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Ethical implications of genetic susceptibility testing: NeuroGenEthics and the "Angelina Jolie effect"

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Abstract. An increasing interest in genetics of aggressive behavior has developed in literature over time and specifically regarding genes involved in dopaminergic and serotonergic systems, sex steroids and glucocorticoids. The same could be said for mood and anxiety disorders, psychosis, schizophrenia syndromes and antisocial and criminal behavior. This has led to the idea that it was possible to make genetic tests applicable in psychiatry with the ability to define a risk profile. However, the results obtained to date are mostly contradictory, un-replicable and lack standardized protocols and the legal frames are not clear. The results found were that there wasn't a simple mendelian transmission or connection of a few genes. Today, we have to overcome the genetic determinism and generalize it in an interdisciplinary perspective without neglecting the ethical, legal and social issues and without slipping into a sort of "Angelina Jolie effect".

Key words: neurogenetics, predictive testing, vulnerability, un-patients, criminal trial

Introduction

The belief that behavioral traits are transmitted from one generation to the other is very old (1). Aspects of human personality such as intelligence, extroversion and introversion, social or antisocial behavior, substance abuse, the constant search for new sensations, are some of the topics of greatest interest and the object of study of behavioral genetics (2). The recent development of innovative methods of molecular biology has led to the sequencing of the human genome and has opened up the study of the molecular basis of behavior (3). Furthermore, the question of what are the components of the hereditary behavior was very controversial, due to its heavy social and political implications. In the early twentieth century, when genetics as a science was still in its infancy, there has been a rush to attribute all human traits, including complex types of personalities and even socioeconomic status, to the effects of individual genes which are inherited according to a mendelian model; this extremist position of absolute determinism fueled the eugenics movement aimed at the genetic improvement of the human species (4). In the second half of the century, however, there has been a net change as a result of several factors: the specific criticisms of the new results obtained by some geneticists, the birth of the modern social sciences and the aversion for the implementation of the ideology of eugenics (5). In any case, after years in which prevailed the tendency to avoid this kind of study, in many states, research about correlations between genetics and personality, genetics and antisocial behavior and crime are increasing.

Some research centers are able to predict, assessing the personal genetic profile, the degree of stress tolerance, the threshold for depression and pathological anxiety, the threshold of tolerance to exposure to psychological trauma (6-8). The results of these genetic experiments can spread the notion that behavior, including that of man, is genetically determined. Unfortunately, the media often report titles such as "Discovered the homosexuality gene", "Identified the gene of enterprising", "Found the gene for depression" and so on (9, 10). These three cited examples, which cor-

respond to real cases ended up in the newspapers, have been blatantly denied, as well as many others.

Over the last 20 years, literature has been developing an increasing interest about genetics of impulsive-aggressive behaviors, especially related to genetic variants on key neuromodulators involved in the control of aggression (serotonin, dopamine, sex steroids, glucocorticoids and arginine vasopressin), which represent possible biological markers of predisposition toward criminal and violent behavior (11).

Starting from this scenery, came up the idea that it was possible to carry out genetics tests, applicable for example in forensic psychiatry able to establish a genetic risk profile that could represent an objective test and also influence imputability (12).

Several studies have been conducted in this field, but results were mostly contradictory or not replicated. It should also be said that, for mood and anxiety disorders, as well as for most common psychosis and schizophrenic syndrome, a simple Mendelian transmission was not found or related to a few limited genes that play a primary role (13).

The technical impossibility to decode a single complex phenotype is particularly evident when considering the study of brain function, one of the most fascinating topics since it is involved in the connections between body and mind, between material structure and abstract reasoning, between genetically determined cellular composition and environmental influences (14).

On the basis of these considerations, the Working Group of Forensic Genetics of the Italian Society of Human Genetics at the present time, does not recognize a scientific validity in the use of genetic testing for susceptibility to behavioral traits in any way, and especially so in the complex and delicate context of forensic genetics. It is believed that these tests are not useful, scientifically invalid and unfit to achieve the purposes for which they are executed (15). An integrated approach including biological, psychological and social variables seems more appropriate, although the relative contribution of the above mentioned factors and the most appropriate methodology for their investigation are still subject to debate (16). In the outlined framework, one question arises: What role should be taken by medicine? Is there a conflict of values if we consider, on one side the principle of autonomy of the patient and on the other, the principle of beneficence and justice peculiar of medicine?

Social and Ethical implications

The bioethicist George Annas in 2000 imagined that the decoding of the human genome identified the DNA molecule in a sort of medical records (17). He had also anticipated that, before reaching that goal, it would be necessary to answer some basic questions, including: who is authorized to create the 'CD', which contains the genetic information? Who keeps it? Who controls the use? In that way, the 'CD' may be treated as sensitive medical information. Eighteen years after that prediction, this scenario seems at hand.

Not only the goal to reduce the cost of the human genome sequencing and thus to make it available has been reached, but more importantly, the techniques able to process large-scale biological samples are now available in many laboratories and so citizens are under the increasing pressure by an "health market", which emphasizes the predictive and preventive potential of these analysis.

The ethical issues that are pointed out in predictive genetic tests are framed under normal procedures of medical ethics: protection and autonomy of the person undergoing the test, privacy and confidentiality, the share of the genetic information with at risk relatives, fairness (equity) and non-discrimination. These arguments are widely debated during studies on the applications of clinical genetics, forming the core of the bioethical reflection (18, 19).

When (and if) Genetic testing should be offered

Genetic tests are heterogeneous. In medical practice, they are mainly used with diagnostic purposes. The diagnostic tests are performed on people who have, or are suspected of having, a particular disease; attempting to resolve the question is whether the patient has or has not a specific disease (20). Genetic tests are instead classified as pre-symptomatic, when they identify the risk of developing a disease in the future in a person not suffering at the time of the analysis and who belongs to a family in which one or more in-

dividuals have a late-onset disease. A pathological result of the analysis indicates that the person is likely to develop the disease at some point in his life, if he lives long enough (eg. Huntington's disease) (21). Finally, the predictive genetic tests covering many common diseases, in which the risk of disease is increased or reduced, but with a level of accuracy much lower than that of other genetic tests (eg. ApoE4 and Alzheimer's disease) (22).

It is widely believed that the increasing knowledge about the human genome can determine an indiscriminate spread of these genetic testing often without a required medical application. A genetic test should allow individuals and their families to identify, understand, and especially checking out their risk of contracting certain diseases. The challenge is to ensure that genetic tests are offered in the most effective and fair way with high quality standards. This can be achieved only if genetic tests are considered as an integrated service, and not just as an activity of the laboratory. The gap between the diagnostic and therapeutic capacity should never been forgotten in the case of the development and application of a genetic test. The ability to predict that an individual will get sick or, still in perfect health, is predisposed to contracting the disease, especially when there is no therapeutic treatment or prevention, may result in a high cost in terms of psychological and social implications and create particular problems of an ethical and legal (23).

Genetic testing and the "Direct To Consumer" medicine

Over recent years the widespread use of Internet and web search engine, led to the emergence and flourishing expansion of a market based on the commercialization of "Direct To Consumer" (DTC) genetic testing. A dozen of sites can be found through Internet, that sell the whole entire analysis of the genome (23 andMe, DeCODE Me, etc.) or targeted analysis on the study of susceptibility to complex diseases such as the psychiatric ones (DNA Direct, Direct Health Test).

More and more people will have free access to genetic testing of any kind, without a close medical supervision, and will have a large amount of information about their health status, without having the right tools to interpret and manage and with the lack of guarantee on the respect of the privacy regarding own data. The field of genetic tests sold directly to consumers, is the subject matter of a heated debate for more than fifteen years: dating back to 2003, the first survey on DTC tests, was conducted by the British Human Genetics Commission (HGC) (24).

Since then the situation has not changed with regard to the regulation of this business: there aren't clear laws in many European countries, and in some countries do not even exist guidelines (25). In the last years the caution indication for these initiatives, has not been able to curb the marketing of predictive or susceptibility tests, which are often no scientific validated and which are offered outside protocols and standards with which the medicine should be approached with the diagnostic and technological innovations.

Despite the controversies in the USA, the first test to detect genetic tendency to mental illness is already on the market. It's called Psynome, it costs $ 750 and one can simply order it on the Internet (26, 27). The kit to collect the saliva sample, on which the test will be performed, directly arrives at home; it only takes a drop to reveal if in the DNA are present genetic variants associated with the risk of developing bipolar disorder, a disease that dangerously alters the mood mechanisms and affects on 1% of the adult population. John Kelsoe, a geneticist at the University of California and father of Psynome, argues that the test will help physicians and patients, dramatically reducing the time required for diagnosis of the disease, which now takes an average of seven years. By analyzing the DNA of hundreds of families, Kelsoe found that when two particular gene variants are present in the Gkr3gene, the risk of developing the disease could double. The conditional tense, however, is a must, because, as the American geneticist Francis Collins, head of the Human Genome Project, told to the magazine 'Science' (28) it is not shown which genes are actually involved in bipolar disorder, which is considered a complex disease, where environmental factors affect genetic ones.

The increasing availability of these tests directly accessible to the consumer, outside of strict medical supervision, makes imperative for professionals to continuously update on the types of tests on the market, on the possible applications in the health field, on

the potential and limitations related to genetic testing, and on the interpretation of the results. DNA testing is not a game or a curiosity, but a tool of science still evolving, to which approach, with a serious health motivation and with the help of a geneticist or physician.

Genetic Counseling and Informed Consent

In the case of predictive genetic tests, ensure a high quality service means also taking care and worrying about the social and psychological effects associated to them. Special attention should be placed in communication, as giving a clear information on the service, but also on the interpretation of the results through proper counseling. All National, European and International documents offering Recommendations and Guide Lines on genetic counseling, consider it indispensable and even imperative, either before or after testing, especially in the case of pre-symptomatic, susceptibility or probability tests (29). It will, increasingly respond to people who want to know their susceptibility or resistance to multi factorial diseases or their suitability for certain treatments. It will not, therefore provide a "certain" risk in relation to a specific disease, but to be able to communicate very complex concepts about the nature of "probability" in the information of this type of tests.

Similarly to what observed for the susceptibility testing related to pathological phenotypes, the test prediction of human impulsive-aggressive behavior suffer the same limits, with particular reference to the positive and negative predictive values as well as those relating to the specificity and sensitivity. Important questions are about how much genetic counseling is necessary for the user to understand these concepts and what may be the best strategies to communicate (30).

The exercise of self-determination, that is true, both in the decision to be tested and even to escape from it, however, is not devoid of effects, to evaluate with full responsibility. First of all it involves rights: who decides to be tested, has the right to receive and exchange data acquired freely, without pressure, to ascertain the truthfulness of the information concerning the analyzes performed on his body, to choose which information can be spread to others and to exercise the "right not to know".

However, there are also duties. Who decide to take the test might reflect on some personal effects related to the outcome of these tests such as severe depression after the unveiling of predisposing to progressive diseases, anxiety and conflict between acceptance / refusal to change lifestyle as a preventive measure, awareness of the procreative risks and the effect on other family members.

Therefore, the consulting service offered to the individual must encourage his self-awareness so that he becomes able of taking decisions accepting the related psychological and social implications.

The consent act, following the genetic counseling, it's the documentation of the received information and testimonial of the positive determination of the subject to undergo a genetic test (31); informed consent is defined only when the person has received, in an appropriate manner, all the relevant information and is therefore in a position to understand the risks, benefits, limitations and the ethical, social and psychological implications related to genetic tests and so the multidisciplinary of competence is very significant.

The access to results and the psychological impact

The psychological repercussions of the individual who is undergoing genetic susceptibility testing, and consequently of his family, is a fundamental chapter that requires special attention. The emotional consequences that the result of a genetic test could generate, is sometimes difficult to manage (32). The discovery of an average risk of contracting certain disease, for some people is better than living with stress and anxiety caused by ignorance. One might have the feeling that the information could be useful because that means one can try to do anything possible to prevent, restrict or delay its onset. For others could be like discovering to have already a disease and that may cause the feeling of being alone, anxious, frustrated, and maybe feel ashamed.

To perceive themselves, and to be perceived by others, as people "at risk", and therefore as different compared to common expectations of "normality", can indeed influence the development of the sense of self and self-esteem; in fact the certainties of social acceptability are increasingly dependent from the adaptation

to a dominant model of physical and mental health efficiency (33).

Discrimination and Stigma

Genetic information are sensitive data, thus require that the fullest protection of safety and confidentiality of the treatment are to be given, this is foreseen from the privacy policy and from a relational point of view, based on the principle of confidentiality. Currently the greater dissemination of medical information between multiple parties did increase in public opinion, the fear of being subjected to discrimination as a result of broader knowledge of their genetic condition which has not opposed a more accurate confidentiality of the data. The rejection of discriminatory behavior based on the genetic profile is now widely shared on both legal and ethical (34). In practice, however, is still a concept that suffers from exceptions and different interpretation, especially in the context of work activities and, in certain circumstances in insurance, industry and business.

Especially in countries with a liberal economy, episodes of "working selection", of "scholar ship selection" and of "failure to progress in career and in leadership roles of greater responsibility", were observed on the basis of genetic evaluations mainly related to susceptibility testing of organic disease, but also to aptitude genetic test for psychological and psychiatric disorders.

In the insurance sector, the situation is even more complex, however, the question about the lack of insurance coverage for health or life does not arise in Europe and in those states that have adopted systems of universal coverage of health risks. A monitoring on European regulations shows that only Italy (35, 36), France, Belgium and Denmark have the statutory prohibition on the use of genetic testing in the conclusion of insurance. Other countries have chosen or a moratorium path (Finland and Germany) or a limited use strictly related to the thresholds value of insurance (England, Holland, Switzerland, Sweden).

Beyond what may be the discrimination by an insurance point of view, disciplinable in different ways, there are other forms of discrimination and stigmatization more subtle and, unfortunately, quite common in the social life and more complex to eliminate. Alongside the non-discrimination, has recently appeared the no-stigma principle that does not necessarily affect the exercise of an individual right resolving in a psychological attitude of hostility or discomfort towards those who are perceived as "different". The "DNA mystique" is likely to be harbinger of the deplorable forms of classification and of "social control" which could result in selective drifts and "politics of exclusion" in many context of social life (37).

"Un-patients"

For a long time medicine has been a primarily "palliative" function in respect of the patient, for whom he had little healing resources to offer. With the development of scientific medicine, major diagnostic and therapeutic advances have made possible not only to better understand the disease, but also to treat it more effectively trying to intervene in its early stages. The additional step was even more ambitious: to identify the "potential disease". The Angelina Jolie's choice to have both breasts removed because carrier of gene variant Brca-1 which greatly increases (over 80%) the risk of developing an aggressive and often fatal breast cancer, caused a stir and created great confusion (38), such as the decision of a British manager to have his prostate removed for the same reason (39).

Nowadays this excess of knowledge is likely to create more doubts than certainties. The "certainty language" is not commonly used in medicine, instead, the "probability language" is the most used one. Even predictive medicine, in the presence of specific genes that predispose to cancer or the onset of severe neurodegenerative diseases simply expresses the high possibility that these pathological conditions develop in that individual, not that the disease will manifest itself certainly. Is that an aid to health or an obstacle to a quiet and peaceful existence? The risk is to make life medicalized, making feel sick who is actually healthy.

These conditions emphasize how the new reality of predictive genetic testing might undermine the concepts of health and illness, therapy, and doctor-patient relationship.

The "un-patients" are a new class of people within medicine: they are not "patients" in the classic sense, since they do not show symptoms and signs; they are

people who share genetic predispositions and who might live in the expectation of the hypothetical appearance of any sign of disease, who organize their lives according to the medical examinations or laboratory tests, and who end up feeling sick or even develop psychosomatic symptoms.

Genetic vulnerability and criminal trial

Giving excessive importance to these biological characteristics can lead, following a consequential logic, (slippery slope theory) (40), to the predetermination of future ways of behaving of the individual, to the point of justifying the application of preventive measures, in order to reduce the risk of deviance of those who, following this address would be considered predestined, according to a probability calculus, to express an impulsive-aggressive attitude. From a criminal justice system, related to the commission of an offense, one might lead to a preventive model that, regardless an unlawful conduct, would legitimize the compression of personal freedom only for the presence in the DNA of the suspected person, of peculiar properties predisposing to violence and crime, which would open the way to selective scenarios of Lombrosian memory (41). The knowledge of the genetic correlation between aggressive and impulsive behaviors are progressively and dramatically increasing, but not as they are increasing regulatory and legal frames within which these data and knowledge must enter. It is conceivable that the defense lawyers will ride this evidence to subtract the defendants from legal liability, as it is conceivable to fall deviant behavior in terms of a state of disease, genetically determined. The magistrate then, will face with new situations for which, he may not be called to order a prison sentence, but the obligation of therapy that would prevent further criminal conduct (42).

Conclusions

The issue discussed in this dissertation is rather complex and a quick analysis of the literature allows to assert the following propositions: heredity varies depending on disorders; in spite of the obvious genetic basis of common forms of psychopathology, it must be remembered that inheritance is not synonymous with inevitability, given that even the most heritable disorders can improve with psychological treatments; the interplay between genes is important. The simple heredity of a liability gene or the exposition to momentary events often don't leads to mental illness. Genes and environment influence each other; the results of molecular genetics are contradictory. No clear consensus on the location of putative genes for the development of defined psychiatric disorders has been revealed. These data highlight the limits of current psychiatric diagnostic phenotypes in relation to genetic analysis and show that the use of genetic testing on a clinical level does not offer relevant information. In particular, the assessment of social dangerousness is a psychiatric clinical evaluation with relevant consequences on the prognosis. Genetic analysis for its current structural characteristics and for the information that can now provide, it is not able to take into account the dynamic, evolutionary and transformative aspects inherent the complex notion psychiatric social dangerousness.

All this aspects, in conclusion, can generate: risky short-circuits (defensive forensic psychiatry); reduction in the accuracy of clinical assessment; aggravation of social stigma and consequent worsening of prognosis (circular causality); flattening of forensic psychopathology research on existing case law. It must therefore be cautious in the use of genetic data, which will undoubtedly require a wider statistical validation and a more precise definition of their validity and explanatory.

We are in front of two principles: the first is the autonomy of the individual, the second is the role of Medicine.

On one hand the autonomy of the individual who – whereas duly informed – is in a position to choose whether and when undergo a genetic test, undertaking the responsibilities of his own choice.

On the other hand the role of Medicine, which has its own values besides values conveyed by the community. Medicine must decide if and in which conditions some treatments may to be available. Medicine also responds to the principle of beneficence and the principle of justice, since – to avoid any discrimination or inequality, some form of public intervention is definitely required.

At present, it seems that the first principle has wide relevance and is broadly considered while the second is not thoroughly studied nor considered. Moreover it's Medicine itself – in the sense of social entity – that is still too week and unable to take accountability for those crucial decisions.

Indeed, it is Medicine which needs to create those boundaries of legitimacy for certain interventions, boundaries within which the independent choice of the individual may unfold. We will then be able to avoid an anachronistic paternalism but at the same time we'll be finally able to safeguard beneficence and to promote justice.

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