

The Gender Genital Gene Genie

By Sophia Siedlberg, Advisor on Genetics

Organisation Intersex International

© 2001

As someone who is intersex, the worst career move I ever made, in terms of my self esteem, was to become a "Bio-informatics" developer. The relationship between this strangely named profession and my condition would at first appear tenuous, until, that is, you realize who it is I sell or distribute "Bio-informatics" software to.

Bio-informatics is a branch of software development that specializes in things like sequencing DNA, macromolecular modelling, protein/peptide analysis, and so on. So having established this, you can guess who some of the users would be: those strange and mildly confused individuals we all know as geneticists.

Geneticists tend to fit a stereotype. They make proclamations about a "gene for this" and a "gene for that" and often appear in the media discussing "The Human Genome Project" where they initially thought they could categorise every human being on the planet according to a set of simplistic criteria. Problem is there is a paradox here. You need a very, very large genome of some 100,000 genes, all expressing singularly for a specific purpose, to set up such a simplistic model of the given gene pool. In plain language, you need to have each and every gene

doing one single thing. For example, when you need to have a gene for "gayness", you say, "Ah, we have a single gene that makes someone gay". This sparkling example of a single gene paradigm was espoused a few years ago by one Professor Dean Hamer, who, by a slight of Mendel's Astrology and a blob somewhere in lane in his electrophoresis box (migrated fragment of chromosome X) that seemed to appear every time the owners of said gene on chromosome X said they were gay. Well, in the great scheme of things, this gene was given the name of "Xq 28". Now anyone who knows their genetics will tell you that this gene has yet to be named because "Xq" only defines the location of this gene, not any official name referring to its purpose, function, resulting proteins from the coding exons, etc.

This is where single genes cease to become a "paradigm", that is an "established model" to us lesser mortals. What does this gene actually do? What peptides, proteins, enzymes, etc. does it code for? And what function do these coded proteins, etc. actually do to make someone gay? The reality is of course far more complex. Whatever the gene codes for will interact with something else, sometimes whatever another gene's exons code for. This is a type of polygenic expression, as opposed to the single gene concept of "monogenic" expression. The smaller the number of genes found in a genome would indicate the higher probability of genes interacting with each other rather than their simply expressing directly as a single gene. So when the human genome project announced, with some disappointment, that there were only 33,000 genes, you can imagine the bewilderment. "It is more complex than we thought!"

And this is where I get myself all in a hysterical fit of laughter. You see geneticists love to say the following: “XX equals a girl, whatever you say, even if ‘she’ is born with a penis, has a six pack, looks like Arnold Schwarzenegger, and says that “she” is a regular guy. Those XX chromosomes say that really deep down she is a woman.” Or “XY equals a boy, whatever you say, even if ‘he’ is born with a vagina, looks like a supermodel, has all the attributes of a woman, she is secretly a man.”

Of course they counter this with: “Oh, but that is gender identity,” (Yeah, right.) So, if a man who looks like a man, acts like a man, identifies himself as a man and does ‘guy’ things, this is a “psychiatric disorder because he has XX chromosomes.”

Oh, yes and if a woman looks female, has all the attributes of a supermodel, etc., she is of course a ‘deluded male’ if she has XY chromosomes. I mean you have to admit that this is the ultimate expression of spin-doctoring, claiming that a real life human being is deluded because they have a body that does not fit the chromosomes, and this spin-doctoring is even funnier when you look at ‘gender identity’ which is little more than the misuse of linguistic conventions to define (stigmatise) people.

The sordid term they really use (to define people as chromosomes) is “true gender” or “genetic sex”. Now this is all built around two observations. First, that most people born with XX are “female” and most people born with XY are “male”. But as anyone with a brain will tell you, this is not always so. Secondly, we are given a single gene justification for all this in

the form of “SRY”, a gene on the Y chromosome. Yes, it does produce a protein that differentiates gonadal tissue into testicular tissue, called TDF. But with a mere 33,000 genes, and the demonstrable complexity of “sex determination”, the monogenic SRY concept does not add up.

This is where many of the more unimaginative geneticists come to a dead end. They are so stuck with “XX/XY and “girls don't SRY!” that when the obvious, “polygenic expression” slaps them in their faces, they go “DUH!” and then run to the protein scientists, who themselves tend to say, “Well, it is far more complex than that.”

The reality is more complex. With AIS alone, there are numerous categories, and they can be as a result of many different AR (androgen receptor) mutations. These can be deletions, frame shifts, substitutions, missense mutations and so on. 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). But 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 1 particular mutation equals 1 particular phenotype because other genes interact or by expression vary the outcome in many different ways. The more alleles there are of a given gene the more complex it gets within the gene pool. In plain terms, we are all individuals!

But given that I can start quoting examples of genes that are not in X or Y, but the autosomes, that contain AR coding

exons; the whole edifice of "XX/XY/and Girls don't SRY" starts to crumble. In sheer panic the geneticists (known as Genies) run around collecting blood samples from any hapless intersex person they can get their hands on and then run to the lab. And after a little spin of the centrifuge, you will find them with their Licor machines, electrophoresis boxes, or micro-arrays (micro array, hmm!), desperately trying to simplify the picture into "boy or girl". And then you will find them pouring over their inheritance charts, with that Boolean arrogance (Mendel's theory) trying to determine who is to blame for transmitting these "bad genes".

They get to find the exons in the offending genes and the mutation and then, there is the challenge of the resulting peptides. Mention Chou Fasman equations and watch them puff up and say, "This determines the shape of a peptide by assigning specific values to the amino acid residues." And when you say something really awful like, "Let's think of prions. You know CJD, Mad Cow disease, or Mad scientist. How come you can get the same sequence but one becomes Beta sheets and the other becomes Alpha helices?" And then we are into proteomics when pointing out that Chou Fasman equations have limits. OK, prions (the cause of mad scientist disease) are a different matter, but a good illustration. The proteins behave in many strange ways, take many strange shapes, and as such interact in many strange ways. And there are many reasons for that.

And it takes a protein scientist to look at this with an intuitive eye, good protocol, as well as some damn good lab facilities. They need to crystallise these proteins, throw X-rays at them,

and use specialised software (Plug) to assess the results. The genies run into the wild blue yonder trying to figure out what to do next.

The bottom line is this. There is no such thing as an absolutely "genetic" male or "genetic" female in much the same way as there is no absolute "male" or "female" gender identity. Just a spectrum of expressions. There is no such thing as a "true gender", just a bias. The whole edifice of trying to make an intersex child "fit" into some more absolute image of one or the other sex is rank stupidity. This is why I find my self-esteem undermined when some genie hits me with, "Oh, I need to find a way of using computer models to prove you don't exist." But then if I don't exist, because of my intersex birthright, how can I have a brain to comprehend what the genie has in terms of specification, a brain to code the software, a brain and hands to actually type the code for the software, and arms and legs in order to physically give this work to the genie? Suffice to say I am fussy about who I distribute software to these days.

I am left wondering when a Genie pops up in my "in-box" what they are about to come out with. And perhaps one day, when they get their heads round the concept of consciousness, self awareness and become a little introspective, will they discover a gene for arrogant quacks? "AQ-PrP1". I still hope for that day as the status bar says, "Receiving messages," and the inbox folder becomes highlighted. The only geneticist I would trust would be the geneticist who can discuss proteins with equal understanding. The example of WNT-4 is a prime example of just how divorced from biological, as well as social, reality some geneticists can be.

There is a maxim that often holds true. It goes like this: the more complex a system, the less predictably it will behave. For example, many people who buy a new computer tend to think that there is a set way to deal with problems that may arise. So what sometimes happens is that they will buy a patch or a utility and install it, only to find that the computer does not do as it is supposed to after the installation, often to the despair of the owner.

Quite often there is a simpler solution. If it works, why potentially make it worse? Another example would be to dismantle a washing machine in order to put the clothes into it just because someone says you cannot use the door. And then expect the washing machine to work once you have re-assembled it with the clothes in situ. Well, recently a gene on chromosome one, the, aptly named "WNT-4" has become a potential symbol of this kind of systemic "fix it at your peril" paradox. Consider the following account from the Scientific American (1):

"Gene Duplicate Causes Sexual Ambiguity

In one out of every 3,000 births, the physician cannot tell the new parents what some have waited to hear. But the results of a study described in the Journal of Human Genetics may offer new hope to parents whose infants are born sexually ambiguous. According to the report, researchers have determined that a second copy of a sex determination gene known as WNT-4 can change an embryo from male to female, which often results in

ambiguous genitalia. The finding could help doctors more accurately and quickly identify an externally ambiguous baby's gender. (sic)

Geneticist Eric Vilain of the University of California at Los Angeles and his colleagues identified WNT-4 as one of several genes that determine sex. Whereas most genetic defects stem from the absence or mutation of a gene, genital defects arise when WNT-4 appears twice on the chromosome. WNT-4, it seems, "influences the sex determination pathway at each step of the way," Vilain notes. "We discovered that when the amount of the gene fluctuates even slightly at any stage in the genetic blueprint, it changes the embryo from male to female."

The WNT-4 study results will enable researchers to use genetic testing to help identify the causes of genital ambiguity. Moreover, scientists might one day even be able to treat a defective embryo in utero. "Our findings suggest that clinicians could identify the WNT-4 duplication prenatally," Vilain remarks. "If this proves true, in the future we may be able to correct the defect in the womb and restore the embryo to its original male status. This may repair the genital malformations before the child is born."

Notice how the emphasis is made about parents" "may offer new hope to parents whose infants are born sexually ambiguous." As if stating that the parents are the ones who are afflicted and the child is the passive bystander, or property that

causes embarrassment. What I am saying is really simple. Such theorising about future medical approaches is both deeply questionable from an ethical standpoint as well as indicative of that persistent, near genocidal, hatred of intersex people.

Biologically there are a number of questions I have. It has become obvious from the findings of Professor Vilain that we are looking at polygenic expression here. The question is why does it seem so important to say that even in recognising polygenic components to sex determination that run through the autosomes. "If the foetus has a "Y" chromosome in the 23rd pair, it must be made into a boy, or it is established as being male." This is a contradiction. There is a pathway of autosomal entities involved, the complexity of which is not understood, and to satisfy the need to say "Y=BOY" or "X=GIRL", the solution is to risk altering numerous coding exons to "fit" the fact that chromosome Y or X is present, but with no regard to the potential health risks that may be involved. The possibility of compromising the individual's health is far greater by taking the "autosomes will obey the sex determinants" approach, rather than just accepting the fact that "Y does not always = boy" and "X does not always = girl".

The main reason for objections to a notion of "designer babies" has more to do with the not so clear model of polygenic expression. You can re-engineer a gene in some area but what that will mean in terms of other genes interacting with it will for the most part remain unclear. This study has demonstrated this quite starkly. Current attempts at using somatic gene therapy have shown this to be the case to some extent, with numerous examples of the end result not being what was

expected. There is little or no concept of risk management in this suggestion that a prenatal treatment for intersexed conditions can be implemented. And like earlier methods of "treating" intersex conditions, there is a danger that such intervention will do more harm than good.

Dr. Money for example claimed that "gender identity" was psychological, and a product of upbringing. This was proven to be wrong. The reason is most likely because the people in his care were not even consulted. The risk of course is that of having been forced to live as someone else. In the case of surgical intervention, to also face the risks of later complications. The problem with the cause and effect model of treating intersex people does not account for the fact that there are so many genes containing coding exons that can alter the "sex" of the foetus. This in itself should be a reason to stop and think before trying to dictate who is what and who will be what.

So, in brief, the very suggestion shows an obvious lack of understanding about the dynamics of polygenic expression. There is discussion here, not about a "single gene" disorder, but "polygenic gene" correction. It is difficult simply trying to treat a single gene with a single outcome, let alone forcing a gene to interact in context with other genes. In this case, more frighteningly, to remove a second copy of the gene in question altogether. So this brings me back to my little pun about the name of this gene. WNT-4. The irony here is that the name of this gene reminds me of a certain computer operating system that behaves just like a polygenic contextualisation, as a complex system. See the not so useful patch or utility as the

"chromosomal material" and see the host operating system as being the polygenic array. Q.E.D.

On an ethical level, if intersex people are regarded so poorly by society that society would sanction such uncertain uses of genetic manipulation, when somatic gene therapy on single gene conditions has yet to become viable, I really wonder about society itself and its attitude towards those it considers unable to fit the two sex system, when discussing a very theoretical assumption that you could patch up the genome at such a complex point.

The reality here is simple. XX does not equal a girl and XY does not equal a boy. The genes involved in the sex determinants evidently are part of a broader picture. And to try to make the picture fit in such a limited way is no different from the surgical mutilation of intersex children, based on the flawed assumptions laid down by society and not genuine science.

And then I have to ask myself what this means: "The finding could help doctors more accurately and quickly identify an externally ambiguous baby's gender." If by "gender" they mean "how they themselves will identify", then they are on Planet funny farm. I mean they can't even get to grips with the most basic aspects of human behaviour with respect to genetic causality, yet alone self identity. And if they don't mean "self identity" when saying "gender" then, they really need to qualify the remark, because it is very vague and meaningless in that context.

Footnotes:

1: Eric Vilain:

In 2005 Professor Eric Vilain distanced himself from the quotes in the press about his research, stating that he felt somewhat pressured by some people to include numerous statements to the effect that his research can lead to the sort of "medical practices" that were being proposed. Interestingly enough he later came out with another paper that was quite insightful with respect to the polygenic model. But again, it seems that he was "asked" to procure an "application" which consisted of a "test" to determine the "brain sex" on an intersex child, so surgeons can mutilate accordingly. It was when he was confronted over that research that he finally distanced himself from those advocating these somewhat draconian medical "practices".

2: The Trend:

Unfortunately, despite Professor Vilain distancing himself from all this, it has become evident that others have taken up the "cause" with respect to enforcing what will clearly be unethical "medical practices". Dr. White of the Texas University would be one example (2). The bottom line of this discussion and the above amended article is a simple one. People diagnosed with intersexed conditions are fed up with the secrecy, lies, shame and such levels of disrespect that sink so low, that people with intersex conditions even considered "sub human" to the point where they regularly face medical professionals suggesting "treatments" that are akin to the sort of malpractice and vivisection that was synonymous with the Nazi T4 project. Let's not try to spin-doctor these ideas into something else. Prenatal modification of a foetus, by use of somatic gene therapy (suggested by Vilain) or hormonal intervention suggested by White, in order to make them "fit" with what society expects, is procuring designer babies.

3: The ethical questions, technically speaking.

When most people think of designer Babies, current medical techniques actually do not produce such. Most often we read of this idea being associated with pre-implantation: screening where an embryo will be selected from a batch and implanted during fertility treatment, if that embryo is known to be free of certain genetic conditions. This does not involve any human intervention to actually modify the resulting child.

Rather, these techniques are used to "ensure" that the child that is born, has the "best chances". Rightly, people raise questions about how this is eugenics by the back door as this is a very precise new twist on selective breeding. However this process is not actual modification of the fundamental biology of the embryo. We are talking selective screening, not designer babies. However, the use of genetic modification and hormonal modification are. What never ceases to amaze me is how those people I know to be backing this modifying approach are often of a religious school of thought and are openly opposed to pre implantation screening claiming that to be "procuring designer babies". It seems very strange that modifying the genetic or hormonal make up of an unborn individual is considered ethical. This is remarkably inconsistent.

4: Conclusion:

The impression I get from this whole sordid affair is that society would be prepared to suspend any notion of ethics or even morality when it comes to the treatment of people diagnosed with intersex conditions. Even those who originally partook in this distanced themselves from it (Vilain) and yet there are still those (White) who "strain on a gnat and swallow a camel", to borrow a biblical text, who would appear to be very upset about pre-implantation techniques during fertility treatment, using terminology like "designer babies". And yet they appear to advocate that which would truly be creating babies to order in order to satisfy social norms, by pr natal modification.

References

- 1: Scientific American: News In Brief. Wednesday, May 02, 2001.v
http://www.sciam.com/news/0502_01/2.html
- 2: Ontogeny of adrenal steroid biosynthesis: why girls will be girls
Perrin C. White, Department of Pediatrics, University of Texas
Southwestern Medical Center, Dallas, Texas, USA.
<http://www.jci.org/cgi/content/full/116/4/872>