

How diseases became “genetic”

Como as doenças se tornaram “genéticas”

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Abstract *This article examines the origins of the term “genetic disease.” In the late 19 and early 20th century, an earlier idea that diseases that occur in families reflect a vague familiar “predisposition” was replaced by the view that such diseases have specific causes, while Mendelian genetics provided then clues to the patterns of their transmission. The geneticalisation of inborn pathologies took a decisive turn with the redefinition, in 1959, of Down syndrome as a chromosomal anomaly, then the development of tests for the diagnosis of other hereditary pathologies. At that time, geneticists distinguished “hereditary” diseases that run in families, from “genetic” conditions that are the result of new mutations during the production of egg and sperm cells. In the latter case, the inborn impairment is produced by an anomaly in the genetic material of the cell, but is not hereditary, because it is not transmitted from one or both parents. In the late 20th and early 21st century, new genomic technologies blurred the distinction between hereditary and genetic impairments, extended the concept of genetic disease, and modified the experience of people living with such a disease.*

Key words *Heredity disease, Genetic disease, Down syndrome, Genomic technologies*

Resumo *O presente artigo tem o objetivo de examinar as origens do termo “doença genética. No final do século XIX e início do XX, a vaga ideia que a doença manifesta entre familiares refletia uma “predisposição” familiar, foi substituída pela visão que essas doenças possuem causas específicas, enquanto a genética mendeliana forneceu as pistas para os padrões de transmissão da doença. A genética das patologias congênitas deu uma guinada decisiva, em 1959, com a redefinição da Síndrome de Down como uma anomalia cromossômica e, depois, com o desenvolvimento de testes para o diagnóstico de outras patologias hereditárias. Naquela época, os geneticistas distinguiam doenças “hereditárias” como aquelas que acometem os elementos de uma família, de condições “genéticas” que são o resultado de novas mutações ocorridas durante a produção dos óvulos e espermatozoides. Neste último caso, a deficiência inata é causada por uma anomalia do material genético da célula, porque não é transmitida por qualquer um ou ambos os pais. No final do século XX e início do XXI, as novas tecnologias genômicas obscureceram a distinção entre deficiências hereditária e a genética, estenderam o conceito da doença genética e modificaram a experiência das pessoas que vivem com esse tipo de doença.*

Palavras-chave *Hereditariedade, Genética, Cromossomos, Síndrome de Down, NIPT*

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Hereditary diseases before genetics

An interest in traits that children inherit from their parents – the father’s hair, the mother’s eyes – may be as old as civilizations, but interest in diseases that run in families is documented from the 17th century on, when physicians started to systematically record families with an unusual concentration of abnormal traits^{1,2}. The search for “morbid heredity” was intensified in the 19th century. At that time, this concept included a multiplicity of causes, such as familial traits (“likes begets likes”) intensified by intermarriage, but also alcoholism, tuberculosis, and venereal diseases, especially syphilis. Tuberculosis and syphilis were classified as “hereditary causes” of pathologies because, until mid-20th century, the term “heredity,” especially in its lay uses, englobed all the elements that could affect the “quality of the seed” and fetal development. Maternal conditions that may affect the fetus, such as syphilis, tuberculosis or alcoholism could therefore be described as “hereditary”³.

In late 19th and early 20th century physicians – especially those linked with the rapidly growing eugenic movement – were concerned by heredity of “feeble mindness”, and its potential threat to society⁴⁻⁷. The British psychiatrist George Edward Shuttleworth (1842-1928), author of the textbook, *Mentally Deficient Children: Their Treatment and Training*, proposed to distinguish between “acquired mental deficiency,” produced by accidents of childbirth or childhood by events such as trauma, a febrile disease or intoxication, and “inborn mental deficiency,” produced before birth by “formative defects”. Shuttleworth included in the latter category conditions such as microcephalus (too small brain), hydrocephalus (the accumulation of liquid in the skull), “mongol” feeble-mindedness, (today, Down syndrome), “cretinism” (today, thyroid insufficiency), and anomalies produced by diseases of the pregnant woman, such as epilepsy, syphilis and eclampsia (seizures during pregnancy). Mental deficiency which stems from “formative defects” (that is, impairments acquired before birth) Shuttleworth pointed out, is frequently associated with visible physical defects such as hare lip, deficient ear lobes, missing fingers, unusual shape of face or crane anomalies. A trained physician should be able to recognize the physical traits of mental deficiency even in relatively mild cases. Such traits are often more exaggerated in advanced cases⁸.

Shuttleworth saw “feeble mindness” as reflecting a complex mixture of inherited and ac-

quired traits. Another British psychiatrist, Alfred Frank Tredgold (1870-1952) whose *Textbook of Mental Deficiency*, first published in 1908, then actualized and reedited until the author’s death, became a key source of knowledge on this question in the English-speaking world, put the accent on the role of “pathological heredity” in producing “feeble mindness”. Mental impairment, Tredgold believed, is nearly always “hereditary,” a broad term which included advanced parental age, alcoholism, syphilis and tuberculosis. Tredgold included the last two pathologies among causes of hereditary “feeble mindness”, because, he argued, the geneticists’ claim that infectious diseases do not affect “germ plasm” is not plausible. It is difficult to believe that a systemic disease such as tuberculosis does not degrade the quality of sperm and egg cells⁹. At first, Tredgold was a moderate eugenist. He did believe that the majority of inborn impairment were inherited, but also that society cannot do much to prevent them, mainly because impaired children are frequently born to parents who do not display marked signs of “degeneration”. In the 1930s, perhaps under the influence of ideas propagated by the German Nazi and their British sympathizers, Tredgold changed his mind, and converted to the idea that the sterilization of selected categories of “degenerates «and the prohibition of marriage of people from “tainted” families» will reduce the burden of hereditary diseases in society”¹⁰.

Tredgold views on the effectiveness of eugenic interventions such as sterilization to reduce the frequency of “feeble mindness” were strongly opposed by the British geneticist, Lionel Penrose (1898-1972). Penrose coordinated in the 1930s a large study on the possible inheritance of mental conditions, the Colchester Survey. In the final report of this survey Penrose explained that very few mental disorders, were truly “hereditary” that is, followed a Mendelian pattern of transmission¹¹. Among the latter he singled out two diseases, Huntington’s chorea and phenylketonuria (PKU), both undoubtedly hereditary – and very rare. Penrose was especially interested in PKU, seen by him as an exemplary hereditary pathology. PKU is produced by the organism’s decreased ability of metabolize the amino acid phenylalanine. The accumulation of phenyl alanine in the blood leads to intellectual impairment, seizures and behavioral problems. This condition was first described by the Norwegian physician and biochemist Ivar Asbjorn Folling in 1934¹². Penrose coined the name phenylketonuria and demonstrated, thanks to the data collected by the

Colchester Survey, that it was a hereditary recessive disorder^{13,14}. PKU was presented by Penrose as a rare case of heredity of a mental impairment, and, at the same time, a strong argument against eugenicists' claims. He had calculated that about 1% of the British people are carriers of the PKU trait. It was pointless to try to control the reproduction of all the individuals with this trait, while controlling only the affected people (assuming that they will have offspring in spite of their severe mental impairment) would have practically no effect on the frequency of the "defective" gene in Britain, and would not prevent the birth of children with the targeted condition. Only a lunatic, Penrose concluded, would wish to sterilize 1% of the population to prevent the birth of a handful of harmless imbeciles^{15,16}.

Aneuploidies and the rise of "genetic conditions"

In the 1940s and 50s, significant portion of experts believed that while a small number of diseases such as PKU or hemophilia correspond to the description of "pure" hereditary conditions that obey Mendel's laws, the majority of pathologies described as "hereditary" are produced by multilevel interactions between heredity and environment. This view became however more complex after 1959, following the description of the consequences of the presence of abnormal number of chromosomes (aneuploidy) – and the rise of an important new category of diseases which were "genetic" but not "hereditary". The condition that played a key role in the transformation of understanding of "genetic diseases" was Down syndrome.

Down syndrome was seen for a long time as puzzling phenomenon. Researchers who studied children and adults with this conditions, noted a surprising similarity of their physical traits; hence the early, racist, designation of people with this condition as individuals with "mongoloid idiocy" or "mongols". "Mongolism" was first designated as a distinct entity by the physician John Langdon Down (1828-1896), a superintendent of the Earlswood Asylum for Idiots, in Surrey, England. In an article published in 1866, Down described a "Mongolian type of idiocy." In the late 19th and early 20th century physicians stressed the homogeneity of facial traits of people with "mongoloid idiocy"^{17,18}. At the same time they noted that such physiognomic similarity masked a great variety of physical and intellectual manifestations. Some "mongoloid" children were born with heart or

digestive anomalies while others did not have such anomalies; some had very severe intellectual limitations while others, especially when they received well-adapted and compassionate education (contrary to received ideas, already in the 19th century selected institutions and educations provided such education) made important progress, and some were able to live quasi-autonomous lives and hold jobs.

Researchers rapidly arrived to the conclusion that "mongolism" in all probability a shared biological basis, but also that it does not run in families. Children with this condition were nearly always born to non - affected parents, and had non-affected siblings. In the 1930s, Lionel Penrose had shown a strong link between maternal (but not paternal) age and woman's probability to have a child with "mongolism". His hypothesis was that this condition is product of a joint effect of genetic predisposition and unknown factors linked with the mother's advanced reproductive age. Another expert on "mongolism" Clemens Benda (1898-1975), an Austrian physician who worked in the US, rejected Penrose's hypothesis and argued that "mongolism" is a metabolic disorder produced by hormonal dysfunction. Such a dysfunction is more pronounced in women over 40, but can be found in younger women too, because many children with "mongolism" were born to young mothers¹⁹.

The understanding of "mongolism" – or as it was renamed in the 1960s, Down syndrome – had radically changed in 1959, when this condition was redefined as presence of abnormal number of chromosomes. Normal human cells contain 23 pairs of chromosomes. Each pair is composed from one chromosome originated from the mother, and another from the father, with the exception of sex chromosomes: biological women have two x chromosomes, one from each parent (chromosomal formula 46,XX) and biological men have a X chromosome inherited from their mother and Y chromosome inherited from their father (chromosomal formula 46,XY). The gametes (egg and sperm cells) contain 23 chromosomes each. People with x Down syndrome have three, instead of two copies of chromosome 21 (trisomy 21). In the great majority of cases (the sole exception are rare cases translocation of a segment of chromosome 21 on another chromosome) the presence of three copies of chromosome is the result of an error of production of gametes, not a condition that occurs in families.

Until 1956, scientists did not have a reliable method to visualize human chromosomes, and

they mistakenly believed that all human cells have 48 chromosomes. In 1956, two researchers, the Indonesian-American cytogeneticist, Joe Hin Tjio, and the Swedish geneticist Albert Levan, developed a new method of staining human chromosomes and had shown that humans cells have 46 chromosomes²⁰. The development of an efficient method of visualization and counting of human chromosomes made in turn possible the study of aneuploidies (presence of an abnormal number of chromosomes). 1959 was named the “miracle year” of human cytogenetics – a discipline which studies genetic changes on the level of cells²¹. That year three researchers from the Necker Hospital, Paris, Raymond Turpin, Marthe Gautier and Jerome Lejeune, found out that “mongolism” was correlated with the presence of three copies of the chromosome 21^{22,23}. The same year a British group: the geneticist Charles Ford from the Medical Research Council’s (MRC) Radiobiology Unit at Harwell, the physician and geneticist Paul Polani from Guy Hospital, London, and their collaborators, linked Turner syndrome – a condition characterized, among other things, by the under-development of sex glands in girls – with an absence of one X chromosome (chromosomal formula 45,0X) while Patricia Jacobs and her group from the Medical Research Council Human Genetics Unit at the Western General Hospital in Edinburgh, linked Klinefelter syndrome a condition characterized, among other things, by the under-development of sex glands in boys, with the presence of a supplementary X chromosome (chromosomal formula 47,XXY)²¹. The following year the geneticist Paul Edwards from the University of Birmingham, UK, described the trisomy 18 (Edward’s syndrome) and Klaus Patau from the University of Wisconsin in Madison (USA) trisomy 13 (Patau’s syndrome) – these two syndromes produce very severe inborn anomalies^{24,25}. These findings opened a new era of studies of inborn genetic conditions.

Hereditary diseases, genetic conditions and prenatal diagnosis

Description of the links between inborn defects and the presence of an abnormal number of chromosomes provided a powerful boost for the development of medical genetics, previously a marginal domain of studies²⁶⁻²⁸. As the Canadian geneticist Clarke Frazer, explained: “genes were interesting hypotheses but here was a cause of genetic diseases that physicians could actually see”²⁹. The scientific uses and practical applica-

tion of studies of chromosomes revolutionized human genetics, but also medicine. Physicians had grasped that clinical genetics is as important to the understanding of human pathology as anatomy and physiology. Description of clinical consequences of presence of an abnormal number of chromosomes led to a distinction between inborn conditions defined as “genetic,” since they were produced by changes in the genetic material of the fertilized egg, and present in every single cell of the body and those defined as “hereditary” because they were transmitted from one or both parents³⁰.

In the early 1960s, cytogeneticists were able to diagnose chromosomal anomalies in individuals with impairments produced by these anomalies, while biochemists were able to diagnose hereditary conditions such as metabolic diseases, often produced by a lack of an essential enzyme, by displaying the absence of this enzyme in cells of the affected individuals. It was not possible, however, to detect these conditions before birth. In 1968, Henry Nadler from Northwestern University Medical School, Chicago, developed a method of cultivating fetal cells suspended in the amniotic liquid. It was possible to sample these cells through the insertion of a needle into the amniotic cavity of a pregnant woman (amniocentesis)^{31,32}. In the early 1970s, amniocentesis was a risky technique, linked with an estimated 5% risk of miscarriage. On the other hand, it made possible a prenatal diagnosis of severe hereditary diseases as Nieman-Pick disease, maple syrup urine disease, Tay Sach’s disease, or mucopolysaccharidoses^{33,34}. Previously many women who had affected children refrained from a further pregnancy, because they knew that they had 50% chances to have another child with the same condition if it was dominant, and 25% chances if it was recessive. The liberalization of abortion in many Western countries in late 1960s and early 1970s allowed these women to test early in pregnancy whether the fetus was a mutation carrier, and if that was the case, to terminate the pregnancy. Unsurprisingly, many among them strongly supported an approach that allowed them to have children free of a “family malediction”, and were willing to risk a spontaneous miscarriage to achieve this goal.

In parallel, the possibility to culture fetal cells in a test tube opened the way to a prenatal detection of chromosomal anomalies such as Down syndrome^{35,36}. At first, since amniocentesis was a risky procedure, it was not proposed to women of “advanced maternal age” at higher risk of giv-

ing birth to a child with Down syndrome³⁷. In the late 1970s, the introduction of ultrasound to visualize the trajectory of the needle employed to aspirate the amniotic fluid reduced the risk of post-amniocentesis miscarriage to 1% environments³⁸. This technical improvement favored the introduction of testing for an age-related Down risk^{39,40}. Gynecologists at first proposed this test only to women over 40, then over 38, and finally over 35⁴¹. In the late 1970s, prenatal tests for presence of hereditary diseases and abnormal number of chromosomes were performed in the same laboratories by the same specialists. Yet, they addressed very different risks. Women who knew that they and/or their partner were carriers of a hereditary condition had either 50% or 25% probability to give birth to an affected child. Women of “advanced maternal age” had a much lower risk (1-3% according to age) to give birth to a child with Down syndrome. Moreover, many among these women were not aware of their risk, and had to learn about it either from health professionals or the media. The Lancet’s editorial from 1977 stated that in the last five or six years in Europe, only 300 abnormal fetuses were aborted following a diagnosis of a chromosomal anomaly of the fetus, a very modest dent in the annual total of about 100,000 babies with such anomaly born in Western Europe during that period. The editorial recommended a vigorous campaign to educate women about links between maternal age and Down syndrome⁴². Such educational effects were successful; in the early 1980s, more women became aware of age-related risks, and some explicitly demanded an amniocentesis⁴³. The detection of Down syndrome – an inborn impairment which is much more frequent than hereditary metabolic diseases and hereditary diseases of the blood – became the main target of search for genetic anomalies of the fetus and later for population-based screening for such conditions^{44,45}.

Abnormal development and abnormal genes

In the first half of the twentieth century, the main causes of newborns, babies and young children mortality were infectious diseases and childbirth related problems. Extension and improvement of the safety of hospital births, the development of antibiotics, and the generalization of childhood vaccination, greatly reduced newborn and child mortality in industrialized countries. After the Second World War, inborn

anomalies became the first cause of such mortality, increasing the physicians’ interest in this subject⁴⁶. The description, in 1941, of severe birth defects produced by an infection with rubella virus, then, following the explosion of atomic bombs in Hiroshima and Nagasaki, the role of radiation in producing inborn anomalies, were additional sources of interest in such anomalies. However, until the 1960s, birth defects were seen as a relatively minor domain of medical research.

One of the pioneers of study of teratology (literarily, the study of monsters) was the pediatrician Joseph Warkany (1902-1992)^{47,48}. Born and educated in Vienna, Warkany moved in 1932 to Children’s Hospital in Cincinnati, Ohio, where he worked for the rest of his life. Warkany’s interest in birth defects was rooted in his studies on the effects of vitamin D deficiency, and in his familiarity with cretinism (a congenital deficiency of thyroid hormones), a condition frequently found in the Austrian Alps. In the 1940s and 50s, Warkany and his colleagues conducted studies the effects of nutrition in pregnancy, and investigated possible causes of prematurity and low birth weight. Thanks to their efforts, teratology became a recognized, although modest, medical sub-specialty. The interest in teratology increased in the 1960s as a consequence of the thalidomide disaster, an epidemic of severe birth defect in children of mothers who took a popular anti-nausea drug, thalidomide, early in pregnancy. The striking images of “thalidomide children” born without upper or lower limbs or both, attracted attention to risk of malformations during pregnancy. It led to development of birth defect registries, and epidemiological studies of causes of anomalies in newborns.

In the 1960s and 70s the US pediatrician, David Smith (1926-1981), played a key role in systematization of study of inborn impairments. In the early 1960s Smith collaborated with the geneticist Klaus Patau, who studied chromosomal anomalies and described trisomy 13. Smith’s main interest was, however, not genetic but fetal development (embryogenesis). Smith explained that chromosomal anomalies such as Down syndrome were “internal dysmorphogenic influences,” while infections such as rubella, and maternal factors such as severe diabetes or a malformation of the uterus, were “external dysmorphogenic influences.” In many cases a malformation produced by external cause was similar to the one produced by internal one. For example, cleft palate can be the result of a genetic anomaly or a faulty growth of the embryo produced

by maternal factors. Moreover, the distinction between external “maternal factors” and internal “genetic factors” is far from being absolute. Maternal factors can modulate gene expression and contribute to the variability of phenotypical profiles produced by a mutation. Smith’s view of dysmorphology was decidedly oriented toward a multi-factorial understanding of developmental delays and an integrated view of human embryogenesis which did not privilege genetic factors over others⁴⁹.

In 1966 Smith coined the term ‘dysmorphology’ to replace the emotionally loaded term teratology and facilitate communication with parents of children with inborn impairments⁵⁰. In 1970 he published a highly influential textbook, *Recognizable Patterns of Human Malformation: Genetic, Embryonic and Clinical Aspects*⁵¹. This book rapidly became a reference volume for pediatricians, clinical geneticists and ultrasound experts who dealt with the expression of inborn defects. Consecutive editions of Smith’s *Recognizable Patterns* (Smith died in 1981, but his colleague and friend Kenneth Jones continued to publish new versions of this book; the 7th edition was published in 2013) illustrate the evolution of dysmorphology. Such evolution is reflected in the steady growth in the books’ size (the first edition had 368 pages, and the 7th, 989) but also the rapid increase in number of inborn syndromes linked to changes in the genetic material of the cell. In the first, 1970 edition of this book only a small fraction of the described inborn malformations, mainly aneuploidies, were attributed to known genetic causes. In the, 7th edition of this book, 80% of the catalogued malformations were linked with identified genetic anomalies⁵². That edition included for the first time a separated chapter on “molecular syndromes,” diagnosed thanks to the development of new molecular biology methods such as fluorescent hybridization in situ and genomic hybridization. The rapid diffusion of these technologies, especially in the 21st century, accelerated the process of “geneticization” of inborn pathologies.

Genetic diseases in the genomic era

The first cytogeneticists counted human chromosomes. The usual technique was to stain the chromosomes using some variant of Levan’s and Tjio’s technique, photograph them, and then cut the photograph, and pair the chromosomes, to check whether indeed there are two of each pair. In the early 1970s cytogenetics devel-

oped a new staining technique – banding – that was able to distinguish parts of chromosomes, and see whether the chromosome is missing one segment (deletion), has one segment twice (duplication) or has a segment from a different chromosome (translocation). At first the banding technique made it possible to identify a small number of chromosomal anomalies. In the late 1970s and early 1980s the perfection of this technique – more than 1000 bands were identified on human chromosomes – made possible the identification of smaller changes in the chromosome’s structure, and greatly expanded the number of detected chromosomal anomalies⁵³. The perfection of the banding technology opened an era of intensive cytogenetic studies. Such studies were extended to fetal cells too. The term mutation, previously applied to “Mendelian” diseases produced by changes in a single gene, became increasingly associated with “syndromes,” a group of anomalies related to changes in chromosome’s structure. Syndromes such as Prader Willi/ Angelman syndrome, Cri de Chat syndrome or Williams syndrome often involve changes in numerous genes associated with missing or duplicated part of a chromosome. Syndromes tend to be associated with a large number of impairments and are frequently, although not always, linked with developmental delays and the presence of abnormal (dysmorphic) traits⁵⁴.

From the 1980s on, a DNA-based technology, fluorescence in situ hybridization (FISH), made possible a more refined analysis of chromosomal anomalies. FISH looks for the presence of specific – and known – anomaly in the cell. Segments of DNA (probes) carrying the genes one is looking for, are marked with a fluorescent stain. The probe is then mixed (hybridized) with fixed (in situ), denatured chromosomes (chromosomes with an opened helix structure) of the tested cell, and is allowed to attach to its complementary sequence. The presence of a hybridized fluorescent probe – that is, the existence of a complementary sequence on the tested DNA – is then revealed under light that excites the fluorescent dye. Fluorescence is visible to the naked eye or measured with specialized instruments. FISH and akin approaches are used when physicians have a relatively precise idea of what the mutated genes they are looking for are, either because they are present in the family, or because a clinical observation, such as visualization of a skeletal anomaly in a child or a fetus, points to the direction of a specific condition.

When physicians suspect that a patient has

a genetic anomaly but do not know what this anomaly may be, or, alternatively, they had made a tentative diagnosis but a genetic test disproved it, they frequently apply a different approach, comparative genomic hybridization (CGH). CGH (also called chromosomal microarrays) is an extension of FISH technology to the study of the whole genome of a cell. DNA from the tested sample is labeled with a red fluorescent dye, while DNA from a reference sample is labeled with a green dye. The two samples are then mixed and the observers measure the ratio of red to green fluorescence at each chromosome. Deviations of the expected 1:1 ratio indicate the presence of the anomaly in the tested DNA. The test, initially used in the same way FISH was and destined to the study of isolated cells, was made much more efficient through the use of fragments of DNA printed on a chip (microarrays), an approach that makes possible a very rapid comparison between DNA sequences.

FISH and CGH are complementary technologies. FISH answers the question, “Is the mutation X present in this patient?” CGH answers a different question: “Is the patient’s genome normal?” and if an anomaly is found, indicates where it is located. CGH is especially useful for the search of chromosomal anomalies such as deletions, duplications and translocations. When, following a display of a structural anomaly by CGH geneticists suspect the presence of an already identified mutation, they can use FISH to confirm that this indeed is the case. Taken together, these technologies greatly extended the number of mutations linked with human impairments, and increased the perception a growing number of conditions, such as autism, as “genetic”⁵⁵. They also proposed new, genetic, explanations of pathological phenomena. For example, physicians knew that children with born with heart anomalies may display developmental delays as well, but they viewed such delays as a secondary effect of a heart defect that might have perturbed the circulation of blood to the brain. Recent genetic studies proposed a very different explanation: heart anomaly and intellectual impairment are produced at the same time by the same mutation⁵⁶.

From 2012, a new technology, non-invasive prenatal testing (NIPT) grounded in the analysis of circulating free fetal DNA (cfDNA) in maternal circulation made possible to verify whether the fetus carries an abnormal number of chromosomes or displays chromosomal anomalies by examining fetal DNA present in the pregnant woman’s blood. The test has a high degree of ac-

curacy, although experts strongly recommend to confirm a positive result through amniocentesis. Before the advent of NIPT, physicians had access to fetal genetic material only through a sampling of fetal cells, usually through amniocentesis, a stressful and still a risky procedure. With the development of commercial NIPT, they obtained such access – although as for now (2018) restricted to limited number of mutations – through a simple blood test performed early in pregnancy. This technology allows therefore a risk-free screening of all the pregnant women for the presence of chromosomal anomalies. In many Western European countries in which this test is gradually integrated into monitoring of pregnancy covered by a national health insurance, NIPT is proposed (in 2018) only to women defined as being at higher than usual risk of having a child with one of the autosomal trisomy, 21, 13 or 18. In countries, such as the US or Brazil, in which NIPT is distributed through free market (and may, or may not be reimbursed by the pregnant woman’s health insurance) this test is often employed by low risk women who want a rapid confirmation that the “baby is all right.” Moreover, many of these women chose the “extended” version of NIPT, that looks not only for three copies of chromosomes 21, 13 and 18, but also for sex chromosome anomalies (Klinefelter, Turner, XXX, XYY) and the presence of selected chromosomal deletions or duplications. Testing for the latter conditions may produce new dilemmas for pregnant women. The case of DiGeorge syndrome, illustrates such dilemmas.

DiGeorge syndrome is produced by a deletion of a part of chromosome 22 (22q11del). It is a relatively frequent anomaly; its estimated frequency is 1 in 2000 live births (the estimated frequency of Down syndrome in industrialized countries is 1 to 700 live births). DiGeorge syndrome is linked with numerous physical defects, mild to moderate cognitive impairments (the mean IQ of people with Di George syndrome is in the low 70s, but approximately 30% are in the normal range of 80 to 100) and high occurrence of psychiatric disorders, above all schizophrenia⁵⁷. Scientists estimate that 30% of cases of Di George syndrome are transmitted in families as a dominant mutation (that is, can be defined as “hereditary”), and 70% are new mutations (that is, can be defined as “genetic”)^{58,59}. Experts stress the importance of multidisciplinary management of this complex condition. Children with Di George syndrome suffer from feeding difficulties, infections, and many need surgeries for congenital heart and pharynx

anomalies. In later life, people with this syndrome have difficulties with long – term communication, and have learning, behavioral and mental problems: many of their symptoms correspond to the definition of autistic spectrum disorders^{60,61}. The great majority of adolescents and adults with this condition need some kind of educational and psychiatric support, as do the great majority of their caretakers, nearly always their parents. Numerous adults with DiGeorge are in psychiatric care⁶². Others live “normal” lives, and some never learned about their mutation.

Reproductive guidance of people with DiGeorge syndrome is a challenging problem. People diagnosed with this syndrome following its diagnosis in their child or in a fetus, have nearly always a milder form of this condition. On the other hand, since DiGeorge syndrome has a variable expression, it is impossible to predict the severity of pathological manifestation in a child of a person with mild variant of this syndrome. Before the advent of CGH, a prenatal diagnosis of DiGeorge was grounded in the observation of morphological anomalies, such as heart and palate defects. The growing use of CGH to study miscarried or aborted fetuses enlarged the number of anomalies linked with DiGeorge syndrome because in many cases the study of genetic material of a miscarried or aborted fetus that was not initially suspected to have a DiGeorge syndrome revealed a deletion of a part of chromosome 22⁶³. With the lowering of costs of molecular biology tests, search for DiGeorge syndrome became a part of a routine investigation of structural anomalies of the fetus revealed by obstetrical ultrasound. It is further extended in countries in which many pregnant women undergo “extended” NIPT testing. These women, the majority of which probably had never heard about DiGeorge syndrome, may learn that their future child may face challenging physical cognitive and psychiatric problems. They may also learn that this child may have only mild physical and mental disabilities and may lead a “normal life”, which, if s/he is lucky, will be unburdened by knowledge of being a mutation carrier.

Life with – or without – genetic diagnosis

A diagnosis of a genetic disease – often made in an affected child – may be very important, even – as alas, it is frequently the case – it does not lead to a cure. An accurate diagnosis can provide an explanation of the difficulties encountered by this child, reduces parents’ culpability by

showing that the child’s difficulties were not produced by something they did, allows to predict the child’s future, and indicates appropriate medical, educational and psychological interventions. It can also favor contacts between people affected by a given condition and promote solidarity and a disease-centered activism^{64,65}. If the condition is “genetic”, that is, is the result of a new mutation, its diagnosis does not involve, however, decisions about reproduction. If the condition is “hereditary” and is transmitted in families, people who learn that they or their partners are mutation carriers may however face complex reproductive decisions. The nature of such decisions depends often on the ways a given condition is conceptualized and framed. The finding that a disease is transmitted in families may or may not be the determinant element in the way people perceive it. The practical consequences of the definition of a given pathology as “hereditary” may depend on its history, the pattern of its management by the medical profession, the nature of its manifestations, and sometimes on existence or not of active association of patients that puts to the fore its hereditary aspect.

Some “older” hereditary diseases such as hemophilia or sickle cell anemia were historically defined as transmitted in families. Other diseases, such as Tay Sachs disease (a metabolic disease invariably fatal at a young age), or thalassemia (a blood disorder which today is not incompatible with life but often produces a severe impairment), became strongly identified as “hereditary” through mass campaigns that aimed at their elimination such as the efforts to eliminate Tay Sachs disease among Ashkenazi Jews, or efforts to reduce the prevalence of thalassemia in Cyprus or Iran^{36,66-68}. In Israel, the ministry of health is actively promoting the identification of the carriers of hereditary diseases such as Tay Sachs, cystic fibrosis or familiar dysautonomia with an explicit aim of preventing the birth of children with these conditions through a combination of pre-conceptional diagnosis that in some cases may lead to a couple’s decision not to marry or not to have biological children, early prenatal diagnosis coupled with a selective abortion and, more recently also pre-implantary diagnosis – in vitro fertilization followed by a diagnosis of disease – linked mutation in embryos, and implantation of embryos devoid of this mutation^{69,70}.

Other diseases, although clearly without any doubt resulting from a mutation transmitted in families have a more fluid status. Phenylketonuria (PKU) is a hereditary recessive condition,

but since it is considered curable / preventable through the maintenance of low phenyl alanyl diet, its hereditary dimension is often minimized¹⁶. Conditions such as polycystic kidney disease (in the majority of the cases, a dominant hereditary disorder) and heterochromatosis (a recessive hereditary disorder) are seen mainly as “diseases,” not mainly as “hereditary.” The weak focus on their transmission in families is probably related to the fact that they have a highly variable expression (some people who inherit the disease-related gene are sick, while others are healthy), great differences in the time of appearance of symptoms in affected people and the severity of the symptoms, and the existence of an efficient therapy. People with polycystic kidney disease and heterochromatosis are often more concerned about getting the right diagnosis and an adequate treatment for their symptoms – if they develop them at all – than about the transmission of a hereditary trait to offspring^{71,72}. Moreover, these pathologies are not seen as belonging mainly to the jurisdiction of geneticists, but to the domain other medical specialties, respectively nephrologists and hematologists. These specialists tend to be more concerned about diagnosis and care of an already existing condition than about its inheritance. Finally when a predominant understanding of an inborn condition is not shaped by a powerful disease-focused organization – which do not exist for polycystic kidney disease and heterochromatosis – affected people and their families may have more possibilities to construct their own narratives about the meaning of life with this condition. Such narratives may include the rejection of the label “hereditary.”

The sociologists Michel Callon and Vololona Rhaberisoa followed the story of a patient, Gino,

from the Réunion island, who resisted the diagnosis of a genetic disease (limb-girdle muscular dystrophy- LGMD) that runs in his family, and did not seem concerned by risk inheritance of this disease by his children and grandchildren. While Gino’s brother, Leon, was very active in the muscular dystrophy association of Réunion, Gino refused all contacts with this association. His passive but obstinate resistance to enter the biomedical space in which he is defined as a carrier of “faulty” gene, allowed him to reject a definition of “genetic kinship” imposed from outside, and the moral decisions an entrance into this network will automatically entail. By refusing genetic testing, Gino kept his freedom to define the kind of bonds between people that are important for him. When he rejected his brother’s pleas to get tested whether he carried the LGMD gene, and explained that he “does not want to know,” Gino affirmed his right to be himself, not the person others want him to be⁷³.

Today’s industrialized societies – and increasingly also those of “intermediary” and developing countries – are dominated by biomedical rationality. Yet, people are still free to either elect to live in diagnosis and in prognosis or to live elsewhere. They can choose to what degree their diagnosis defines what essentially they are at a given moment of their life. Even those diagnosed with a lethal condition still can elect to see themselves above all as “waking dead,” as being alive – or both⁷⁴. As the historian of medicine Charles Rosenberg explained, diagnosis and prognosis do not determine the ways individuals deal with them. Diseases, Rosenberg proposes, “are stages on which we perform as individuals and as moral actors. In the West’s bureaucratic and technology-dependent environment, it is ironic that in some ways pain, sickness, and incapacity remain a final and ultimately inaccessible citadel of individuality. We are shaped by our diagnoses, but we are not reduced to them”⁷⁵. Genes are (still?) not us.

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