Chapter 15
Ethical Issues in the Genetics of Complex Disorders
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Introduction

Over the past decade, our knowledge about the role of genetics in relation to both health and disease has advanced greatly, largely as a result of the sequencing of the human genome. Present and future genetic research will no longer be focused solely on monogenic disorders such as sickle cell anaemia or cystic fibrosis but more and more on so-called complex disorders. These conditions are complex in a number of ways. First, multiple genes are involved in predisposing or protecting individuals from the disorder in question. Second, such multiple genes do not always simply cause or prevent a condition but rather increase or reduce the risk of developing that condition. Third, such conditions can be complex in the sense that a given genetic background can interact with environmental features and/or aspects of an individual's behaviour and lifestyle. Fourth, given the nature of inheritance patterns and the way that genes are "shared," the focus of medical interest cannot only be upon individuals but must also consider the impact upon group or population health. Such clinical complexities also generate ethical complexity.

Future research is likely to be rich in terms of discoveries about the role of genetics in human health and disease, providing greater understanding about the complexities outlined previously, and the opportunity to create potential therapies for both treating and preventing the development of such conditions. This chapter seeks to outline and discuss the ethical issues relating to all of the issues of complexity previously outlined. It will begin by outlining the nature of ethics before turning to four important sets of ethical issues. The first focuses on risks and benefits, the second is on problems in gaining understanding and consent, the third is focused on public health issues, and we end by discussing issues of justice and discrimination.

Ethics: A Brief Introduction

Ethics is a normative discipline concerned with how we ought to live our lives together, including how to act and what kinds of dispositions and behaviours we should encourage. The focus is usually on relationships with other human beings, but there is no reason to restrict it in this way. Ethics can include considerations relating to animals, societies, environments, etc. Ethics is also distinct from the law, although the two can be related in a number of complex ways. For example, even if the law is clear on an issue, knowing and applying the legal answer to a question does not guarantee that we will have an ethical outcome; the law might be subject to ethical critique in that it may have unethical consequences. In empirical disciplines, such as genetics, we look for experimental evidence to support or reject hypotheses. In ethics, we use reasoning and reflection to establish an ethical position on a particular issue. While many ethical issues are subject to disagreement, this does not mean that any answer will do. Ethical positions need to be justified, and this can best be thought of as requiring us to have reasons for them. Such reasons can be judged in terms of whether they take into account all the relevant considerations, whether the results of their application might have a negative impact when applied to other cases, whether they are consistent with other commitments that we have, etc.

In this section, we begin by seeking to identify which ethical values are relevant for thinking about a complex disorder such as stroke. One common approach is to identify four principles as capturing such values. They are beneficence (doing good), non-maleficence (do no harm), justice, and respect for autonomy [1] . The advocates of this approach hold that these principles can be supported whatever someone's theoretical commitments might be. The idea here is that these principles are supposed to all be of equal value. However, they can come into conflict, and where they do, we will need to decide which one takes priority over the other(s). Respect for autonomy tends to be the principle that people invoke most often [2] . However, there is no reason to think that respect for autonomy, for example, should always be the principle that takes priority. The frequency of this appeal to autonomy perhaps tells us most about the general rankings that such values tend to have in particular societal contexts (e.g., in this case, liberal, democratic, Western societies) [3] . These four principles may be a good place to start to think about ethics, but we do not need to think that this list captures all of the relevant considerations. For example, the four principles might be criticized for focusing ethical discussion on individuals. Only justice might be paradigmatically what we might call a social principle, one that intuitively focuses on how *we* ought to live together rather than how *I* ought to act toward others. Such a dominance of individualism has tended to be the tradition within recent discussions in ethics. This approach has, however, been increasingly criticized by many, including feminists, communitarians, and many advocates of public health ethics [4] . Many of these critics are keen to emphasis the social nature of being a human being and the importance of both relationships and the social, economic, and political context in the generation of our identity and behaviours. They argue that this should be a key part of how we think about ethics. This is particularly important here because genetics necessarily involves relations with others because genes are shared across families and populations. Take, for example, recent discussions in public health ethics that have tried to broaden what counts as a harm or a benefit to include benefits and harms to populations and groups not just individuals [5] . Public health ethics also emphasizes the importance of prevention as well as treatment. In addition, much discussion has focused on public health practice and policy and the legitimate limits to government action or action on behalf of a whole population through the employment of law or public policy to enforce (or even coerce) certain desired actions for the sake of the public's health. This involves governments having to take a view on what counts as a good life, for example, in relation to how much free choice to restrict to bring about other goods such as health. This opens up the accusation of paternalism by the state, where this is held to be morally wrong because the government should not be deciding how we should live our lives. This is an important issue for this chapter as aspects of our environment and behaviour that may influence the impact of our genes on complex disorders are potentially open to manipulation by government. To what extent does a government have obligations to protect us from harm in such scenarios? This links up with ideas about responsibility, in that the corollary of the focus on autonomy in healthcare might well be that we tend to hold individuals to be responsible for the consequences of their choices. Is this fair? How are we to judge such issues when we are talking about complex interactions between genetics and environmental and/or lifestyle factors? We will return to these issues below in our discussion of key ethical issues that arise in relation to complex genetic disorders.

Ethical Issues

In this section, we outline four main groups of ethical issues raised by complex disorders. They are potential risks and bene fi ts, potential problems in gaining understanding and consent, issues related to a public health focus, and potential justice and discrimination issues.

Risks and Benefits

The importance of research into the role of genetics in stroke can be justified by appeal to at least two different types of benefits. The first is to appeal to the intrinsic benefits that come about as a result of conducting such research in terms of producing knowledge due to greater understanding about stroke. Human beings are inquisitive animals; we want to understand how things work and how they go wrong. Research into genetics allows us to come to know much more about the natural world. The second set of potential benefits focuses on the extrinsic benefits, the value to which we can put such knowledge in terms of both potential treatments for the conditions themselves or their symptoms and consequences, as well as the potential benefits through understanding the importance of prevention in terms of seeking to avoid or reduce the risk of the development of a condition through the taking of a drug or modifying the environment or lifestyle. Certainly, research in the area of complex disorders such as stroke holds out the promise of both benefits.

There is every reason to believe that such work will bring about significant benefits in terms of reducing morbidity and decreased mortality, but this needs to be weighed against the potential ethical problems that might emerge. This weighing or balancing needs to be fair in terms of not being over critical and pessimistic about potential problems but also not just believing that because something can be done it should be done. Unquestioning optimism for genetic advances to transform the landscape of health and disease is inappropriate: science can produce fantastic benefits but can also, on occasions, cause harm. This position requires us to be modest, to accept the idea that sometimes we get things wrong, that we often have to stop and reflect upon on what has happened and choose a new direction. So what are the potential problems?

Genetic Prediction

Genetic prediction for individuals carries many potential risks of harm. These will include such things as the potential for stigmatization due to genetic labelling, possible false reassurance if the test suggests a low risk, as well as a contribution to the general increase in medicalization within society. This is the idea that as more and more of our lives are understood in terms of clinical factors, our lives are (and perhaps even ought to be) under the influence of medicine. It is also possible that knowledge about one's risk of genetic conditions may result in a reduction in autonomy if that knowledge thwarts the pursuit of other personal plans for the future or important individual values. For example, certain lifestyle factors of importance to the individual might be held to be too "risky," and continuing such actions might result in the assumption of responsibility for the consequences and feelings of guilt as a result of the outcomes. Details about an individual's genetics may often not be considered to be "just another bit" of information but as having a certain special status. Indeed, there is a danger of a certain kind of fatalism as result of coming to think that genetic determinism is true, that we are condemned to live particular kinds of lives because of our genetic inheritance, and perhaps thinking that there is little point in doing anything beyond accepting the "inevitable."

Consideration of these kinds of risks will also have implications for family members and society in general. The potential harms of genetic determinism may be reduced by addressing the ways in which people develop an understanding of genetic risk. It is important that people understand that risk in relation to many complex disorders such as stroke may be modified through individual and population interventions, whatever their genetic inheritance might be. For example, other risk factors relating to stroke include high salt intake, low exercise, and being overweight. The genetic contribution to risk needs to be seen in the context of all risk

factors, rather than genetics being seen to be the dominant and determining factor. The way that all such risks are viewed will in turn be affected by the perceived accuracy and degree of confidence in the prediction, the way that clinicians talk about the risks and place them in context, the performance of such testing relative to other possible current risk factors (e.g., lifestyle factors, family history), and the type and quality of the regulation of providers of the supplied genetic tests.

One potential danger over time is that responding to complex disorders means that we gradually change the way that we think about health and disease. In contrast to monogenetic disorders, stroke genetics enables the identification of genetically "at risk" individuals rather than individuals who have a disease now or will inevitably develop one in the future. Many of the individuals held to be at high risk will never suffer a stroke (and many not identified as genetically at risk will do so). Being "at increased risk" is not to suffer from a disorder in the traditional sense of the word, nor is it to be a "patient" in a traditional sense. In stroke, by defining a new health category of genetically at-risk individuals, we are potentially expanding and redefining our understanding of disease and health with potential implications for employment, insurance, and even personal relationships (could being at high stroke risk render an individual unable to find a long-term partner or have children within a such a relationship?). It is unclear what the implications might be for individuals or society resulting from these developments.

It is certainly true that a clear and common understanding of what we mean by disease and health is central to the discussions about the ethical acceptability of medical research and healthcare interventions at both the individual and population level. It is therefore essential that we scrutinize the ways in which genetic information is generated and used to ensure that these fulfil legitimate healthcare and public health aims. However, while it should be noted that these potential risks are real, they still need to be carefully weighed against the potential benefits before a decision is made about what to do. As it happens, it is not clear that any of these risks are sufficient to constitute what we might term a categorical moral objection to genetic research, testing, or interventions. However, recognition of these risks should be used to inform researchers, regulators, and policymakers to ensure that potential harms are minimized when today's research is translated into tomorrow's clinical practice.

Potential Problems in Gaining Understanding and Consent

If anything has been central to medical ethics over the last 40 years, it is the requirement that an informed consent ought to be obtained before treatment or participation in research [6] . It is important to see that if the potential health benefits of scientific advances in genetics are to be realized at a population level, there needs to be widespread uptake of genetic testing and agreement to corresponding interventions (e.g., taking drugs or lifestyle modification). Informed consent is standardly held to require a free decision by a competent individual on the basis of an understanding of what is considered to be relevant information. However, there are a number of reasons to think that obtaining consent in relation to complex disorders will be far from straightforward, because there are a number of factors that suggest that giving meaningful and comprehensible information about such conditions to people will be challenging.

As outlined in our introduction, there are multiple levels of complexity in such disorders. Explaining paradigmatic cases of monogenetic disorders with classical Mendelian inheritance patterns is hard enough, but with complex disorders, there are many potential opportunities to misunderstand. For example, in complex disorders, multiple genes are involved in

predisposing or protecting individuals from the disorder in question. Such multiple genes do not always simply cause or prevent a condition but rather increase or reduce the risk of developing that condition. We already have good evidence that many people find it hard to understand risk probabilities within the setting of informed consent relating to risks of harm. Do we know if they will understand being told that they are 29% more likely than average to have a stroke? If we then factor in that many complex disorders may also have other risk factors such as environmental features and/or aspects of an individual's behaviour and lifestyle, how is meaningful and comprehensible information to be given at the individual level about this complex multifactorial and interactive background? A misunderstanding of risk may create a sense of genetic fatalism leading individuals to reject reasonable interventions as pointless as "it is all in the genes". The information provision and discussion will be further complicated by the nature of inheritance patterns and the way that genes are "shared"; the focus cannot only be upon individuals but must also consider the impact upon group or population health. In relation to informed consent, this is likely to involve explaining what implications any genetic findings might have for relatives. Again, the opportunities for misunderstanding these issues are significant.

Many of these issues are not unique to genetic testing. For example, individuals are routinely tested for diabetes. Such testing identifies a significant number of people as having impaired fasting glucose (IFG). People with IFG are at increased risk of developing diabetes and cardiovascular disease, as are their relatives. These risks are modifiable with dietary, behavioural, and therapeutic interventions. The ethical issues raised by screening for diabetes have been well debated and are not considered an insurmountable barrier to such screening.

However, genetic testing for complex disorders is importantly different in a number of ways. In some individuals, hypertension or IFG may resolve with weight loss or exercise. An individual identified as genetically at risk for stroke may be able to substantially modify their risk but cannot change his or her genes. Consequently, the potential for stigmatization and prejudice is greater. A further important difference is that genetic testing could be used with equal accuracy in children (and even antenatally as discussed in the next section). If it is difficult for a competent adult to understand the significance of a 29% increased risk of stroke, how much more difficult would it be for parents? While early risk identification might permit valuable interventions at an earlier stage, it might also limit a child's choices and have a negative impact on their welfare through imposed lifestyle restrictions and societal labeling. Gaining informed consent in this situation requires not just understanding of the complexities but also robust evidence on the benefits and harms of risk identification in children.

We have so far focused on stroke, but the methodology used to investigate stroke could apply to other complex disorders such as mental illness where there is little in the way of primary prevention or even for behavioural traits for which no effective interventions exist. If such tests are developed, should access to testing rest with the individual ("Do I have a right to know my genetic makeup?") or with society? Assuming that informed consent is not impossible to obtain, it might be argued that the kinds of potential harms we are talking about can be accepted as reasonable if individuals are given the information and they decide what to do on that basis. At this point, it is worth reflecting on the risks associated with a range of interventions and actions that are accepted as reasonable or desirable in hospitals every day, such as bariatric surgery with a mortality of around 1% in a morbidly obese but otherwise well individual or potentially toxic chemotherapy for advanced cancer. Is an informed consent enough to legitimate such actions? Many people clearly think so, but it is interesting to reflect that as a society, we would not consider participation in a violent sport with a 1%

mortality desirable even with consent, and we go to considerable lengths to prohibit the use of recreational drugs even when users consider the benefits to outweigh the risks. There is therefore the potential that some forms of genetic testing and research will not fulfil legitimate healthcare aims, and as such, informed consent alone will not render them ethically acceptable.

Public Health Policy Issues

We have argued in the previous section that consent is, of course, considered to be a necessary requirement for the ethical acceptability of interventions in surgery and medicine—at least where such action will address legitimate healthcare aims. However, in the arena of public health, it is not always possible to gain the informed consent of all parties affected by an intervention. The aims of public health are distinct from those of clinical medicine, in that perhaps the key aim is to protect and promote population health. However, public health is not solely interested in aggregate health, as other aims of public health might include the identification, reduction, or removal of health inequities within a population [7] . Public health interventions can be controversial because of these aims, but we already accept intrusions into our private lives and personal liberties (e.g., the widespread ban on smoking in public places, high taxation on alcohol) on the grounds that such actions are necessary to prevent disease and promote health. So a challenge in thinking about genetics in relation to complex disorders from the perspective of public health is the degree to which we focus on and prioritize population outcomes.

In thinking about future public health interventions for complex disorders such as stroke, it is important to factor in that, as already mentioned, the risks of the disorder eventuating are increased through various lifestyle factors such as diet, weight, and exercise. In assessing whether to introduce any large-scale population-level intervention, the relative risks of genetics and these other factors will have to be calculated. It is at least possible that a focus on lifestyle change will be more cost-effective than a focus on genetics. More generally, it is also important to consider the relative merits of prevention versus treatment, whether "prevention" includes advice about lifestyle change and/or genetic testing. In cost-effectiveness studies (and clinical care), there is perhaps a bias in favour of treatment over prevention. This is understandable because those requiring treatment are visible; they are in hospital as an emergency or are consulting their family physician. Most codes of professional conduct place emphasis upon doing what is best for your patient (with the implicit message that the wider implications of that action are less important or perhaps even irrelevant). It is much harder to see the impact of preventive activities because when successful, you are measuring an absence of cases for treatment. The success of preventive programs is to be measured, largely, at the population not the individual level.

At least some possible public health interventions relating to complex disorders might take a population-level preventive focus. For example, primary prevention or screening programs might be developed with the aim of reducing the number of strokes by testing for the relevant "at-risk" gene combination(s) in large groups (based, perhaps, on family history or phenotypic traits) or even the whole population (perhaps within a certain age range). There are a couple of well-known potential dangers with all such interventions. The first is that there may be both implicit and explicit coercion of individuals to ensure participation. Secondly, such programs have the potential to increase health inequalities if uptake of such testing is differentially distributed in the population, with the creation of a genetic underclass as the most dramatic outcome. This is more likely to become a real issue if genetic testing is largely available through private rather than publicly funded medicine.Nonetheless,

experience from publicly funded primary prevention programs shows that the potential to increase health inequalities remains.

The other potential area for population-level interventions relating to such disorders is in antenatal screening. Perhaps, testing may be straightforward and routine for such complex disorders in the future. However, testing and possible abortion of fetuses because they have an increased risk of a complex disorder will be controversial. This is especially so given all the doubt discussed about whether an increased risk will eventuate in a disorder and the role that might be performed by lifestyle changes to mitigate any genetic risk. If an antenatal screening program were to be introduced, the arguments about potential implicit coercion would grow because even if state-sponsored eugenics is unlikely, societal expectations of genetic responsibility and "hygiene" may be enough to raise worries here.

Justice and Discrimination

Genetic research generates information about both individuals and groups. Such information allows us to identify, classify, and divide individuals. It is this capacity that creates potential ethical challenges relating to justice and discrimination. Many of these issues are, of course, not unique to the issue of genetic information. However, it warrants special consideration because of the quantity and speed with which such information can be acquired and processed; the fact that the information is "controlled" by medical science, in the sense that other personal information such as family history and lifestyle factors can be accessed and assessed without the help of medicine; and the fact that our current dominant cultural approach to medical science as value-neutral activities may mean we tend to accept genetic "truths" uncritically.

In addition, polygenic traits are in many ways ethically distinct from single gene disorders in that the wide range of conditions and traits, which can potentially be classified and examined, are liable to affect much of the population and are therefore likely to trigger debate among the public and policymakers. Given the fact that polygenic traits are generally risk predictors rather than disease identifiers, and that perceptions of and approaches to risk will differ between individuals, the correct path for policymakers is unclear. Polygenic traits span the spectrum from what might be considered preconditions for relatively uncontentious diseases, for example, ischemic heart disease (although even here what counts as disease or early/preclinical disease and within normal variation is subject to debate) to behavioural traits (e.g., criminality), which are not currently considered to fall in the medical domain and that until now have been socially and culturally defined. This may lead us to attempt to "get rid" of such "bad" gene sets or unfairly label carriers of these gene sets as "criminally inclined." Furthermore, since criminality has strong socioeconomic associations and therefore racial associations, we may create spurious associations with race and ethnicity, which may, in turn, reinforce existing bias and prejudice.

Throughout history, we have used labels such as skin colour, sexual orientation, or social class to differentiate between groups of people and justify inequalities in the way these groups were treated. Labels may be ethically reasonable or even desirable if they identify a morally relevant difference and are needed to pursue a morally acceptable aim. For instance, distinguishing between individuals who do or do not have the mental capacity to make a particular healthcare decision is desirable provided the distinction is used to further the welfare and rights of the individual concerned. However, our legacy of prejudice and human rights abuses provides good reason to be cautious when faced with new ways of labeling individuals.

Redefining complex disorders as genetic disorders is likely to drive researchers and policymakers toward genetic approaches to these disorders. However, polygenic disorders result from an interaction between genetic makeup and environmental factors. Focusing on genetic factors may detract from the socioeconomic factors that are responsible for much injustice in disease burden and indeed rebrand such differences as a natural consequence of biological difference. Even if pharmacogenomics interventions become available, we need to make sure that we do not extend the possibility of inequities across a new range of therapeutic options. Potential therapeutic advances should in part be assessed in terms of their impact upon equitable health outcomes.

Conclusions

This chapter has briefly reviewed a number of the ethical issues that arise from the development of knowledge relating to the genetics of complex disorders. As we have seen, the weighing of potential harms and benefits will be extremely difficult, as will the provision of relevant information to service an informed consent. These factors mean that it is appropriate for these issues to be more widely discussed by policymakers, the public, and the media. Such discourse requires widespread fluency in the language of genetics and risk. Here, the onus, at least in part, is on the scientific and medical community to engage with the ethical issues and communicate effectively with the public. The role of public health is potentially an important one in relation to responding to the genetics of these disorders, but a focus on "improving" population health is not straightforward here and could prove extremely contentious. In exploring policy options, we should always keep in mind the potential for discrimination and seek to ensure that what we might term "genetic justice" is our primary aim.

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