The Faraday Institute for Science and Religion

University of Southampton Centre for Biological Sciences

CHRISTIANS·IN·SCIENCE

Human genes and gene editing

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Who am I?

Profession
Appearance
Character
Location

23andMe

The superhero assessment decodes secret information in your unique DNA, giving you unprecedented insights into where your super-powers lie…

This product is not a diagnostic test and cannot predict your future health… Use of this products is not intended to be a substitute for professional medical judgement. Please consult your doctor if you have a question about a medical issue

It's in their DNA!

The love-cheat gene: One in four born to be unfaithful, claim scientists
Daily Mail, Dec 2012

'Gangster gene' violence claim
The Sun Jan 2009

The mean gene: The gene that makes people stingy with their cash
Daily Mail Nov 2010

From genes to hormone levels, biology may help to shape political behaviour.
Nature 2013

Ciggies? It's all in your genes
The Sun Aug 2007

Gluttony gene: May be behind big appetites
The Independent March 2012

Liberal genes
The Guardian Oct 2010

The happiness gene
The Times Jan 2016

The Geneticism Gene:
Is there a gene that predisposes some people to think that behaviour is determined by genes?
The Guardian (letter Oct 2010)

It's in their DNA!

Suggests determinism:
Please…. Don't use that phrase!

"We used to say think that our fate was in the stars. Now we know in large measure, our fate is in our genes."

James Watson

Genetic Disorders

Achondroplasia
Alpha-1 Antitrypsin Deficiency
Antiphospholipid Syndrome
Autism
Autosomal Dominant Polycystic Kidney Disease
Breast cancer
Charcot-Marie-Tooth
Colon cancer
Cri du chat
Crohn's Disease
Cystic fibrosis
Dercum Disease
Down Syndrome
Duane Syndrome
Duchenne Muscular Dystrophy
Factor V Leiden Thrombophilia
Familial Hypercholesterolemia
Familial Mediterranean Fever
Fragile X Syndrome
Gaucher Disease
Haemochromatosis
Haemophilia
Holoprosencephaly
Huntington's disease
Klinefelter syndrome
Marfan syndrome
Myotonic Dystrophy
Neurofibromatosis
Noonan Syndrome
Osteogenesis Imperfecta
Parkinson's disease
Phenylketonuria
Poland Anomaly
Porphyria
Progeria
Prostate Cancer
Retinitis Pigmentosa
Severe Combined Immunodeficiency (SCID)
Sickle cell disease
Skin Cancer
Spinal Muscular Atrophy
Tay-Sachs
Thalassemia
Trimethylaminuria
Turner Syndrome
Velocardiofacial Syndrome
WAGR Syndrome
Wilson Disease

Disease mutations

Point mutations

e.g. Cystic fibrosis, sickle cell anaemia, Thalassaemia
GAG (Glu) – GTG (Val)

Rearrangements

Chronic Myeloid Leukaemia
Burkitt's lymphoma

Expansions

Friedreich's Ataxia $(GAA)_n$
Huntingdon's disease $(CAG)_n$
ALS $(GGGGCC)_n$

1-4% of our genome is related to Neanderthals (and other hominids)

Greater amounts of Neanderthal DNA in Asians and Europeans than Africans

Interbreeding happened about 60,000 years ago in the eastern Mediterranean and about 45,000 years ago in eastern Asia. Both after the first *H. sapiens* had migrated out of Africa

“Neanderthals are not totally extinct; they live on in some of us.” *Paabo*

Reaction of social conservatives.
After the discovery of the Neanderthal genome a majority of bloggers on the white supremacist website Stormfront.org congratulated themselves for their genetic uniqueness and claimed Neanderthal DNA was responsible for the "intellectual supremacy" and "physical prowess" of Europeans.

Human Genes?

In a chimpanzee and a person the same genes create two different beings, not because the many of the genes are different, but because genes are switched on and off in different patterns.

The head of a chimpanzee is a different shape to that of a human because the genes involved are switched on for different lengths of time - the jaws of a chimp grow for longer than those of a human at a similar stage of development, and the cranium grows for a shorter time.

Human Genes?

ARHGAP11B
Found in humans – not chimpanzees

A gene appearing after the divergence from chimpanzee controls neural progenitors proliferation and can cause neocortex folding .
ARHGAP11B is a human-specific gene that amplifies basal progenitors and is capable of causing neocortex folding in mouse. This likely reflects a role for ARHGAP11B in development and evolutionary expansion of the human neocortex, a conclusion consistent with the finding that the gene duplication that created ARHGAP11B occurred on the human lineage after the divergence from the chimpanzee lineage but before the divergence from Neanderthals

Science (2015) 347, 1465-1470

https://www.mpg.de/10851125/a-tiny-change-with-considerable-

ISR INTERNATIONAL SOCIALIST REVIEW online edition

International Socialist Review
Issue 38, November–December 2004
Genes, Evolution, and Human Nature

Is Biology Destiny?

Review

Trends in Genetics

The genetics of politics: discovery, challenges, and progress

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"Genes for…."

Friendships Moderate an Association between a Dopamine Gene Variant and Political Ideology

Jaime E. Settle University of California, San Diego
Christopher T. Dawes University of California, San Diego
Nicholas A. Christakis Harvard University
James H. Fowler University of California, San Diego

The Journal of Politics, Vol. 72, No. 4, October 2010, Pp. 1189–1198

combination of variants associated with political ideology have so far been identified. Here, we hypothesize that individuals with a genetic predisposition toward seeking out new experiences will tend to be more liberal, but only if they are embedded in a social context that provides them with multiple points of view. Using data from the National Longitudinal Study of Adolescent Health, we test this hypothesis by investigating an association between self-reported political ideology and the 7R variant of the dopamine receptor D4 gene (DRD4), which has previously been associated with novelty seeking. Among those with DRD4-7R, we find that the number of friendships a person has in adolescence is significantly associated with liberal political ideology. Among those without the gene variant, there is no association. This is the first study to elaborate a specific gene-environment interaction that contributes to ideological self-identification, and it highlights the importance of incorporating both nature and nurture into the study of political preferences.

"An increasing number of studies suggest that biology can exert a significant influence on political beliefs and behaviours, … genes could exert a pull on attitudes concerning topics such as abortion, immigration, the death penalty and pacifism".
Nature 490: 466-468

NEWS FEATURE

466 | NATURE | VOL 490 | 25 OCTOBER 2012

The anatomy of politics

From genes to hormone levels, biology may help to shape political behaviour.

"it is difficult to change someone's mind about political issues because their reactions are rooted in their physiology".

Belief in genetic determinism tends to lead to more conservative political ideologies.

- If human nature is fixed by our genes then we cannot change society
- The problems lie not in the structure of society, but in some of the individuals who make up society. The solution is therefore to change, or even eliminate, the individuals, not to challenge existing social structures.

Characteristics such as "pauperism," criminality, and "feeble-mindedness" were biologically inherited. Though capital punishment is a crude method of grappling with the difficulty [of those with inferior genes] it is infinitely superior to that of training the feeble-minded and criminalistic and then letting them loose upon society and permitting them to perpetuate in their offspring these animal traits

Charles Davenport Heredity in Relation to Eugenics (1911)

Sterilization of the feeble-minded

"Three Generations of Imbeciles Are Enough"

Justice Oliver Wendell Holmes, Jr. (Buck v. Bell)

1927 Supreme court case upholding a Virginia law that authorized the state to surgically sterilize certain "mental defectives" without their consent.

It is better for all the world if, instead of waiting to execute degenerate offspring for crime or to let them starve for their imbecility, society can prevent those who are manifestly unfit from continuing their kind. . . . Three generations of imbeciles are enough.

Gene for……

Y-chromosome and criminality?

One of the strongest links between criminality and genetics is the Y-chromosome which is possessed by all males (over 90% of all prison populations are male), yet being male in itself does not lead to criminal behaviour (most men are not criminals).

Gene for…..

Aggressive behaviour?

Monoamine oxidase (MAO-A) – "warrior gene"

(MAO-A) breaks down neurotransmitters such as serotonin (5HT), noradrenaline, & dopamine

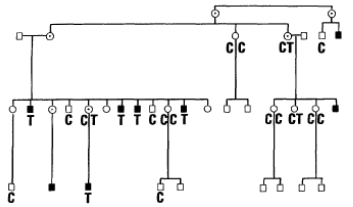
Dopamine levels are related to aggression

Gene for…..

Aggressive behaviour?

In one Dutch family with a history of male aggressive behaviour there was a complete deficiency of monoamine oxidase A (on X chromosome) - a point mutation was identified in the eighth exon of the monoamine oxidase A structural gene.

CAG mutated to TAG
Gives a truncated protein



Brunner *et al.*, (1993) *Science* **262**, 578-580

Dutch Study Conclusions

- "Syndrome" identified in this family
  - Mental Retardation
  - Violent behavior
- "Behaviour" varied over time and across generations
- Caused by mutation in MAOA eliminating enzyme
- Extremely rare- no more cases reported

Gene for…..

February 17, 1991, Stephen Mobley robbed a Domino's pizza store in Hall County, Georgia where he shot the store manager, in the back of the head.

Mobley admitted the crime and showed no remorse

Mobley's lawyers requested that he be tested for the MAO-A genetic abnormality. They argued that this might explain his actions in an effort to save him from imposition of the death sentence.

The judge stated that the law was not ready to accept such evidence

Mobley's father subsequently sacked his son's lawyers

Dunedin Multidisciplinary Health & Development Study

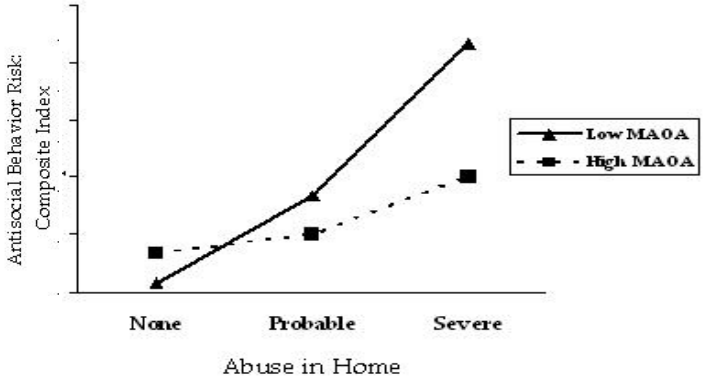
1,037 children (52% ♂) assessed every 2-3 years birth to age 26 (~ general population)

Genotyped variable region in MAOA promoter
- 3 repeats associated with low MAOA activity
- 4 repeats with high MAOA activity

This is **not** the MAOA mutation
- Mutation= NO MAOA activity
- Polymorphism = altered (more or less) activity

Compare 2 polymorphisms with environmental factors

Dunedin Multidisciplinary Health & Development Study



Published online 30 October 2009 | Nature | doi:10.1038/news.2009.1050

News

Lighter sentence for murderer with 'bad genes'

Italian court reduces jail term after tests identify genes linked to violent behaviour.

On the basis of the genetic tests, Judge Reinotti docked a further year off the defendant's sentence, arguing that the defendant's genes "would make him particularly aggressive in stressful situations". Giving his verdict, Reinotti said he had found the MAOA evidence particularly compelling.

http://www.nature.com/news/2009/091030/full/news.2009.1050.html

What do we gain from this knowledge?

No easy answer

Nature (2013) **413**, 133

Demands to analyse Connecticut school shooter's DNA are misguided and could lead to dangerous stigmatization, or worse.

- Associations only hold for groups: many might carry the same genes, yet without any pathology
- People who carry the same mutations could be stigmatized.

  "to identify a genetic variant is more straightforward – but arguably less informative – than to characterise the complex environment of the individual"

Genes and responsibility

What would you do with this information?

Lighter or tougher sentences?
Prosecutors could use the same genetic evidence to argue for tougher sentences by suggesting people with such genes are inherently 'bad'.

Guilty before committing any crime?

If people know their genetic risk, but fail to act on the information are they responsible and blameworthy?

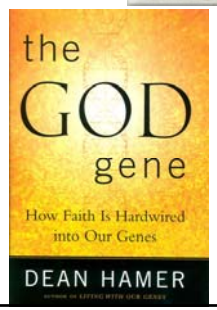
But genes do not automatically turn their owners into killers. There are many people with this genetic baggage who have never transgressed — around 30 per cent of Caucasians carry the same variant of MAO-A.

Nature/Nurture
Genes/Environment

BOTH

Genes may affect our potential,
but they alone do not determine or define it.

Genes provide the potential for personhood, but they alone are not sufficient to make us human. The genome supports social learning and development.



Hamer claimed a correlation between the Self-Transcendence score and the presence of a variant polymorphism of the VMAT2 gene

"A Gene That Accounts for Less Than One Percent of the Variance Found in Scores on Psychological Questionnaires Designed to Measure a Factor Called Self-Transcendence, Which Can Signify Everything from Belonging to the Green Party to Believing in ESP, According to One Unpublished, Unreplicated Study."
Review of the God Gene in Scientific American, Carl Zimmer

FUNVAX

Vaccine against the VMAT2 gene to inhibit fundamentalism

Fundamentalism Vaccine.

Is a HOAX!

The Pentagon may vaccinate large populations in the Middle East with what is being called FunVax – a fundamentalist vaccine. ***As explained by Pentagon researchers, the FunVax uses an airborne virus to indiscriminately infect populations considered high risk for religious fundamentalism.*** *The virus in this vaccine purportedly has been tested and shown to reduce fundamentalism and religiosity in all who are infected by damaging what is called the "God gene."*

Many *nongenetic* factors affect our development.

Development and Epigenetics

DNA modification – regulating gene expression

We do not inherit just "naked DNA"

Environment within the cell

- 3000 proteins
- 7500 mRNA
- 1000s of miRNAs

Context of the cell and other genes

Maternal context

"The new science of epigenetics reveals how the choices that you make can change your genes – and those of your kids"

Nature/Nurture Genes/Environment BOTH

The Faraday Institute for Science and Religion

Genes may affect our potential, but they alone do not determine or define it.

Genes provide the potential for personhood, but they alone are not sufficient to make us human. The genome supports social learning and development.

Simon Weston visits the Genome Centre in London

"And this peak here suggests actually that you have the gene variant that is not associated with resilience.
AT: So how do you feel about this, Simon?
SW: I don't know, I think I'm probably leaning towards being slightly happy about that, in the sense that … it's the sort of, the nurture element rather than the nature element. I always wanted it to be about who I am, not what I am. …it's not what happens, it's what you're prepared to do about it that counts..."

http://www.bbc.co.uk/guides/z2qxfrd

Nuffield Council on Bioethics
http://nuffieldbioethics.org/

Gene editing tools

What if we could cut out/replace a faulty gene, using 'molecular scissors' and 'cut and paste'?

TALENs

Transcription activator-like effector nucleases

ZFNs

Zinc finger nucleases

CRISPR–Cas9

Clustered Regularly Interspaced Short Palindromic Repeats

New Scientist

Daily news 5 November 2015

Gene editing saves girl dying from leukaemia in world first

UCART19, an allogeneic "off-the-shelf" adoptive T-cell immunotherapy against CD19⁺ B-cell leukemias
Knockout the TCR alpha gene
Knockout the CD52 gene makes donor T-cells resistant to the alemtuzumab.
T-cells are engineered to co-express the RQR8 gene as a safety feature, with the aim of rendering them sensitive to the monoclonal antibody rituximab.

Germ cells/Somatic Cells

- Germ Cell mutation:
  - Occurs in gametes (sperm/egg)
  - Does not affect individual person
  - CAN be passed to offspring

Early embryo

- Somatic Cell mutation
  - Occurs in body cells
  - Affects individual in which it occurs
  - CANNOT be passed to offspring

These are examples with somatic cells – affecting only that individual:
What about germ cells or embryos?

In April, Chinese scientists announced that they had used CRISPR to engineer human embryos

Protein Cell 2015, 6(5):363–372
DOI 10.1007/s13238-015-0153-5

Protein & Cell

RESEARCH ARTICLE

CRISPR/Cas9-mediated gene editing in human tripronuclear zygotes

Puping Liang, Yanwen Xu, Xiya Zhang, Chenhui Ding, Rui Huang, Zhen Zhang, Jie Lv, Xiaowei Xie, Yuxi Chen, Yujing Li, Ying Sun, Yaofu Bai, Zhou Songyang, Wenbin Ma, Canquan Zhou✉, Junjiu Huang✉

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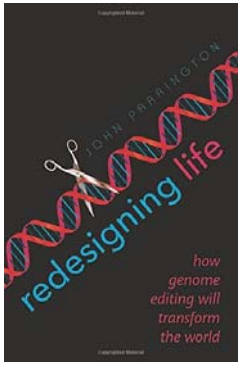
Received March 30, 2015 Accepted April 1, 2015

The words 'revolutionary' and 'breakthrough' can be overused in media reports about new scientific discoveries … But every once in a while, a scientific discovery is made whose impact on society is likely to be so immense that even an abundance of superlatives may not do it full justice. Genome editing looks set to be such a discovery."

John Parrington, Oxford
Redesigning Life: How genome editing will transform the world.



Risk – precautionary principle

What is 'normal'

Genetic 'classism'

Commodification

There has emerged a global consensus that such gene modifications should be forbidden owing to safety concerns, unprecedented informed consent, challenges to human dignity, and the potential for permanent negative impact on future generations, including its abuse for eugenics or enhancement (the parental pursuit of specific traits for non-medical reasons)

Motoko Araki & Tetsuya Ishii
International regulatory landscape and integration of corrective genome editing into in vitro fertilization
Reproductive Biology and Endocrinology (2014) **12**:108
DOI: 10.1186/1477-7827-12-108

The Academy of Medical Sciences · amrc · BBSRC bioscience for the future · MRC Medical Research Council · wellcome trust

Initial joint statement on genome editing in human cells

We recognise that there may be future potential to apply genome editing in a clinical context using human germ cells or embryos, though this is prohibited by law in the UK… This raises important ethical and regulatory questions, which need to be anticipated and explored in a timely and inclusive manner as the basic research proceeds and prior to any decisions about clinical application.
Active early engagement with a wide range of global stakeholders will therefore be needed, which should include, but not be limited to, biomedical and social scientists, ethicists, healthcare professionals, research funders, regulators, affected patients and their families, and the wider public…

http://www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/Genome-editing/WTP059704.htm

Heritable human genetic modifications pose serious risks, and the therapeutic benefits are tenuous, warn Edward Lanphier, Fyodor Urnov and colleagues. 12 March 2015

http://www.nature.com/news/don-t-edit-the-human-germ-line-1.17111

In our view, genome editing in human embryos using current technologies could have unpredictable effects on future generations. This makes it dangerous and ethically unacceptable.
Such research could be exploited for non-therapeutic modifications.

We are concerned that a public outcry about such an ethical breach could hinder a promising area of therapeutic development, namely making genetic changes that cannot be inherited.

Points for debate:

- Should genome editing be allowed in basic research involving human sperm, eggs and embryos?
- Should only embryos left over from *in vitro* fertilization be used in genome-editing research or may embryos be specifically created for research?
- What safety and efficacy thresholds need to be met before the use of genome editing in human reproductive applications could be considered?
- If such thresholds are met, what uses for genome editing in human reproductive applications might be permissible?

Nature 527, 159–161 (12 November 2015) doi:10.1038/527159a

Is it only about RISK?

RISK – off-target effects?

Experiments in mice and in human cell lines suggest that the rate of off-target events is insignificant compared with the number of spontaneous mutations that occur in each generation. Yet the number of mutations may be less important than where they occur.

Is it necessary?

In many instance – no! *In vitro screening* Pre-implantation Embryo Screening

- autosomal recessive disease in which both parents are homozygous (e.g. cystic fibrosis, phenylketonuria
- or an autosomal dominant disease where at least one parent is homozygous (*e.g.* Huntington's disease, familial adenomatous polyposis)

"Advances in technology have given us an elegant new way of carrying out genome editing, but the strong arguments against engaging in this activity remain. These include the serious and unquantifiable safety issues, ethical issues presented by altering the germline in a way that affects the next generation without their consent and a current lack of compelling medical applications."
Francis Collins

Some questions

Is it permissible to modify the genome of an embryo that will otherwise die of a genetic disease?

Is it permissible to modify the genome of an embryo that will have cystic fibrosis?

Is it permissible to modify the genome of an embryo that will develop Huntingdon's disease/breast cancer later in life?

Is it permissible to modify the genome of an embryo to change their eye colour?

People with disabilities are, in my view, unlikely to be queuing up for genetic modification: their priority is to combat discrimination and prejudice.
To 'fix' a genetic variation that causes a rare disease may seem an obvious act of beneficence. But such intervention assumes that there is robust consensus about the boundaries between normal variation and disability. Contrary to the prevailing assumption, most people with disabilities report a quality of life that is equivalent to that of non-disabled people***, and the voices of people living with illness and impairment need to be heard.***

Tom Shakespeare
University of East Anglia

Shakespeare has achondroplasia, a genetic condition that causes shorter than average stature. He says that people with disabilities are just as able to attain life satisfaction as others.

“I have achieved everything I hoped for in life, despite having restricted growth: career, children, friendship and love.” He wouldn’t want to have altered his own genes to be taller, he says

The idea that parents should edit out characteristics that are considered debilitating goes against this drive towards inclusion and could create a harsher social climate for everyone.

“The experience of disability is universal; all people inevitably experience sickness, accidents and age-related decline. At our peril, we are right now trying to decide what ways of being in the world ought to be eliminated,”

Garland-Thomson
Professor of English and Bioethics, Emory University

If he had had the option to edit blindness out of Ruthie’s genes before she was born, he and his wife would have jumped at the chance.
But now he thinks that would have been a mistake: doing so might have erased some of the things that make Ruthie special — her determination, for instance. Last season, when Ruthie had been the worst player on her basketball team, she had decided on her own to improve, and unbeknownst to her parents had been practising at every opportunity. Changing her disability, he suspects, “would have made us and her different in a way that we would have regretted”, he says. “That’s scary.”

Nature 530, 402–405 (25 February 2016) doi:10.1038/530402a

Ruthie’s dad asked her whether she wished that her parents had corrected the gene responsible for her blindness before she was born. Ruthie didn’t hesitate before answering — no. Would she ever consider editing the genes of her own future children to help them to see? Again, Ruthie didn’t blink — no.

Deaf parents who want a deaf child:
“Deafness isn’t a disability—it’s a culture”

Is it wrong to select a deaf embryo?
http://news.bbc.co.uk/1/hi/health/7287508.stm

Slippery slope to non-therapeutic enhancement

‘Don’t edit the human germ line’

Lanphier *et al*. *Nature* (2015) 519, 410

Slippery slope

Many oppose germline modification on the grounds that permitting even unambiguously therapeutic interventions could start us down a path towards non-therapeutic genetic enhancement..

What is “normal”

Human diversity is part of what it takes to make society

Many people acknowledge the free, unmerited nature of life as a gift.

In speaking of an athlete’s or a musician’s “gift”, we acknowledge that there is a fundamentally contingent factor in play. This factor influences not just this or that event but undergirds life fundamentally, especially in its most profound expressions.

“excellence consists at least partly in the display of natural talents and gifts that are no doing of the athlete who possesses them. This is an uncomfortable fact for democratic societies.”