Opinion regarding the application of genetic testing to individual studies, family studies and population studies. (Problems related to DNA "banks", cell "banks" and computerisation).

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Opinion: Genetic testing

With progress in human genetics it has become possible to investigate individual genetic information using a single DNA sample.

Spectacular progress in the acquisition of knowledge has resulted from this technology and ongoing research should lead to further acceleration of this progress. The knowledge thus gained has already been applied to the diagnosis of serious genetic disorders.

Such applications however make it necessary to weigh the beneficial consequences to the individual and for Public Health against the possible perverse effects in both areas.

In practice, it is very difficult to draw a clean distinction between research and its application, they are always at least partially interlinked and overlapping.

Ethical rules are essential in this area.

At the individual level

An individual's genome cannot be used for commercial purposes, because, like other physical components of his person, it is part of his being rather than his assets.

This characteristic of " non-property" does not preclude research and analysis of the constituent elements of the genome.

Such analysis must be of obvious benefit to the subject who submits to it, or to his family, or should be part of a research programme deemed useful by the scientific Community.

- Sampling of DNA for analysis must remain a medical act and be part of medically recognised practice.

- Any determination of the characteristics of an individual's genome should be made only after full and direct information on the planned analysis has been provided and it has been made certain that the full possible implications of the resulting knowledge are understood, with time provided for consideration.

The subject's consent is to be given for specific analysis. If investigations are extended to genome characteristics in a different area than that for which the consent was given at the time of sampling, new information should be provided and new consent obtained. It is possible to withdraw the sample.

- Each individual should, in principle, be made aware of the possible results of the investigation and be informed of their implications. However, as these results, whether they lead to certain or probable diagnosis, can affect the life or the behaviour of the subject, having understood the implications of the analysis for his life each individual should have the possibility to ask, at the time of sampling, not to be informed of the results.

For some basic research, particularly if it aims to investigate risk factors for disorders caused by several factors for which no realistic prevention can be envisaged, it would be better to state before sampling that no results whatever will be reported.

- No result concerning the characteristics of the genome of an individual is to be provided to parents, third parties or any public or private organisation without the explicit consent of the individual. Results provided as part of a medical diagnosis will be reported through a doctor able to fully explain their meaning.

- The individual whose genome is being analysed must be legally capable of consent and must be able to understand the full implications of the results.

If this is not the case (minors....), studies should be restricted to exceptional cases for which knowledge of the characteristics of the genome is essential to analysis of the transmission of a mutated gene responsible for a monogenic disorder required to diagnose a family complaint.

- Parents may request a genetic analysis of their child, only if the disorder related to this genetic information can arise before the age of 18, or if preventive measures can be taken before the age of 18.

- A pregnant woman at risk of a severe single-gene disease may request a prenatal diagnosis on the genotype of the baby she is expecting.

- Sampling on a minor for research purposes only, requires submission of the procedure to a committee of ethics.

Family studies

Genetic family investigations are essential, both for the acquisition of genetic knowledge, and for diagnostic applications. The biological family and the legal family may not be the same, and there should be no disclosure. Knowledge of genetic characteristics is not the collective property of the biological family.

- All the rules listed at the individual level are to be followed and apply to all members of the family, be they potentially at risk or not. The quality of information provided is one of the most important rules to be applied before any sampling.

The method of access to various family members should be subject to certain rules:

- Family members should be contacted personally by the relative requesting the test, if necessary with the assistance of a doctor as it might be technically difficult for him to explain his request.

- It is hardly imaginable that persons who are not aware of a relative's disorder and of the reason for the genetic investigation should be directly contacted on the basis of information provided by a relative. In the case of neuropsychiatric disorders, the subject may not be capable of sufficient judgment to comprehend the information for himself, and may unwittingly provide a distorted message to the family. It is the doctor's responsibility to personally and directly inform each interested party.

The same problems can arise if the subject at the origin of the family investigation is a minor. Access to family members should be through the parents.

Quality of information and training of medical personnel

Quality of information provided is the essential requirement for all applications of genetic testing.

It should be stressed that medical personnel need urgent training in this area through education in medical genetics and through the practical organisation of this medical activity which is not yet recognised as a speciality.

Registers, DNA banks, computerisation

DNA banks necessarily require computerised recording of personal data concerning donors of cells stored in the bank. Consequently, all the rules which apply to keeping and using medical registers also apply jointly to the DNA banks themselves and to the recording of data which unavoidably follows.

These rules were defined in the Opinion published by the Committee on May 6th 1985, and in various other Opinions which clarified and complemented it. They are as follows:

1. registers are to be kept only by a small number of centres approved by a public authority and in accordance with all the necessary scientific and ethical safeguards. The same principle should apply to DNA banks.

2. to meet the need for medical confidentiality centres keeping registers are to be placed under the responsibility of a physician who agrees to consider himself a consultant in his dealings with other practitioners who supply the information which is recorded. He is of course bound by the rules of medical confidentiality and should give these practitioners his views regarding the diagnosis and the therapy to be applied to the case for which information is provided.

3. the law dated January 6th 1978 on Computerisation, Records and Liberties stipulates that any interested party:

a) will be duly informed of his right to oppose the dissemination of information (and consequently also the DNA sampled) about himself, will not have stated his opposition and, in practice, will have given written consent to such dissemination;

b) will have access at any time to the recorded information, through a physician of his choice;

c) will have been advised of his right to ask that the information concerning himself be deleted from the records, if he has a serious reason to do so, and therefore that his DNA be removed from the bank.

4. The Committee feels it is not qualified to pronounce an opinion on whether sampling and transmission of human cells to a DNA bank, and the resultant recording of personal data in a register, is covered by the law dated December 20th 1988, modified on January 20th 1990, which stipulates that an investigator, before undertaking research on human beings, should submit the project to a *Comité consultatif de protection des personnes dans la recherche biomédicale* (Consultative Committee for the protection of subjects in biomedical research), located in the region of the investigator's activity.

5. It should be prohibited for any third party, particularly employers or insurance companies, not only to have access to the information contained in a register, therefore in a DNA bank, which is already implied by the above rules, but also to ask the subject to supply information about himself, contained in the DNA bank.

6. A search for genetic fingerprints and the use of such information should be subject to prior authorization by a legal entity, pronouncing judgment on whether the search and use of the information is justified in law and in practice.

The legislator alone is in a position to put into full effect some, at least, of the guarantees listed above. Adoption of necessary measures to this end is desirable.

General considerations

Progress in molecular genetics has opened a vast field of investigation into individual genetic characteristics.

As with any research, a distinction is to be made between the acquisition of knowledge which creates no new ethical problems, and the use of such knowledge for which it is necessary to weigh the beneficial consequences to the individual and for Public Health against the possible perverse effects in both areas.

In practice, it is very difficult to draw a clean distinction and there is always at least partial interlinking and overlapping.

DNA

First a few properties of DNA (deoxyribonucleic acid) and the possibilities arising from DNA analysis using the technology of molecular biology, should be recalled.

- DNA, holding complete information concerning an individual, is present in its entirety in each nucleated cell of the organism, which makes it possible to study it using various samples (blood, sperm, hair bulb....).

- DNA is stable after extraction from the cell and can be preserved relatively easily for a long time, giving rise to the development of DNA " banks" . Gene amplification techniques can be used to synthesise in vitro a large number (millions) of copies of a given segment of DNA.

- Some blood cells (lymphocytes) can be immortalised and kept in liquid nitrogen, leading to the creation of " cell banks" from which large quantities of DNA can be obtained, when desired.

Hence a single sample will provide complete genetic information regarding an individual, not only the information which can be obtained in the present and for which the sample was collected, but also all the genetic information which it will be possible to extract in the future.

Applications

1. Diseases for which the method of genetic transmission is known

DNA analysis by molecular biology for single-gene diseases has revolutionised this field of pathology. This progress has made it possible to:

- first precisely locate the responsible gene on a segment of chromosome, known as gene mapping

- then in some cases isolate the gene characteristics, and then identify the protein (myopathy, cystic fibrosis)

Localisation of the genes responsible for these diseases (and subsequently identification of the gene) is based on broad family studies.

The analytical technique used is " tagging" of the chromosome segment which includes the mutated gene based on the close relationship with DNA polymorphism. The significance of this polymorphism is generally unknown, but when located close to the gene, and if possible on either side, it can be used to trace the transmission of the gene in a family. Thus in one family the mutated gene will be " linked" to form " A" of a marker, and in another family to form " B" , hence the need to study extensively each family over several generations.

Following research on the position of the gene, this polymorphic locus link analysis is used daily for diagnosis requested by families, to identify healthy carriers of the mutated gene (particularly in x-linked diseases), and possibly to make a prenatal diagnosis.

Furthermore, banks of DNA or cells of diseased persons offer families diagnostic possibilities after the death of the individual, as has been achieved for genetic diseases.

These family genetic studies and databanks are thus essential for diagnosis; even if the gene is known, the same disease can result from many mutations and the particular mutation for a given family offers diagnostic possibilities.

It should be realised that this information needs to be kept available for a fairly long time (at least 20 years) to offer future generations the possibility of diagnosis. This family data also contains information on (legitimate or illegitimate) filiation which must be kept secret.

2. Research on genetic factors possibly related to non-monogenic diseases: multifactorial diseases.

Such research is largely aimed at neuropathology (schizophrenia, manic depressive psychosis, Alzheimer's disease....), cancers, cardiovascular diseases, auto-immune disorders. Research is aimed at discovering the molecular factors of genetic risk, their localisation and their identification.

Groups of increased risk subjects can be identified using these " susceptibility genes" and other factors which increase the risk can be found in these groups (genetic, environmental....). Preventive behaviour to reduce the risk can possibly be evaluated and recommended.

Contrary to the case of single-gene disorders, where the diagnosis for a mutated gene is

certain, even though the way the disease is clinical expressed can vary, in the case of multifactorial diseases the diagnosis is always a probability.

In the case of cancer, almost all types have known hereditary forms, frequent in some cases (retinoblastoma for example), but rare in others. Susceptibility genes for various cancers have already been found. Detection of higher risk patients using susceptibility genes could make it possible to either avoid the development of tumours if there are known environmental risk enhancing factors or to detect tumours earlier by selecting higher risk groups and thus implement therapeutic behaviour or, after the tumour has been discovered, apply prognostic elements leading to therapy.

In the field of neuropathology the situation is, and will remain, more complex: nosology is still frequently modified, genetic penetrance is uncertain, the study of factors linked to the genes and to human environment suffers from methodological weakness, and the results of any research both on the environment or on the subject have particularly dire consequences.

For all this research broad family studies are implemented and lead to the setting up of DNA and cell banks. In the case of many multifactorial diseases, localisation of polymorphic genetic markers, very successful for single-gene disorders, is probably not the only possible strategy. In this area, research is important for knowledge acquisition, but, when one considers the application of such knowledge, the possible long term " benefits" for the individual, the families and for public health are doubtful.

3. Genetic identity testing.

DNA polymorphism can be used for genetic identity tests (DNA fingerprint techniques) (ref. the CCNE Opinion dated December 15th 1989).

Their use in criminal cases (corpse identification, rape....) requires knowledge of the distribution of this polymorphism in the general population. For example, a polymorphism can be frequent in one region and rare in another. Scientific departments working with the police therefore would like to know the distribution of polymorphism in specific populations (as was done in New York). In our country, it is relatively easy to get a good idea of the distribution of these characteristics in regional populations. The problems related to overseas dominions (West Indies for example) or to immigrant groups (North African....) are much more sensitive.

Ethical problems and orientations

Ethical problems are concerned with two different but closely related subjects:

- collection, use, preservation and dissemination of an individual's genetic information obtained through testing;

- collection, preservation, dissemination and eventually use of the DNA, an element of the human body which contains genetic information.

Several ethical requirements should be taken into account when these various operations are performed.

Respect for the right of self-governance

The rights of the individual to make an " informed" decision concerning a test which could reveal the presence of a mutated gene or a susceptibility in his genetic make-up, and which, whatever the result, could have a profound effect on his life, should be respected.

To this end, there are three essential conditions:
- freedom of choice without any coercion,

- complete understanding of the implications of the decision,

- the subject should be legally capable of informed consent.

This requirement of self-governance will apply not only to the subject from whom the initial request originated in a high risk family, but also to all other members of the family, be they potentially at risk or not, and over several generations.

There are several types of problems associated with setting-up these DNA banks.

At the time of sampling blood from all the members of a family, how shall each member be informed, what type of pressure will be applied to obtain blood from unwilling subjects? The subject making the request should personally contact the other members of his family, and this can be lengthy and sensitive.

It is hardly imaginable that persons who ignore the purpose of the genetic tests, and possibly even the precise nature of the disorder affecting their relative, could be contacted directly by a physician who would have been given their name and address by their relative.

Concerning diseases for which a diagnosis can be made, the motivation for the whole family is usually the need to make a prenatal diagnosis for a pregnant woman.

What of the case where only a research programme is involved?

In the case of neuropathology, the patient may not be capable of sufficient judgment to understand the problem for himself, and he can unwittingly spread a false message in the family. It is then the responsibility of the psychiatric practitioner to directly and carefully inform each contacted person.

How can sampling from a minor be justified if the only motivation is research?

The right to know

Each individual must be kept clearly informed of the possible results and their implications. But knowledge can limit the individual's self autonomy.

Such can be the case in situations related to single-gene illnesses where knowledge can modify the behaviour of an individual, for example, in x-linked diseases, a woman's knowledge that she is the carrier of the illness (myopathy, haemophilia....) in dominant disorders, knowledge that one is the carrier of a mutated gene and therefore at risk in the future (Huntington's chorea). The individual can therefore refuse to be informed of the results.

Knowledge of a probability may be more complex, as in the case of " susceptibility" genes. Will a subject be self-governing if a susceptibility gene is found, relating to a cancer or a neuropathology, with no other consequence than the need for systematic tests to transform a probability into a certainty, hypothetically and after an indefinite amount of time? He might well ask if it is appropriate to know of the results concerning a genome characteristic which would only lead to a probabilistic assessment of the risk of a serious disease for which no effective prevention can be advised nor undertaken.

Can a child be told of his " biological destiny" ?

" The hiatus between rapidly increasing predictive capabilities and the capacity for

prevention and cure grows with society's impatience to prematurely apply the results of research, thus raising important ethical questions" (Eric Lander)

" It cannot be said that there should be a correlation between any progress in biological research and an increase in the " right to know" of individuals, and of public and private institutions. An equilibrium must be found between the possible benefits resulting from DNA analysis and other judicial or social values" (Stefano Rodota).

Confidentiality and respect for privacy.

Medical confidentiality must be kept, not only with respect to third parties but also to other members of the family.

Any investigation into an individual's genotype should be undertaken only if he has specifically given his consent. He may well question the extension of research into areas unrelated to that for which the authorisation was given at the time of sampling (for instance due to the length of time DNA can be preserved).

No information whatsoever concerning an individual's genotype should be provided without his specific consent.

Family studies can reveal illegitimate filiation, unknown or kept secret, but for which biological knowledge is essential to the interpretation of results and possibly to their use for diagnostic purposes.

Such information can have beneficial effects for the individual, his health, his family plans. It can also have perverse effects. The problem of the use of this information will arise for employment, for insurance or for any other institution which has an organisational or financial interest in reducing risk.

Alongside the benefit of protecting certain subjects with a high risk related to a professional activity (sensitivity to a toxic substance for instance), there is the danger of marginalising groups of individuals, because of general health risks.

More generally, the question will arise of the management and computerisation of genetic data, particularly in " DNA banks" . Management is essential because the information gathered from these families must be available if required for future generations of the family (for example for children born as a result of the diagnosis).

Information and the training of medical personnel

All these rules of conduct, in practice, are dependant upon the rigorous provision of information, and, consequently, upon good training of practitioners in this area. However, because applications of fundamental genetic research are so recent, practitioners generally have not received such training during their education.

Medical, clinical and biological genetics is not yet a recognized and structured speciality. There is no specialised educational curriculum, no qualifying internship and genetics is not officially a medical speciality.

With the increasing demand and the need for good quality of information, to avoid deterioration, it is important to take into account this practical aspect of the application and to bring to bear the same responsibility and means as are applied to fundamental genetic research.