SCIENCE AND SOCIETY

Disability and genetics in the era of genomic medicine

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Abstract | Genomic medicine offers a growing number of methods to diagnose, cure or prevent disability. Although many disabled people welcome these advances, others have reservations about the impact of genetic knowledge on disabled people's lives, arguing that genetic science might exacerbate the deep ambivalence that society as a whole has towards physical difference and anomaly. It is also possible, however, that being able to specify the genetic bases of disability, and distinguish them from other causative factors, will contribute to a fuller understanding of disability and a better response to disabled people.

The need to think through the ethically complex relationship between disability and genetic knowledge has recently become more pressing, as theoretical advances in genetics begin to be parlayed into clinical interventions[1,2]. Put bluntly, genetics now enables 'something to be done' about disability, and this demands clarity about the kind of 'something' that is socially and ethically desirable. Through the genetic data that are becoming available from sequencing initiatives like the Human Genome Project, from analyses such as haplotype mapping[3,4], and through technical advances in sequencing automation, an increasing number of gene loci can now be prenatally and postnatally detected. Such knowledge could, in principle, be used in large-scale population screening of foetuses or newborns, as well as for individualized testing, and in the more distant future to develop various forms of gene-based therapy[5]. As the possible interventions supported by genetic science become more diverse and sophisticated, the ethical debate is shifting from its initial focus on the legitimacy of prenatal selection against genetic disabilities to grapple with the much more fundamental questions of the way in which society conceptualizes phenotypic variation and impairment. And all this is happening in parallel with the rise of a vocal and politically self-conscious global disability rights movement[6,7].

This article discusses some areas of contention that shape the ongoing relationship between genetic research and the people with disabilities whom such research affects. After highlighting a number of problems, I will also consider positive actions that can be taken to improve the dialogue between disabled people and those involved in genetic research.

> "…the drive to prevent or cure disabling impairment has become one of the primary justifications for committing significant resources of time, effort and money to genetic or other biomedical research…"

Genetics and disability

The logic that connects genetics and disability is pragmatic and clear. Genetics is concerned with unravelling the molecular route(s) from genotype to phenotype. In the most commonly held view, a disability is a phenotype that deviates from the norm: impaired sight or hearing, poor mobility or a range of other physical anomalies. Disability and genetics are also closely linked in a methodological sense. As an experimental science, genetics has relied on mutations that disrupt single steps in the pathways of gene expression in order to illuminate the normal routes of genotype-to-phenotype causation. Therefore geneticists have always been interested in illness and disability as the clinical manifestations of allelic variation, independent of any practical aim of alleviating genetic conditions.

However, genetic medicine now also uses the knowledge gained from basic research to diagnose conditions that have a strongly genetic aetiology and ultimately, it is hoped, to cure them[8]. Assuming that disability is undesirable (something with which most people are likely to concur), scientists and the general public alike will want to use genetic medicine to prevent it. This line of reasoning means that the 'therapeutic imperative', that is, the drive to prevent or cure disabling impairment has become one of the primary justifications for committing significant resources of time, effort and money to genetic or other biomedical research, as a glance at the ongoing media discussion of embryonic stem cell science shows.

Genetics and disabling impairment

Currently the commonest use of genetics in disability, and probably most ethically contentious, is in prenatal diagnosis (BOX 1). Traditionally, this was restricted to preconception genetic counselling of adults from families with known genetic conditions. However, more than a thousand single gene tests are currently available, and with now routine non-genetic prenatal screening for anomalies (for example, by ultrasound), targeted genetic testing is easily integrated into standard antenatal procedures in the developed world[9,10]. Tests such as these raise ethical concerns because, for the most part, the information they give leads to parents having to make a choice between continuing with or terminating a pregnancy — there are still only a small number

Box 1 | **Disability and genetic medicine: applications**

Apart from the promising developments in rational therapies based on increasing knowledge of how gene action is implicated in the aetiology and progress of a condition, genetics offers or has potential for various interventions:

- Prenatal genetic testing generally refers to gene-specific diagnostic tests rather than screening programmes for aneuploidy or other anomalies. On the basis of family and medical history, practitioners and patients can together decide when genetic testing is likely to be useful. Samples from the foetus can now be tested for over 2,000 loci that are associated, directly or indirectly, with disabling conditions. Only a small number of these, however, are in common use; for example, to test for alleles associated with cystic fibrosis.
- Preimplantation genetic diagnosis (PGD) involves the identification of alleles in embryos produced through *in vitro* fertilization (IVF). Embryos are generally tested at the 8-cell stage, and only those with the desired genetic composition are selected for transfer to the uterus. In the UK, PGD is licensed by the Human Fertilisation and Embryology Authority (HFEA) for around 50 conditions, including cystic fibrosis and familial hypercholesterolaemia (see the list of conditions licensed by the HFEA).
- Postnatal predictive or diagnostic testing is also available if a reliable gene association has been identified. However, the clinical indications for predictive or diagnostic testing in childhood, adolescence and adulthood are often different from those of prenatal testing, as are the ethical concerns about potential discrimination, for example, in employment or insurance, against individuals and families with genetic conditions. In the UK, the National Health Service (NHS) currently offers testing for around 400 genetic conditions, through the UK Genetic Testing Network. Genetic testing and counselling of potential parents at risk of known genetic conditions, in the form of preconception testing, is used to inform reproductive choices.
- Pharmacogenomics is the study of how genotypic variations affect drug responses. It currently has no widespread clinical application and little impact on disabling genetic conditions. This might change if, for example, research establishes links between genotype and responsiveness to drugs preventing the disabling consequences of specific conditions.
- Gene therapy involves providing a correctly functioning version of an aberrant gene to prevent or ameliorate its phenotypic consequences. Clinical trials of somatic gene therapy have been disappointing, with limited success in a small number of conditions, and gene therapy is unlikely to have direct impact on disabled people in the near future.

of conditions in which prenatal genetic diagnosis means that effective therapeutic interventions (*in utero* or soon after birth) can be made. With the advent of preimplantation genetic diagnosis (PGD) it also becomes possible to perform testing or screening at an earlier stage, identifying embryos that carry undesirable alleles and selecting those to be transferred, or in some cases choosing the gametes to be used in fertilization[11].

In addition to these prenatal uses, an increasing amount of postnatal genetic diagnosis in adults and children also assists the differential diagnosis of disabling conditions. The advantages for the individual include speedier provision of appropriate treatment, the presymptomatic identification of late onset or progressive disorders, and getting a better idea of prognosis or inheritance[12–14]. Such information might also inform future reproductive decisions, as has happened in Huntington disease[15,16], and contributes to an overall growth in knowledge about the natural history of a condition.

In terms of treatment, the use of various forms of gene therapy remains a more distant prospect. Germline gene therapy faces technical difficulties and has been largely (if not universally) ruled out on ethical grounds. And although somatic and *in utero* gene therapy have had equivocal clinical success, they are certainly not the treatment of choice for common disabilities[17,18]. Neither has pharmacogenomics yet had much direct impact on disability. This is partly because of the state of development of the science, but also because genetic tailoring of drug treatment is likely to be most relevant to conditions that are better classed as illnesses with long-term disabling consequences (such as diabetes or multiple sclerosis) in which medication might prevent or slow progress of the condition, rather than impairments like blindness, deafness or absence of a limb[19,20].

Disabled people's reservations

Many people with disabilities are strongly supportive of genetics, and as individuals or advocacy groups they are often involved in fundraising and lobbying to promote genetic research[21]. However, it is worth bearing in mind that such enthusiastic support for genetics is not entirely unproblematic. Clearly, disability groups that support genetic research are not primarily interested in the advancement of knowledge for its own sake; while recognizing the need for basic research, their ultimate goal is for genetics to prevent, ameliorate or cure (their) impairment. Their financial and political contribution to genetic research is tied to this agenda, with specific outcomes in mind that are not always congruent with the priorities of scientific research or health policy.

It can come as a surprise, especially to researchers with little clinical contact, that disabled people might be ambivalent or even hostile towards genetics and genetic medicine[22–24]. Given that the therapeutic imperative described earlier provides so much of the justification for investment in genetic research, it is important both practically and morally to understand these reservations. To do so it is necessary to abandon the background assumption, which in my experience is common to many scientists, that understanding lay people's concerns about a technology means identifying what they misunderstand, and correcting it. That is, we need to remain open to the possibility that at least some of the criticism from the disability movement is worth serious consideration: it might be right.

The disability critique

Disability criticisms of genetics are diverse. For the sake of clarity and conciseness I am going to focus on three central related points. First, that the use of prenatal or preimplantation diagnosis is discriminatory and/or eugenic. Second, that the focus on the genetic aetiologies of impairment diverts attention from other causes of disability, so that resources are moved away from interventions that would be more directly beneficial. And finally, that genetics is wrongly used to conflate diverse experiences of anomalous embodiment within an oversimplified concept of genetic abnormality.

Discrimination and eugenics. At one extreme of the disability critique of genetic diagnosis[25] lies the argument that these techniques infringe the future person's right to life. For some proponents, this argument is based on the premise that termination of foetal life is impermissible in

all cases (and sometimes this is stretched to cover the non-transfer of embryos in PGD as well). But more commonly, disability critics will claim that selection against genetic impairments is discriminatory[26–29]. For example, the bioethicist Adrienne Asch has long argued that an impairment is often no more predictive of the happiness or worth of a future life than a characteristic such as gender or social class; if we do not consider it ethically acceptable to exercise prenatal selection in terms of those characteristics, we should not automatically consider it right to do so for genetic anomalies that happen to be detectable before birth.

The discriminatory critique extends beyond prenatal diagnosis to include other interventions. It is true that currently the practical impact of genetic science on disability is largely prenatal, but this may change if and when various forms of gene therapy or other genetic intervention come on stream. The question will then be how far we are prepared to go in terms of innovative (and expensive) health care to ameliorate or eradicate genetically based impairment. Other anxieties concern the potential for postnatal discrimination in insurance, education or employment on the basis of genetic sequence data[30–32].

Some disability critics have put forward versions of the slippery-slope argument, suggesting that using genetic medicine to select against severe impairments will inevitably lead to lower tolerance of minor variations, and ultimately to the rejection of any deviation from the phenotypic norm (or the phenotypic ideal, if genetic enhancements are permitted). Like other versions of the slippery-slope argument that are used in bioethics[33], this claim is open to counter-argument. It is perfectly possible to distinguish between logical and practical slippery slopes, for example, and although there might be no logical barrier to extending genetically based selection or postnatal discrimination to all phenotypic differences, in practice all sorts of social and psychological factors would work against this. There are precedents in which limits to slippery slopes have successfully been set, for example, in legislation covering abortion in most European countries, and so it should be possible to do so here. Given that this is the case, the question is where to draw the line on selection against or rejection of phenotypic difference, and how best to achieve some sort of societal consensus about it.

A third claim is that prenatal or preimplantation selection is no better than a continuation of the eugenic health policies that were prevalent in Europe and North America in the early to mid-twentieth century. As is now well known, the discoveries of early genetics were used to fuel socially discriminatory attitudes, and these gradually morphed into overt, often non-voluntary, eugenic practices directed against people with what were then believed to be harmful heritable traits[34,35].

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These included widespread legislation promoting the compulsory sterilization of disabled people; they culminated in the killing of an estimated 70,000 to 200,000 disabled children and adults during the Nazi Third Reich (BOX 2). What frames the discussion of genetics and disability, then, is not an irrational fear that genetics might be put to unethical use, but a well documented history in which it was[36–38]. Clearly, these morally illegitimate developments were not the inevitable outcome of twentieth century genetics, but the result of scientific ideas becoming available within particular ideological and historical circumstances. Equally clearly, the theoretical questions of whether all attempts to improve human genomes (which is what eugenics is) are unethical, and precisely how contemporary genetics and historical eugenics relate to each other, have not yet been resolved[39–41].

Thus, some disability critics will contend that routine prenatal screening is a straightforwardly eugenic practice just like its historical precedents, with the only difference being that it now happens under the rubric of increased parental choice instead of with the stated goal of improving the common gene pool[42].

Geneticization. Although the disability rights movement's arguments about prenatal testing and PGD focus on selection against foetuses and embryos carrying particular genetic markers, its critique of genetics as a whole has broader scope. Disability theorists and activists are equally concerned about the effects of 'geneticization', a term coined to denote the tendency to explain phenomena, and particularly aspects of human life, in terms of gene action alone[43,44]. The critics' argument is that, with finite economic and human reserves, an exclusive focus on genetic causation distracts from other important factors that cause or contribute to disability. Whereas most geneticists and some disabled people are likely to think that concentrating on genetics is the sensible thing to do given its explanatory and practical power, the critics are less confident. They point out that only a small proportion of disability (about 10% on current estimates) can be traced back to genes. This point is often lost in the media hype about 'genes for' all human ills, but in a global context the majority of disabilities result from ageing, acute or chronic illness, and trauma — including war, one of the leading (and eminently avoidable) causes of physical and mental disability. Critics of geneticization will say they have nothing in principle against using genetics but that, in practice, pursuing the genetic aetiologies of, or cures for, monogenic disorders is simply not relevant if what we are really interested

Box 2 | **Disability and eugenics**

Eugenic efforts to eradicate genetically based disability have a long history. In the early to mid-twentieth century, eugenic ideas were extremely popular throughout much of Europe and North America; the first Eugenics Society was established in Britain in 1907. Many countries throughout this period implemented compulsory sterilization laws focusing on those considered to have heritable defects. It was, however, in Nazi Germany that disabled people suffered most. The now notorious T4 programme, so called because it operated out of Tiergartenstraβe 4 in Berlin, was responsible for the killing of mentally and physically disabled children and adults at a number of centres from 1939 onwards. The expertise acquired in gassing large numbers of people was later transferred to the extermination camps, and T4 centres were also integrated into local and regional disaster planning. Estimates of the number of deaths range from 70,000 to 200,000, with most killings carried out by medical personnel[35,37].

in is alleviating the global burden of disability, most of which has nothing to do with genes. And, so the argument goes, although there might well be a genetic contribution to disability resulting from age or illness, research to identify it might take an unacceptably long time compared with non-genetic interventions.

Disability: heterogeneity. Considering aetiology brings us to something which is often glossed over in the ethics of genetic intervention in disability: the question of what exactly we are talking about. Disability is one of those concepts that we all assume we know what we mean by it, but have difficulty producing a definition when pressed. The word itself is often used imprecisely, and by different constituencies in different ways. The idea of an all-embracing category of 'disability', as opposed to multiple distinct kinds of impairment, is relatively recent. This is semantically important because, although a single term is discursively efficient, it homogenizes the enormous range of manifestations and aetiologies of disability (just as the use of 'scientist' to cover everything from a theoretical physicist to a marine biologist ignores some not insignificant variations). And just as the classification of certain disciplines as sciences might be contested, there is fuzziness and dispute at the edges of the concept of disability. At what point, for example, does an illness become disabling, and how should we distinguish people who are disabled through chronic illness from those who have an impairment but are not ill? What about people who are phenotypically anomalous but reject the suggestion that they are disabled? Too easy recourse to the umbrella term of disability without really being clear what it covers also glosses over the fact that what we find undesirable about disability — its disadvantage, distress or pain — can arise for a number of distinct reasons, not all of them biological.

With a vastly increased technical ability to identify and 'do something about' impairment and anomaly, we (that is, society and scientists) need to be more rigorous about exactly what constitutes the disadvantage of a disability. One of disability activism's most audacious and most misunderstood moves has been to attempt to analyse the disadvantage experienced by disabled people by separating out the biological and socioenvironmental contributions to impairment and disability, respectively[45,46] (BOX 3). This makes it easier to identify those features of disablement that are intrinsic to the phenotype, and those that arise because of the mismatch between the body and social expectations of how a body should look and function[47]. With this redefinition, disability theorists are not claiming that all of disability is a side-effect of social organization, only that it is possible and necessary to distinguish those effects from others that are intrinsic to the phenotype. Ethically, this is important because of the force that the therapeutic justification — the alleviation of the suffering of disability — gives to genetic medicine. If it is true that a significant proportion of the disadvantage of certain disabilities comes from social arrangements and not the impairment *per se*, we should then be aware that prioritizing genetic interventions is choosing to tackle a socially based difficulty through biological means. In some cases, this is probably the right thing to do; but in others, being aware that it is a choice could significantly alter the balance of ethical justification for genetic intervention.

Box 3 | **The impairment/disability distinction**

In 1975 the Union of the Physically Impaired Against Segregation (UPIAS), a British disability advocacy group, published its Fundamental Principles of Disability[46]. In it, an important distinction was drawn between impairment, the physical anomaly or variation, and disability: "…we define impairment as lacking all or part of a limb, or having a defective limb, organ or mechanism of the body, and disability as the disadvantage or restriction of activity caused by a contemporary social organization which takes little or no account of people who have physical impairments and thus excludes them from participation in the mainstream of social activities." This distinction has often been misunderstood as a claim that no such thing as physical impairment exists, rather than as a tool to analyse more precisely the source(s) of the disadvantage of different impairments[67]. Although criticized and revised both within and outside disability studies, the distinction has been analytically and politically useful and widely influential, for example, in the 2001 revision of the World Health Organization's International Classification of Functioning, Disability and Health (ICF).

Teasing out the contributions to disability like this is also useful in clarifying the nuances of terms such as impairment, difference, anomaly and variation in the context of disability. One of the central disability critiques is that genetics is too often used, especially in the popular media, to support a vastly oversimplified picture in which all genotypic or phenotypic variation is an adverse deviation from a norm. To counter this, some disability theorists have more controversially argued that not all impairments, or all aspects of the experience of disability, are fundamentally undesirable[48]. Two good examples come from the Deaf community and to a lesser extent people with achondroplasia, a form of restricted growth. In both cases, some parents express the positive wish to have a child with the condition rather than without[49–52]. Parents with achondroplasia might often refuse prenatal screening for example[53,54]; and in a well known case reported in 2002, a deaf couple in the United States used a sperm donor with a genetic form of deafness in order to increase their chances of having a deaf child[55,56]. Empirical research suggests that deaf people often have a degree of preference for a deaf child, and a rather smaller number would consider acting on their preference with the use of selective techniques[50,57] (BOX 4).

This preference becomes problematic when genetic counselling services or reproductive medicine are asked to help parents have a child with one of these impairments. For many people, the idea of deliberately opting to have a child with a disability, or of not taking up the possibility of avoiding its birth, is deeply troubling. Many members of the Deaf community would respond that they do not consider their audiological anomaly to be a disability, but rather a form of human variation, and one that has given rise to a culture of its own with members who want to see their community continuing into the future. On the other hand, those who are against 'choosing deafness', which includes some deaf as well as hearing people, will argue that even if individual disabled people should have the liberty to express preferences like these, they have no accompanying right to expect genetic medicine to help satisfy them.

These debates came to a head in the UK in spring 2008. Clause 14(4)(9) of the draft Human Fertilisation and Embryology Bill[58] states that, "persons or embryos" known to have a genetic abnormality with a significant

risk of transmitting a serious mental or physical disability, serious illness, or any other serious medical condition, "must not be preferred to those that are not known to have such an abnormality." Although at the moment it is unclear exactly how this would be interpreted in practice, it could mean that a deaf couple undergoing PGD would not be able to choose embryos carrying a gene associated with a genetic hearing impairment. Although the clause, and the explanatory note explicitly tying it to deafness, was criticized by some bioethicists and genetic counsellors[59] as representing too much interference by government in parental reproductive choice, members of the Deaf community have condemned it as an unjustified act of discrimination. Unjustified because it is based on two assumptions: that deafness is always a severe disability and that this judgement is universally held.

Box 4 | **'Choosing deafness'**

In addition to anecdotal evidence, there is empirical work demonstrating that culturally Deaf, hard of hearing, and hearing parents of deaf children can differ in their attitudes to having a deaf child. Middleton *et al.* asked 87 delegates at a Deaf Nation convention (1998)[50] and 1,314 other individuals (2001)[68] about their attitudes towards prenatal genetic testing (see table; –, not asked). Similar results were found by Stern *et al.*[57]

	Hearing parents of deaf children	Hard of hearing	Deaf
1998			
Would have prenatal test for deafness	–	–	16%
Would prefer deaf children	–	–	15%
Think genetic testing for deafness devalues deaf people	–	–	46%
2001			
Would consider prenatal test for deafness	49%	39%	21%
Would consider terminating deaf foetus	16%	11%	6%
Would prefer deaf child	–	–	2%

The cultural impact of genetic knowledge

Advances in genetic knowledge affect more than just the purely biomedical understanding of human variation. Inevitably, they also influence broader cultural attitudes, and over time they transform how societies think about normality and abnormality[60,61]. For example, the idea that there exist 'genes for' defined conditions and behaviours has been taken up by popular discourse[62–65], along with the belief that genetics is engaged in identifying those genes so that the characteristics they are 'for' can be appropriately manipulated. Genetics has been less successful in conveying an accurate picture of the complex and unpredictable relationship between genome and phenotype, or the hazards of using genetics to ground theories of normal human characteristics or behaviour. As a result, media reports of progress in genetic sequencing and the subsequent clinical applications reinforce the misperception that genetic information objectively and unambiguously draws the contours of normality and abnormality for genotypes, phenotypes and, ultimately, people. Many disability theorists feel that, as genetics moves out of the laboratory and into the world of industrialized health care and media-led public opinion, it is being used unreflectively to establish the acceptability of human forms. I would argue that this use of genetics cannot be justified if the boundaries of acceptability, in reality, have as much or even more to do with cultural standards or social convenience as with biology.

Outlook

There are ways of promoting better, more mutually enlightening interactions between genetics and disability. One example would be the setting up of forums to which disabled people have access, in which they could put across their perspective on genetics and its relationship to their experience. To be effective, this must mean a genuine dialogue with both sides prepared to give proper consideration to others' points of view, and preferably mediated by people with relevant experience (for example, the Policy, Ethics and Life Sciences Research Centre at Newcastle University runs a variety of public engagement and deliberation events). Disabled people should also have a presence on research and clinical ethics committees, either as individuals or represented by interest groups, and should be consulted and involved in relevant policy-making decisions. It would be naive to think that the simple step of including disabled people on ethics and policy bodies will magically solve all problems, but inclusion does raise the chances of addressing issues that might otherwise get lost. In the wake of the furore over clause 14(4)(9), for instance, it became apparent that the extent of the protest against it was completely unanticipated by the bill's drafters. The media coverage was not just an opportunity for informing the public, but led to a meeting between genetic counsellors, representatives of the Department of Health and Deaf organizations. The outcome included the Department of Health's agreement to remove the reference to deafness in the explanatory notes and to clarify how the clause might be interpreted in practice. It is too early to see what this might mean concretely, but it indicates the advantages of properly involving, from the outset, the people most directly affected.

The general public also deserves more sophisticated reporting of the link between genes and disability, in order to pick up on the ambiguities and uncertainties and take into account changes in opinion within genetic science as it advances. Much has already been written about how to improve communication between scientists and the public via various information media[66]. It might also be the case that geneticists need consciously to craft a different popular narrative that emphasizes the evolutionary basis for genetic flexibility, and explains how the resulting diversity generates multiple continua of physical variety. This narrative would note that some genetic markers genuinely do indicate the limits of biological viability or tolerable suffering. But elsewhere, although genetics enables us to predict (more or less) the phenotype an organism will have, it cannot say much about how that phenotype will be experienced in an individual life, as this will be influenced rather more by his or her environment and how the society she or he lives in responds to difference. In addition, this account would point out that these are social and ethical judgements that cannot be deduced from biology.

I would also suggest that those working at the cutting edge of contemporary genetics should be thinking in terms of a new kind of social responsibility; not the responsibility for how genetic knowledge is put into practice, but a care for the forms and routes by which the 'meaning' of genetic variation is culturally disseminated. Clearly, that kind of responsibility demands sensitive monitoring of the discourses of disability, normality and science in public life, along with better cooperation between the theory and practice of genetics, and the experiences of disabled people.

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doi:10.1038/nrg2453
Published online 2 September 2008

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Acknowledgements
My thanks to A. Clarke and A. Middleton, and to two anonymous reviewers, for their helpful comments.

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