Law, genes and bioethics: A biomedical perspective

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1. Introduction: what is a complex trait?

"We wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest"[1]. This statement by Nobel Prize winners James Watson and Francis Crick sparked the first genetics revolution in 1953. Fifty years later, with the completion of the human genome project, a second genetic revolution took place with the publication of the first draft mapping the complete human genome sequence[2]. With time, errors in the first draft were corrected and a swift flourishing of powerful technologies are nowadays enabling the sequencing of many thousands of human genomes per year, a number that is constantly growing. "We used to think that our fate was in our stars, but now we know that, in large measure, our fate is in our genes" stated James Watson at the start of the Human Genome project. Now, twenty years later, he would probably admit that the project fell short in keeping these promises, for two reasons. First, our fate is much too complicated to be all written in our DNA; second, whatever might be written in the DNA, reading it is just the first step of a much more complex task we have not yet accomplished, that is, to understand it.

Our genome is often metaphorically described as a text. The genome has an alphabet, the four bases A, C, G and T forming the 46 long "books" (our chromosomes) where the text is contained. And it has a lexicon, 21.000 or so words or genes[3], i.e. the regions of the genome that are transcribed into RNA and then translated to create proteins. Knowledge of these genes already allows us to diagnose many genetic diseases, including muscular dystrophies, hemophilia and cystic fibrosis, all disorders that are caused by the malfunctioning of a single gene.

However, we do not yet understand the genome syntax. The diseases causing the heaviest health burden (like cancers, cardiovascular and neurodegenerative disorders) depend on multiple interactions among many genetic and environmental factors, i.e. are complex traits that do not behave according to simple Mendelian inheritance laws. Because the genes involved in these diseases are many, each playing a limited role, their identification and use to estimate disease risk has proved difficult. While we are far from achieving a general, clear understanding of the genetic bases of complex diseases, even more

[1] J.D. WATSON, F.H.C. CRICK, *Molecular structure of nucleic acids: A structure for deoxyribose nucleic acid*, in *Nature*, 171, 4356, 1953, 737-738.

[2] International Human Genome Sequencing Consortium, *Initial sequencing and analysis of the human genome*, in *Nature*, 409, 2001, 860-921; J.C. VENTER et al., *The sequence of the human genome,* in *Science*, 291, 2001, 1304–1351.

[3] D.R. ZERBINO, A. FRANKISH, P. FLICEK, *Progress, challenges, and surprises in annotating the human genome,* in *Annual Review of Genomics and Human Genetics*, 21, 2020, 55-79.

incomplete is our understanding of the genetic bases of non-pathological complex traits, such as those related to personality, cognitive abilities or emotions. These traits do recur in families, and hence there is reason to suspect that genes play a role. However, it is notoriously hard to dissect the effects of shared genes from those of shared environments. One example of a particularly unsuccessful attempt to identify the genes governing a complex trait has been the search for IQ (Intelligence Quotient) determining-genes. A recent, colossal study of nearly 80,000 subjects led to the identification of 22 candidate genes, which, however, could globally account for just 1,5% of the differences between very high and very low IQ values[4].

While science struggles to address these issues, the advancement in knowledge already poses many outstanding ethical and legal problems. Below, we discuss some of these issues.

2. Criminality genes

Despite all, deterministic views have all but disappeared in biology, and are well documented by the century-long search for genes determining criminal attitudes. Much like intelligence, criminal behavior is another ill-defined topic, and so it comes as no surprise that the investigation of criminality genes has been as frustrating and vain as the search of intelligence genes. Around 1960, the idea that an extra Y-chromosome in males could lead to criminal behavior achieved popularity, largely through the media. The first case of a man carrying an XYY chromosome complement was described in 1961, and four years later Patricia Jacobs published a survey of 315 men at a hospital for developmentally disabled in Scotland, 9 of whom (all characterized as violent criminals) apparently carrying an extra Y chromosome[5]. In 1968, a US serial killer, Richard Speck, was described as XYY in three articles on the New York Times. In fact, Speck had a normal chromosome set, but this fake news contributed to create the myth of the XYY man as a congenital criminal, which persisted even when M. Court Brown failed to confirm it in a large study (more than 5000 subjects) in Scottish prisons[6]. The Y chromosome is a small chromosome; the simplest explanation for Jacobs' findings was that she mistook for Y chromosomes some dark spots on the printed photographs. Yet, as late as 1974, 13 men and boys with XYY chromosome complement were sentenced to chemical castration in Maryland[7]. The scientifically unsupported stereotype of XYY men as violent criminals lasted for decades after its scientific dismissal; it was used as a plot device in horror films such as Dario Argento's *The Cat o' Nine Tails* (1971) and David Fincher's *Alien 3* (1992).

In later times, another gene, *MAOA*, mapping on the X-chromosome, enjoyed a transient popularity as a criminality gene. *MAOA* codes for a protein, monoamine oxidase A, involved in the metabolism of several neurotransmitters, such as dopamine and serotonin, and hence is a key regulator of many functions of the brain. A low-activity variant, *MAOA-L*, was identified in a Dutch family in which several males had shown borderline mental retardation and abnormal behavior

[4] S. Sniekers et al., *Genome-wide association meta-analysis of 78,308 individuals identifies new loci and genes influencing human intelligence,* in *Nature Genetics,* 49, 2017, 1107-1112.

[5] P. Jacobs et al., *Aggressive behavior, mental sub-normality and the XYY male,* in *Nature*, 208, 1965, 1351-1352.

[6] M. Court Brown, *Males with an XYY sex chromosome complement,* in *Journal of Medical Genetics*, 5, 1968, 341-359.

[7] R. Pyeritz et al., *The XYY male: The making of a myth,* in Ann Arbor Science for the People Collective (eds.) *Biology as a social weapon,* 1977, 86-100.

including impulsive aggression, arson, attempted rape, and exhibitionism[8]. When the *MAOA-L* variant was detected in 17 out of 46 Maori men, it took very little to attribute to it the warlike attitudes of the entire Maori population and to christen the variant as "warrior gene"[9]. However, successive studies in one of the world populations showing the lowest rates of violent crime, Taiwan, found an even higher percentage of carriers of *MAOA-L*[10]. Far from being a warrior gene, the *MAOA-L* variant is now known to be widespread (of course, in different proportions) in all populations studied so far.

3. DNA evidence on genetic determination of behavior in court

Nobody denies that genes play a crucial role in the development and function of the brain. However, for no gene so far it has been possible to establish a causal relationship with any specific behavioral trait, largely for the complex determination of such traits. Still, there have been multiple attempts to use genetic evidence in court, to claim that a defendant could not be considered fully responsible for her/his actions because such actions were somehow genetically determined. Two rather famous case studies have to do with *MAOA*. In 1991, Stephen Mobley killed John Collins in a pizzeria, in Georgia (USA). His lawyers asked for a genetic test, claiming Mobley could carry a *MAOA* variant predisposing him to violence. The judge stated that no scientific evidence justifies the test, and Mobley was condemned (and ultimately executed in 2005). On the contrary, a judge of the Appeal Court of Trieste innovated world jurisprudence, by granting Abdelmalek Bayout genetic (with T, not with R) extenuating circumstances because, according to the experts, he was "heterozygous carrier of a *MAOA* variant predisposing him to become particularly aggressive under stress situations". Bayout, an Italian citizen, in 2007 had bought a 20cm-long knife, ambushed and stubbed to death Felipe Novoa Perez, who had previously made fun of him. Confronted by the same request as in the Mobley case, the Trieste judge decided instead to ask for an expert opinion. At any rate, the two experts that were chosen, a biochemist and a psychologist, seem to have some problems with genetics, since male cells contain only one X-chromosome, and hence Bayout cannot possibly be heterozygote for any X-linked gene.

Nineteenth century science was deterministic and looked for laws establishing a tight relationship between causes and effects. With exceptions, 21st century genomics recognizes the limitations of our ability to know, and hence is probabilistic[11].

4. Genomic data obtained from patients in clinical studies: is consent really informed?

Despite all hindrances and limitations, the advent of innovative screening and diagnostic tests based on genetic fingerprinting opened the way for radical challenges to the classical concept of evidence-based medicine, shifting towards proactive interventions in the ambitious perspective

[8] H.G. BRUNNER et al., *Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A,* in *Science,* 262, 1993, 578-580.

[9] R. LEA, G. CHAMBERS, *Monoamine oxidase, addiction, and the "warrior" gene hypothesis,* in *The New Zealand Medical Journal,* 120, 2007, U2441.

[10] N.J. KOLLA, M. BORTOLATO, *The role of monoamine oxidase A in the neurobiology of aggressive, antisocial, and violent behavior: A tale of mice and men,* in *Progress in Neurobiology,* 194, 2020, 101875.

[11] WILLIAMS R., WIENROTH M., *Social and ethical aspects of forensic genetics: A critical review*, in *Forensic Science Review*, 29, 2017, 145-169.

of a patient-tailored healthcare. Major investments in sequencing technologies and genome-wide association studies (GWAS) allowed the implementation of large-scale genetic datasets with the related health and phenotypic data, enabling geneticists to characterize variants associated with complex traits and common diseases. These approaches may represent a step toward the development of a predictive and individualized, patient-centered medicine. However, ethical and legal constraints underlying these new insights often failed to keep pace with the scientific and technological advancements. While in the next future several millions of individuals are expected to have their genome sequenced, concerns are growing about how consent is obtained, use of the genetic information collected, threats on genetic privacy and risk of discriminations based on DNA signatures. For example, many clinical trials sponsored by pharmaceutical industries envisage the collection of biological material from patients and the sequencing of their genome. These intentions are not always clearly stated in the informed consent that patients sign to enroll in the study, nor is often clearly described the use that the company will make of this information. In other words, large genetic datasets are becoming the property of private companies, that expect to generate profit (not only knowledge) out of them.

Availability of genetic information may entail the risk of discrimination based on identification of particular traits or risk of disease, leading for example to loss of job opportunities or higher insurance rates. Therefore, genetic privacy stands in urgent need for regulation, in particular for genomic data access and sharing but, even more importantly, for the individual's consent to their use. In order to delineate a dedicate framework on personal data at EU level, the General Data Protection Regulation (GDPR) entered into force in May 2018, with the purpose of defining all the details required for personal data sharing at an international level, along with the obligations for individual data usage and processing[12]. However, the advent of the GDPR raised some discussion, in particular with regard to the legitimacy and utility of obtaining such a broad consent.

5. Gene editing

A third genetics revolution has just begun. Products of gene therapy aimed at modifying the gene pool of human cells are already an established and rapidly expanding reality in the clinical practice, with thousands of potential new gene therapies submitted every year to the regulatory agencies[13]. The advent of sophisticated molecular techniques, the most promising called CRISPR-Cas system, makes now possible to easily and precisely "hack" the human genome[14]. There is an urgent need to engage in a public and expert dialogue about the use of these powerful tools. This issue became dramatically clear two years ago, when the Chinese scientist He Jiankui declared to have generated the first gene-edited babies using the CRISPR/Cas9 system, in the attempt of avoiding the vertical transmission of HIV from a seropositive mother. An announcement that outraged the public opinion

[12] L. Marelli, G. Testa, *Scrutinizing the EU general data protection regulation. Science*, 360, 2018, 496-498.

[13] R. Ramezankhani et al., *Two Decades of Global Progress in Authorized Advanced Therapy Medicinal Products: An Emerging Revolution in Therapeutic Strategies,* in *Frontiers in Cell and Developmental Biology*, 8, 2020.

[14] R. Jansen et al., *Identification of genes that are associated with DNA repeats in prokaryotes,* in *Molecular Microbiology,* 43, 2002, 1565-1575; H. Li et al., *Applications of genome editing technology in the targeted therapy of human diseases: mechanisms, advances and prospects,* in *Signal Transduction and Targeted Therapy,* 5, 2020.

worldwide: "He was widely criticized for ignoring important ethical consideration and exposing the girls to unknown risks for an uncertain benefit", as stated in a Nature magazine editorial[15]. One year later, eighteen scientists and ethicists from all over the world called for the adoption of an international moratorium on all clinical uses of heritable genome editing, suggesting a permanent ban on all germline cell gene editing[16].

6. Patenting of nucleotide sequences

Aside from the undeniable value for the present and future of medicine, an issue arising with the ability to re-shape the characteristics and structure of genes is the protection of the scientist's discovery as an intellectual property, i.e. by means of patents, whenever the requirements of novelty, utility and non-obviousness are met. Gene patents are issued to cover the composition of a specific nucleotide sequence and/or the functional or diagnostic employments of derived products. However, it is debated if products that derive from a gene sequence should be considered inventions or discoveries. Numerous ethical and practical concerns arise on how these patents could be exploited, with reference in particular on the potentially detrimental effect on the process of discovery and development of new diagnostics and therapeutics. Although several theories have been proposed to assess the legitimacy of gene patents, there is still a compelling need of clearly defined rules for genetic patentability. Indeed, the practical criteria for granting authorizations of gene patents are quite different among the various countries, and it remains urgent to develop clear and effective guidelines based on international best practices.

7. Conclusions

There is no simple and handy solution for many of the issues raised in this article. The debate is in progress; often, and not unpredictably, scientists, bioethicists, law experts and legislators tend to pay special attention to specific and different aspects of the problems. Needless to say, any lasting solution will have to be respectful of all points of view, finding a balance between the desire to fully exploit the new opportunities offered by science and the protection of individual and collective rights. This is not an easy goal.

[15] D. CYRANOSKI, *Baby gene edits could affect a range of traits,* in *Nature,* 2018.

[16] E.S. LANDER et al., *Adopt a moratorium on heritable genome editing,* in *Nature,* 4, 2019.