

Reducing uncertainty in intersex conditions

What can genetics do?

Draft of presentation to meeting (*Hope, Hype and Hysteria: Living With Genetic Uncertainties*) of the Postgraduate Forum on Genetics and Society

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Blue text = Review comments by AISSG UK

INTRODUCTION

TITLE SLIDE:

Intersex can refer to a variation of a newborn's genitals, a chromosomal variation that the person might not be aware of, or a person's sexuality. [I've not heard of a variation in sexuality being classed as an intersex condition. Doesn't 'sexuality' usually refer to sexual orientation? Are you suggesting that gays and lesbians, for example, are intersexed?]

What all these people have in common, in order to be considered intersex, is that their sex chromosomes, gonads (i.e. ovaries and testis) [you mean testes, plural] and genitals are not consistent with what is thought of as a 'normal' male or female.

My PhD research is focused on how the biological category of sex is formed in science. When I began to research into intersex conditions I was shocked by how they had been treated by the medical field. *This talk will introduce intersex and some of its areas of uncertainty, yet it should be noted that I am focusing on the areas where genetics may*

prove useful. This should not be taken as an attempt to minimise the importance of social and personal uncertainty, but rather an attempt to stay on topic for the conference.

SLIDE TWO; Defining Intersex

At the simplest level intersex is defined as an ambiguity or uncertainty concerning an individual's physical sex status (UKIA; 2000). Intersex is defined by support groups in terms of biological characteristics; chromosomal pattern, anatomy or physiology. Alice Dreger, an academic on the board of the American intersex association, [Incorrect name, it's the 'Intersex Society of North America' (ISNA) and you may want to quote their web site, <http://www.isna.org>, at end?] defines it as a general term for any form of congenital mixed sex anatomy (Alice Dreger, Intersex). The lack of reference to the medical intersex conditions is in keeping with Dreger's idea that what is needed is 'social acceptance of human diversity and an end to the idea that difference equals disease (Dreger, Shifting the Paradigm of intersex treatment).

While the label of intersex creates a general group, it excludes transgender and transsexuals, which some transgender activists have argued the older medical label of hermaphrodite didn't (cite). [I've not heard this later claim before. The term hermaphrodite refers specifically to mixed sex organs. In the mythological sense it refers to a being with a complete set of both male and female organs, a situation that cannot exist in the human species. It doesn't say anything about brain sex or gender identity, so I don't see how it can relate to transsexuality or transgender.]

The term 'hermaphrodite' has fallen into disuse since, as well as giving the misleading idea that the person has complete sexual organs of both sexes, it carries negative connotations of its 'exotic' use in pornography. In spite of this, it is still used in some medical papers and publications (i.e. The Merck Manual of Diagnosis and Therapy) [The term '*male pseudo-hermaphrodite*', for conditions like AIS, is still used also - Prof Hughes in Cambridge, and others, still tend to use it I think, even though groups like ours have told them that women with AIS-like conditions find it offensive].

SLIDE THREE; Medical diagnosis

During what Fausto-Sterling calls the Age of Gonads doctors viewed hermaphrodites as endocrine disorders and categorized them into the five groups based on their gonad histology. The human fetus is not a default female, but rather until about the sixth week it has bipotent gonads which can, depending on the molecular signals, develop into a testis or an ovary. [Well, the default route is female, in the sense that once you get past the 'bipotent' stage, the backup route will be a female phenotype in an XY foetus unless male hormones are able to act on the body tissues. As happens in AIS.] (Re; slide, Streaking is where the gonad is formed by both testis and ovary tissue). These medical terms are still used today by some for the phenotype, however this next slides shows how the conditions are currently classified.

SLIDE FOUR

Endocrine profiles, and biomolecular knowledge has given a more precise *indication of the underlying cause to the mechanisms of these conditions*. CAH and AIS are caused by variations in specific genes, while Turner and Klinefelter [Klinefelter] syndrome are caused by chromosomal variations. Developmental factors are thought to be important for partial or mixed gonadal dysgenesis while Hypospadias, and Timing defect are related syndromes [What do you mean by Timing defect?].

SLIDE FIVE; Uncertainty in diagnosis

The question arises to the frequency of these conditions and estimates range between 2% and 4% of live births (Anne Fausto-Sterling & Money). However these frequencies are based on diagnosis by the medical community of ambiguous genitalia, and as Fausto-Sterling (cite) has pointed out, what constitutes ambiguous genitalia is highly subjective. [And many intersexed individuals, e.g. those with CAIS, Swyers Syndrome, Leydig Cell Hyperplasia, have regular female genitalia]

My final word on introducing the subject of intersex is to indicate the type of medical treatment which the medical field have considered necessary. The birth of an intersex infant has traditionally been viewed as a medical emergency where sex must be

diagnosed as soon as possible followed by surgery. CAH can be life threatening, but requires endocrine treatment, not what many see as cosmetic surgery of the genitals. Intersex conditions are quite frequently referred to as the 'one of the most challenging problems' within endocrinology, urology and surgery.

Johns Hopkins Children's Centre has issued the guidelines stating that sex re-assignment should only take place up till 18th months. They also note that if it occurs within the 1st month it is much more likely to be successful, and this may force the parents to choose within in short shift of having their child diagnosed as intersex. It has also been a persistent part of the medical procedure not to inform the patient in adulthood of their medical history, and in some cases medical records have been destroyed in attempt to hide the 'treatment'.

Intersex conditions have become a 'hot topic' in medical journals, and the some journals such as the British Medical Journal have included letters and responses from the Intersex community.[For example, 'Intersex is a Psychosocial Issue'. Letter by AISSG UK in the [British Medical Journal](http://www.bmj.com/cgi/eletters/324/7342/919#25792) (25 Sept 2002). See [bmj.com/cgi/eletters/324/7342/919#25792](http://www.bmj.com/cgi/eletters/324/7342/919#25792)] The working party for the surgical management of children born with ambiguous genitalia by the British Association of Paediatric Surgeons in 2001 can also be seen as a willingness of the medical field to engage with adult intersex patents. However this does not address the conflict of interest that surgeons must have when medical boards asked them to review the success rate of their own operations. *Perhaps one of the most important epistemological questions would be how to over come this; perhaps by use of double blind questionnaires carried out by non-surgical staff.*

What can DNA do? (Clinical /carrier/pre-natal)

SLIDE SIX; Usefulness of Genetics in diagnosis

The diagnosis of intersex conditions involves a range of tests, which are dependent on the exact condition being diagnosed. These tests include; Blood tests (7 specific types) Urine

tests, Imaging, Genital Skin Biopsy, Examination under Anaesthetic, Gonad Biopsy, Gonad Histology, DNA studies, Anti-Mullerian Hormone, Familial Analysis, HCG test, Explorative surgery.

There are a number of novel factors regarding the use of DNA with intersex conditions as, barring the standard test of karyotyping (for Klinefelters and Turners), DNA plays only a small role in the clinical diagnosis. Rather, hormonal evidence and biochemical assays which test how the enzymes function are more important. The reason for this is cost, scarcity of facilities, and not being able to tell how a base variation will affect the functionality of the enzyme. Thus one study into how the AIS condition was diagnosed in the UK showed that out of 278 clinical cases reported as AIS, biochemical endocrine investigated was performed in 98% of PAIS and 48% of CAIS. Yet mutational analysis of the AR gene was performed in only 37% of the cases (102 of cases). (I.A. Hughes, 2001?)

Patient information concerning Complete AIS states that 'the gene for CAIS can only be identified in 2/3 people with the condition'. Thus testing for this gene can't rule out a patient from having the condition only positively identifying them. This reference to the AR gene located on chromosomes 12 as being the gene for CAIS is problematic since the conditions can be caused by different receptor genes (?).

Within molecular biology it is not only important which gene is variant, but also what type of mutation occurs; deletion, frame shift, substitution, or mis-sense mutation. As Sophia Siedlberg, a Bio-informatics Developer in the United Kingdom has noted "It can happen in one gene and cause a very profound effect, but you can have something like 40 or so types of mutation resulting in the same phenotype (Body type). At the same time you could have one type of mutation resulting in many different phenotypes. This is because, while you can pinpoint a single gene, the expression of that gene causes a cascade of consequences rather than just one particular mutation equals one particular phenotype because other genes interact or by expression vary the outcome in many

different ways.’ *This brings in the question of what type of gene is being sought after, a Gene D or Gene P (Lenny Moss, cite).*

Thus within a clinical setting, tests such as the sex hormone-binding globulin (SHBG) response to stanozolol gives a clearer measurement of AR function. It detects receptor defects due to mutations within the entire gene, including the DNA-binding domain, as well as being fast, simple and cost effective (1997 Eur J Pediatr).

SLIDE SEVEN; Uncertainty in diagnosis

The second condition shown on the slide, CAH also shows the same variation in genetic causes. This condition is caused in a genetic XX foetus where one of the 6 enzymes fails to function in producing the hormone cortisol. 90% of these cases are caused by deficiencies of the enzyme 21 hydroxylase in the cytochrome P450, so called CYP21 deficiency. The second largest cause is the CAH enzyme 11-beta hydroxylase, and other enzyme mutations are exceedingly rare.

Variations can occur throughout the gene, all of which may affect the functionality and expression of the gene differently. (Dr Gerard Conway, the Middlesex Hospital).

It would of course be possible to sequence specific parts of a person’s genome and show the exact DNA variation. Such studies were done during the research into AIS receptor genes, yet it has been compared to ‘searching for a needle in a haystack’ (UKAIS).

[Reference for above quote is http://www.aissg.org/25_gnosis.htm Also incorrect citation - we are ‘AIS Support Group (AISSG -UK)’ not UKAIS] Now that the receptor genes have been characterized the research funds have dried up.

DNA Screening

SLIDE EIGHT; Influence of genetics on the medical

While DNA may not be exceptionally useful in clinical diagnoses, it is useful when screening for carriers and pre-natal diagnose, and is used in AIS and CAH for that

purpose. To detect family carriers in AIS, donated DNA is taken from the intersex person and compared with the family members, however the severity of the genital abnormality can not be reliability predicted for any future child of the carrier (?). Few centers offer screening, though there is a movement to start [missing word] in the Middlesex hospital [UCLH London]. Issues of uncertainty are introduced if carrier status is detected perhaps straining familial relationships, and raising questions for the person's reproductive future. [Paediatric Dept., Addenbrookes Hospital, Cambridge have done carrier testing, but only as a research procedure and at a time when there was funding for research on the AR gene - they were able to get their hands on families' data for research purposes and families got the test done in return. Nowadays, Cambridge will test family members in their NHS lab, as long as the index case has already been identified by their research lab. But yes, the Middlesex (UCLH Trust) are in the process of setting up the procedures.]

Prenatal screening brings its own issues as shown by a study which reported in the BMJ that there are cases of parents testing for Downs's syndrome and being informed over the phone that the test has shown Turners or Klinefelter (BMJ 2001 322:463-466). The study recommended that the women who are undergoing prenatal karyotyping should be informed of the existence of sex chromosomes anomalies and other variations before having the test. The study also highlighted a case where termination was taken [taken?] before seeing a clinical geneticist, indicating that parents had no uncertainty, or such an extreme form, [Strange phrase - there's no verb, so one assumes that the parents had an extreme form??] that the decision to abort was taken on the bases that their child had a chromosomal abnormality, perhaps because they equate it with Downs's syndrome.

In July, Oregon joined 34 other US states that have mandate [mandated?] routine infant screening for CAH. When CAH is detected prenatal therapy is given using a synthetic hormone called dexamethasone throughout pregnancy. This treatment has been used for a decade in families where there is already a child with CAH. This therapy works best if started before androgens production starts, which is before prenatal diagnosis can be carried out. If at the later stage of testing for the genetic sex of the fetus it is found to be

XY the treatment is stopped. However 7 out of 8 fetuses will be exposed unnecessarily to steroid treatment via placental passage of the drug given to their mothers. While screening and pre-natal treatment seems a very positive step in minimizing surgery and psychosocial issues to the child and parents, there have been few studies for the comparison in the first trimester use of glucocorticoids in human pregnancy, the long-term risks to the mother and child are unknown (Speiser; NADF). Within the UK, prenatal treatment has been available for the last 15 years, for families affected by CAH, and the Scottish pilot screening study indicated that national screening could be carried out easily. Undoubtedly the parents are under pressure to accept treatment, yet the risks are not well documented, and one wonders to what extent they could refuse.

The WNT-4 gene has also been reported, in the BBC (title, date) and more scientific media to be the cause of ambiguous genitalia. The gene found by UCLA in 2001 was stated to 'convert an embryo from male to female and often resulted in ambiguous genitalia' (cite). They indicated that it would allow physicians using amniocentesis (and molecular testing) to identify the genetic causes of sexually ambiguous genital in newborns. The scientists used the argument that it was 'particularly useful because it shortens the period of uncertainty faced by parents of children born with ambiguous genitalia.' The lab had further plans to explore if they could reduce the chromosomal dose of WNT-4 in the embryo of pregnant women and hypothesized that they would be able to 'correct the defect in the womb', restoring the embryo to its original male sex and 'repair the genital malformations before the child is born.' Sophia Siedlberg has voiced the concern that this may be one area where public option would be for the use of DNA therapy. [\[and AISSG-UK wrote to the author of the paper arguing against 'correcting' such defects. See "Vilain on WNT-4" in ALIAS No. 19 \(AISSG-UK newsletter\), Summer 2001. Ingrid, please see the PDF that I sent which displays the relevant text from ALIAS No. 19\]](#) The scientists did say that the gene was rare adding that 'anyone is potentially at risk.' However looking at the scientific paper published in the American Journal of Human Genetics one finds that the hype concerning the double dosage of WNT-4 as the cause of ambiguous genitalia was based on animal studies and finding the double gene in one person's genome.

What can DNA do socially?

SLIDE NINE

Genetics is a powerful tool in society; people use it to back claims for nutritional supplements, dieting fads, IQ, religious belief (a gene for god), and not lastly the difference between male and female humans. Germaine Greer stated in correspondences to an AIS individual concerning her book, 'What constitutes femaleness?' [This reads as if the book is titled 'What constitutes femaleness?'. It may possibly be a chapter title, but is not the title of her book, which I think was 'The Whole Woman'. The chapter on which we engaged her in discussion was called 'Pantomime Dames'] It is my considered position that femaleness is conferred by the final pair of XX chromosomes. Otherwise I don't know what it is' (Germaine Greer's corresponds with an AIS in response to her book (title? *The Whole Woman*) - cited from the AIS website [Please quote the reference, i.e. <http://www.aissg.org/debates/greer.htm>]). Testing for gender in the Olympic Games followed the same logic of a man being XY and a woman being XX; however this has now been abandoned as testing for gene D did not reveal gene P. However these are academic questions utilizing Intersex cases only benefiting the Intersex communities indirectly. [This last sentence needs a comma? Not very clear what it's saying.] So the question becomes, what social use can genetic knowledge have for the Intersex community?

The first Intersex passport was awarded in Australia to Alex MacFarlane who has Klinefelter syndrome, a genetic 47 XXY. Alex's birth certificate states the gender as indeterminate, which is allowed under Australian law with specialist medical evidence that the person has an intersex condition. The legal definition of sex within the UK is based on the gonads, chromosomes and genital [as determined] in the legal case of Corbett and Corbett in 1970. Prior to that legal ruling transsexualism was considered as an Intersex condition in medicine and the legal field and there are a number of cases individuals having their birth certificate corrected after treatment (surgery). However

with greater understand and the recognition that sex is not held in the chromosomes may lend legal weight to creating Intersex passports.

CONCLUSION

So the final question must be whether uncertainty is good or bad, and undoubtedly the message must be that uncertainty must be balanced with certainty. There does exist both gender and medical genetic determinism with many of the Intersex conditions. Yet the extent and form of that determinism should be understood as uncertain and thus flexible.

- View of the body as a machine
- XX and XY genetic certainty
- Cease to view difference as disease (genetic difference).

References

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WNT-4 <http://www.skfriends.com/does-sex-gene-cause-genital-malformations.htm>

BBC needed as well....

UK CAH <http://www.cah.org.uk/>

TSS <http://www.tss.org.uk/>

UKIA <http://www.ukia.co.uk/>

AIS Support Group (AISSG) <http://www.aiissg.org>

AIS Australia <http://home.vicnet.net.au/~aiissg/>

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