Xplore Health

DISCOVER THE LATEST ON HEALTH RESEARCH

Educators' guide
"Down to the genes"
(Background information)

www.xplorehealth.eu

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1. Introduction

These teacher guidelines will give you information on the Xplore Health module “Down to the genes”. It will first introduce the topic to enable you to prepare your lesson using the different multimedia tools that you will find on the website. The guidelines provide information on the state of the art in this research field and on the ethical, legal and social aspects surrounding this topic.

2. State of the art

2.1. Definitions

Genomics is the study of the GENOME of a given organism, tissue or cell. The genome is made up of DNA, which act as a code of only four letters (the BASES Adenine, Guanine, Timidine and Citosine). The order in which these are combined makes up the code that contains the instructions to construct different components within cells. The DNA contains small segments called GENES, that have the information that will end up building proteins, but DNA also has other SEQUENCES that may act regulating the use of genes or to define the structural parts of the genome. Genomics is actually the science that studies how the code works. This means that it should be able to “read” the code (SEQUENCING the genome), but also understanding it (studying the end results of the code, how the genome translates itself, what is call the EXPRESSION of genes. The DNA in the GENES is TRANSCRIBED into RNA and the RNA is TRANSLATED into proteins, which act as the final structural and functional regulators of life. If the DNA builds the genome, the RNA makes up the TRANSCRIPTOME and the resulting protein repertoire adds up to a PROTEOME. So Genomics has sister disciplines, TRANSCRIPTOMICS and PROTEOMICS, which all together contribute to a better understanding of how living cells, tissues or organisms work, and why sometime they fail. The more we know about the regulation of the code, the more we are able to understand failures or code combinations that may lead to disease. The more we know about the code, the more we will be in a situation to reproduce it and use it for our own benefits, fighting or predicting diseases, but also building animal or vegetal models that can be used as tools for research or living factories used in environmental control, drug production, industrial processes or even functional food production.

Suggested activity / hands on:

With 4 letters AGCT build a SEQUENCE, collect SEQUENCES to build a GENE, collect GENES and linker sequences to build a GENOME, use a “TRANSCRIPTION MACHINE” to turn some genes into RNA strings (can combine pieces from several genes or chop genes into several RNA strings), add up all the RNA stings and that is your TRANSCRIPTOME, which is far more diverse and complicated than the genome, then use random chosen pieces of the TRANSCRIPTOME to build a PROTEOME with a “TRANSLATION MACHINE” that turns RNA strings into proteins (again, proteins can be made from several RNA strings or many proteins can be obtained from a single RNA string, the proteome is far more complex than the transcriptome itself). The hole game can be directed towards the idea of “small changes in DNA can result in huge effects in function”, and also that “there is so much complexity that many functions end up to be redundant, so real damage is very difficult, complexity leads to plasticity”.

The ultimate goal of GENOMICS is, then, understanding how critical are the changes in the code, and if we can use the reading of the code as a predictive tool to anticipate disease or how we will react to a given treatment to disease.

2.2. State of the Art

Pharmacogenomics

PHARMACOGENOMICS is the part of genomics applied to understanding how an individual who has a unique genetic sequence will respond to a given drug. The trend of the last ten years is to adapt the drug development process to pharmacogenomic correlations. In general a 30% of the patients do not respond to a given drug, and this effect can be mostly attributed to individual variations in key gene sequences. The search of significant correlations between sequence SIGNATURES and response to drugs is the key point in pharmacogenomics. The rapid commoditization of WHOLE GENOME SEQUENCE is allowing these signatures to be better understood. As of may 2010 it is technically possible to obtain the complete sequence of the genome of an individual in less than one month and at a cost of less than 50.000€, with several platforms claiming that can be done for less than 10.000€. It is predicted that in the mid term this will be down to less than one week and 1000€, being 100€ the more ambitious goal claimed by the industry (IBM).

Toxicogenomics

TOXICOGENOMICS relates pharmacogenomics in the sense that intends to correlate a given DNA sequence signature with a drug effect, but in the case of toxicogenomics it aims to understand when a given drug will be TOXIC to an individual. Particularly relevant to toxicogenomics are the liver enzymes of the P450 FAMILY. There is a very wide range of genetic variants of the genes that encode for these enzymes that are key for the way the body processes drugs. Subtle variations in some of the genes of the P450 family can lead to variations of three orders of magnitude in the metabolization of drugs between people. P450 gene signatures are among the first toxicogenomic kits commercialized and used in clinical trials for better understanding the efficacy and safety profile of new drugs.

A good example of a European project using toxicogenomics as a tool for delivering non animal predictive models for the assessment of the potential toxicity of chemical substances is Carcinogenomics http://www.carcinogenomics.eu/.

Companion Diagnostics (theragnostics)

The drug development process is undergoing a huge change in paradigm. One of the most noticeable ones is the trend to develop a DNA or RNA test at the same time than a drug, and to link the use of the drug to a positive or negative result in the DNA or RNA. Pioneering the trend was the breast cancer treatment Herceptin that is approved only for those women that are positive for estrogen receptor. The world THERAGNOSTICS was coined to define any diagnostic test that has an associate drug which prescription depends on it

Beyond diagnostics: genomic-based prognosis and prediction

Looking for DNA signatures and correlating them with a response to a drug is yet a small part of what genomics is contributing to the improvement of healthcare. Over the last 10 years there have been significant advances in using genomics to establish prognosis (risk assessment on how well or bad can a given disease or treatment go) and predict the outcome of a given treatment, or the appearance of a disease. Physicians are starting to use genomics (in general terms, MOLECULAR DIAGNOSTICS) to make decision on how to treat patients, which combinations of drugs to use, which procedure to apply. This is particularly relevant in oncology, but also in some psychiatric diseases. There are a number of ethical questions around using genomics to predict diseases that have no cure (for example

Alzheimer's), so the right for information should be balanced against the availability of a solution, but our increased understanding of genomics makes us more and more capable of predicting how our body will evolve with time, how it will react to different treatments and how we can prevent the appearance of certain diseases.

2.3. The magic word: personalised medicine

Getting a blood, urine or salive test and having an automated prescription to prevent future and treat current diseases is not that far away. PERSONALIZED MEDICINE is here to stay, and is changing the way new drugs are developed. In certain fields (for example, oncology) the pharmaceutical industry is prioritizing the development of those drugs that can be targetted to specific gene profiles in the tumour. In orphan diseases caused by genetic defects the identification of the mutation allows to define the treatment. In the toxicogenomic field, certain drugs or combination of drugs are not prescribed because of the P450 signature of the patient suggest that the drug will be either completely chopped by the liver before getting to the place or stay in circulation long enough to end up being more toxic than acceptable. There are more than 2000 genetic test available that can lead to informed therapeutic decisions concerning the use of drugs. GENETIC PROFILES (when it is referred to a unique or few genes) or GENOMIC PROFILES (when is referred to whole genome) are being increasingly used to support and complement the development of new drugs. Old failed developments are reevaluated with pharmacogenomic approaches to see if there is any subpopulation that actually responded to the drug, and in fact several drugs have been "resucitated" by means of pharmacogenomics. Key clinical decisions like prescribing aggressive chemotherapy or just wait and see can be based on pharmacogenomic criteria, depending upon the prognostic value of genetic signatures.

Suggested activity:

A 100 card maze with 5 different cards: A, B, C and D are different drugs for the same disease, and card E is a companion kit that helps deciding using cards B, C or D:

A is a "universal" drug card that works well but only in 70% of the patients. Treatment with A costs 100 €; B, C, D work well in 100% of patients provided the E card is used. Using a combination of card B, C, D with E cost 200 €.

Each patient that fails cost 500 €.

Play around with cards to treat 100 randomly picked patients to see what is more effective from the pure economic point of view, besides thinking about the ethics of using a drug that no necessarily will be effective.

In the example, to treat 100 patients with A will cost 7000€ + 15000€ = 22.000€ and leave 30 patients with the disease, whereas to treat the same patient population with B, C or D in combination with the companion kit E will cost 20.000€ and cure everybody. So combined drug+companion kit strategies in a personalized medicine approach may be more expensive on the individual basis, but way more ethics and efficient in the use of resources from the population point of view

3. Ethical, Legal and Social Aspects (ELSA)

In this section you will find a number of opinions and incentives for discussion in class on ethical, legal and social aspects (ELSA) related to genomics:

3.1. Introduction

Medicine of the XXI century is based on new paradigms that, if they become a reality and can finally develop their full potential, will imply a revolution in current medical treatments and substantially improve the quality of life of human beings. One of these paradigms is what is known as **personalized medicine**. Personalized medicine is based on applying individualized treatments (either pharmacological or not) according to the genetic characteristics of the patients. To do so, it is convenient to have an exhaustive knowledge of their genome (genetic material). Although we are not only our genome, its influence on the response to different treatments cannot be questioned. Therefore, the possibility of adapting treatments to the genetic characteristics of individuals has been proposed aiming, to treat them with the minimal effective doses to avoid undesirable side effects (**Pharmacogenomics**) or to prevent toxic effects after extradoses exposition to drugs (**Toxicogenomics**).

However, ethical concerns appear associated to personalized medicine, mostly derived from the required exhaustive knowledge of the genetic characteristics of individuals and, specially, from the use of this information.

3.2. Availability

Availability is a general concern associated to complex and, therefore, expensive technologies (as for example Biotechnology – see document Teachers' guide: Background information in www.xplorehealth.eu. As mentioned in the State of the Art section, the cost of determining the whole genome sequence of a human being is now at around 50.000€. This cost is constantly lowering, and it has been recently announced (Associated Press, 10th January 2012) that a Californian biotechnology company has developed an automated desktop DNA sequencer that decodes the sequence of a human genome in 24h at the assumable cost of 784€ (1000$). At present, this machine uses microchips able to sequence the exome (the part of the genome that codes for the functional proteins), but the company plans to produce a second-generation of microchips by the end of 2012 with the ability to decode the entire 3 billion base-pair human DNA sequence. The hardware necessary to read these microchips has an investment cost of about 117.000€ (149.000$). Assuming this information is completely true, although less than 1000€ per sample and an initial investment of 117.000€ can be regarded as an acceptable cost in developed countries, it can be envisaged as unaffordable by people from the third or even the fourth worlds (the term fourth world refers to subpopulations of socially excluded people amid developed countries' societies).

This issue arises the question of who should pay for the development of these technologies. If it is left to private, profitable, initiatives there is a real risk that the relatively high cost of such technologies make them available only to well developed countries or to economically powerful people amid them, leaving apart rare or neglected diseases due to their low economical interest. On the other hand public, non profitable, initiatives supporting their development should be paid by all tax payers who demand an increasing number of new technologies, from which a prioritization will have to be established. Which place should personalized medicine hold in this prioritization is something that will have to be discussed.

The only way to address this situation is to demand the application of the distributive justice principle to the development of personalized medicine as in other new medical technologies.

3.3. Privacy

Access to individual genetic information, as to any kind of health data, clearly enters in the field of the individual right of privacy.

The right of privacy is a very important right that has been acknowledged as one of the Human Rights (Article 12) and has been incorporated as such in most occidental constitutions.

Privacy has a strong relationship with intimacy because no intimacy can exist without privacy. Intimacy in communication and interpersonal relationships is essential to experience a full life, because intimacy without intrusions from others is necessary to develop spontaneous experiences without any shame. Therefore, privacy allows the freedom to define personal relationships with others and to self-defining too. In this sense, privacy is strongly related to respect and self-respect.

Confidentiality implies the compromise to not reveal data affecting the privacy of the individuals (health data, personal data, etc). It is not an absolute right since in some special cases is contravened (for instance, to denounce illegal acts such as sexual and physical abuse).

A risk of misuse of the information about the genetic characteristics of an individual is unquestionable. This means that such information can be used according to companies' or corporates' interests instead of according to medical objectives that may benefit individual welfare. Examples of healthcare insurances adapting their fees (or even excluding individuals) according to genetic information about, for instance, cancer predisposition have long ago been described. In the same way, but more recently, it appeared in the press (The Daily Mail, 16th October 2011) that a football club from the UK premier league has started to include genetic test directed to detect injury-prone individuals as a criteria to select its players.

However, it is crucial to dodge any genetic determinism that seems to underlie this sort of actions: we are much more than our genome: environment, education and vital circumstances have a clear influence on our personality and our health. Therefore, a simple predisposition should not be taken as a certainty to develop a particular disease in the future.

In this sense, the limit of the huge amount of information that represents the knowledge of the whole sequence of our genome reaches its real dimension.

3.4. Beyond diagnosis: certainty vs. Predisposition

As just mentioned, the question about the limits of information arises when certainty and predisposition are at stake. Questions such as the influence on our life of being aware of having a predisposition of 80% to develop a colo-rectal cancer in the future or how to deal with the knowledge of being affected by a genetic disease that will kill you when you are around 50 years old (such as Huntington disease) are not banal.

Moreover, which genetic defects should be considered relevant and which mere "characteristics" of our own? Which influence should this knowledge have in future generations? Imagine that a big proportion of the human population starts to demand selecting against androgenic alopecia in their male offspring. Shouldn't this attitude change the aspect we will have, as species, in the future? Will then bald people be considered as odd or undesirable?

3.5. The right of knowing and the right of "not knowing"

Considering these situations we have just mentioned and, although information about an individual's own genetic characteristics can be envisaged as something positive, a sort of right of not knowing arises. This right of not knowing is especially relevant when dealing with extremely serious diseases for which no efficient therapies are available. In this case, there is a risk of inadvertently revealing the undesired information by professionals treating the patient involved: for instance, the fact of applying or not a treatment or a diagnostic procedure (even to some relatives) can inform the patient whether he or she has the mutated gene or not. Then a complex situation confronts professionals that, in extreme cases, implies the application of "fake", unnecessary, treatments which clearly goes against medical ethics. One of these cases is "Non disclosing preimplantation genetic diagnosis" for Huntington's disease: if a potentially affected parent invokes his or her right not to know and, after genetic analysis, it is discovered that she or he doesn't have the mutated gene the in vitro fertilization procedure, although unnecessary, must be carried on and a "fake" preimplantation diagnosis must be performed to avoid revealing the patient's genetic characteristics.

Moreover, in some cases the necessity to inform close relatives or even third persons is brought up to preserve the welfare and health of the individual's close relatives. However, if this is the case, it must be done without violating the right of not knowing and considering that information might be inadvertently revealed. In general, the most efficient strategy consists in fragmenting the global information of the case among different working teams so that none of them holds the bulge of the information in order to avoid revealing it.

3.6. The comprehension of information

The amount of genetic information available after sequencing a whole genome is enormous (3 billions of base pairs). Therefore, the comprehension of the meaning of all this information is not a minor question to take into account, even for experts. Differences in the DNA sequence do not always mean abnormality: polymorphisms (genetic variables) are extremely frequent among all existing beings (including, obviously, humans) and distinguishing them from pathological mutations can be extremely difficult or, even, a sort of a conventionality.

Considering that all the information can be difficult for experts to interpret, the situation can be even worse when this information is made available to the general population. There are studies indicating that direct-to-consumers genetic tests offer few information to the general population, since it is not able to interpret and comprehend the results derived from them, specially their limitations and consequences. This situation often implies that results are misinterpreted in a subjective manner by individuals lacking a scientific groundwork that may help them making their own adequate interpretation. For instance, at-home male fertility tests based on different physiological and biochemical parameters associated to sperm viability and more or less related to their fertilization capacity (mobility and sperm concentration) have recently become available. These tests offer the possibility to determine your own fertility inside the intimacy of your home, avoiding uncomfortable medical tests. However, scientists have already warned that "diagnosis without professional advice that normally accompanies it could do more harm than good" (Barras C., 2010). Now imagine that, after having used one of these at-home fertility tests, a man "discovers" his supposed infertility while his wife becomes pregnant: a suspicion immediately appears. If you combine this situation with the use of an "at-home DNA paternity test" which cannot attribute paternity but exclude it (the difference is subtle enough not to be fully understood by many people) the couple is tangled in a mess that surely will affect their life and the life of an innocent child.

The best way to avoid most of the undesirable aforementioned risks is to keep the genetic information from an individual among biomedical professionals, who are supposed to be able to interpret this information, to advise the individual and use it, exclusively, for the patient's own benefit and welfare.

3.7. Alternatives

As we have just discussed, the main risk in personalized medicine is the inadequate use of the genetic information. Obtaining this information seems to represent the first step towards the use of personalized medicine. But, is this information so essential? The advances in induced pluripotent stem cells (iPS) technology offer the possibility to obtain patient-specific disease models to test either drugs or therapies without cumulating his/her genetic information (Robinton D.A. and Daley G.Q.; 2012). However, this strategy still has some drawbacks to consider: iPS seem to "remember" their origin and history in their epigenome (the modifications the genome experience during embryo development and tissue formation), probably yielding different responses to particular treatments according to which tissue they were derived from or to which conditions they have been cultured under. Therefore, if an insight on the response of the whole organism is pursued, how many iPS cell lines must be derived from each patient to be considered as representative? From which specific tissues?

Nevertheless, this is a very promising approach that may solve the threat of misusing genetic information, preserving privacy and confidentiality without renouncing to personalized medicine.

3.8. Aknowledgements

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