view, the genetic diagnosis tests in multifactorial diseases, which could play a highest part in their prevention and treatment, tend to become the main and almost only way for the treatment of these diseases, to the detriment of other lines of medical action more consistent with its multifactorial nature.

**KEYWORDS** Economic Motivation. Medical Motivation. Prevention

**ABSTRACT** In the present chapter it is carried out an evaluation of the motivations which lead to the launching and the subsequent development of the Human Genome Project. In this respect, then ideological, biosanitary and economic factors are considered. Although the importance of the sanitary applications is admitted, both in then diagnostic aspect and, the long term, in the therapeutic one, it is argued that the economic factors were the most important component in the development of the Human Genome Project. It is also discussed the sanitary applications and the problems associated to themselves, derived of the growing influence of the genetic factors in the development of the present day medicine and how the economic interests determine negatively the lines of investigation of multifactorial diseases.

### NOTES

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