Questions from the human genome

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Four questions

• Should every citizen carry a personal genome passport?

• Making a diagnosis where there is no cure: Is this a good or a bad thing?

• Should we offer prenatal diagnosis to everyone?

• Should we allow genetic information in the court room?
The first whole genomes

The Diploid Genome Sequence of an Individual Human

PloS Biology 2007

The complete genome of an individual by massively parallel DNA sequencing

Nature 2008

The diploid genome sequence of an Asian individual

Nature 2008

DNA sequencing of a cytogenetically normal acute myeloid leukaemia genome

Nature 2008

Ozzy Osbourne genome sequencing project

TEDMED 2010
Ozzy Osbourne genome sequencing project

WHAT WILL THE UNVEILING OF A FULL OSBOURNE GENOME REVEAL?

TEDMED 2010
“Given the swimming pools of booze I’ve guzzled over the years—not to mention all of the cocaine, morphine, sleeping pills, cough syrup, LSD, Rohypnol...you name it—there’s really no plausible medical reason why I should still be alive,” he said in the Times.

“Maybe my DNA could say why.”

The results of Osbourne’s genome sequencing project will be presented in full detail Friday at the TEDMED 2010 meeting in San Diego, Calif.
Should every citizen have access to their personal genome?

• Genome Sequencing is now easy, cheap and available

• Even famous people have boring genomes
Should society limit access to personal genome data?
Our experience with clinical exomes
We all have 200 unique variants

• ~20,000 exonic variants
  • Unique variants ~200
    • Silent ~ 60
    • Nonsense/ frameshift ~ 40
    • Missense ~ 95
    • Canonical Splice Site ~ 5
  • Dominant \textit{de novo} mutation in a gene ~ 1
We all have 200 *unique variants*

- **~20,000 exonic variants**
  - Unique variants: ~200
    - Silent: ~60
    - Nonsense/ frameshift: ~40
    - Missense: ~95
    - Canonical Splice Site: ~5
  - Dominant *de novo* mutation in a gene: ~1

And we all have 1 mutation
case 1
by Koen Devriendt

Intellectual disability
IQ ~50
case 2

Intellectual disability

IQ ~50

Bowel malrotation
Exome sequencing 20,000 genes of Ender and his parents

Shows that Ender has just 1 *de novo* mutation. This mutation is in the PACS1 gene.
Exome sequencing 20,000 genes of Ender and his parents

Shows that **Ender** has just 1 de novo mutation.
This mutation is in the PACS1 gene

Exome sequencing 20,000 genes of Siebe and his parents

Shows that **Siebe** has just 2 *de novo* mutations.
One mutation is in the PACS1 gene
Exome sequencing 20,000 genes of Ender and his parents

Shows that Ender has just 1 *de novo* mutation. This mutation is in the PACS1 gene

And they have the same PACS1 mutation

Exome sequencing 20,000 genes of Siebe and his parents

Shows that Siebe has just 2 *de novo* mutations. One mutation is in the PACS1 gene
A new intellectual disability syndrome
Caused by a specific \textit{de novo} mutation of the PACS1 gene

Janneke Schuurs,
Am J Hum Genet, 2012
So what is the point?

What this means for Siebe’s parents:

• The end of a journey: Clarity
• Exoneration of guilt
• Low recurrence risk
• Confusion after ten years
• Hope
Neonatal volvulus
extensive resection > Short bowel

At 10 years: Growth retardation:
• Syndrome?
  OR
• Short bowel?
Neonatal volvulus
extensive resection > Short bowel

At 10 years: *Growth retardation:* 

• Syndrome? OR

• Short bowel?

Normal growth
Now 20 patients with PACS1 Arg203Trp mutation

“We are delighted to make contact with other parents with PACS1. It is incredibly important for us to see how these children can develop."

“And now we have found you. We have been seeing healthcare professionals for many years. Now genetic research has allowed us to finally have our answer too.”
Is making a diagnosis when there is no cure a good or a bad thing?
What causes intellectual disability?

• 1% of all newborns have Intellectual Disability
  \( (36,000 /\text{yr in Europe}) \)

• 70% Unknown

Inherited
Chromosome abnormalities
Consanguinity
Alcohol
Infections
Delivery
Prescription medicines

<30%
A *de novo* hypothesis

There are 20,000 human genes
The average newborn has 1 mutated gene

And

*de novo* mutations can be detected by Genome Sequencing
>60% of Intellectual disability is by *de novo* gene mutations

1000 / 20,000 genes (5%) are *crucial* for the brain

An inconvenient truth

We cannot prevent *de novo* mutations
An inconvenient truth

We cannot prevent *de novo* mutations

So should we offer prenatal testing to everyone?

Non invasive prenatal testing  NIPT
We cannot prevent *de novo* mutations

So should we offer prenatal testing to everyone?

Non invasive prenatal testing  NIPT

Why offer this for Down syndrome (risk 1/1000) and not for other forms of ID (risk 1/100)?
Another inconvenient truth

There is one known risk factor for \textit{de novo} mutations
Rate of *de novo* mutations and the importance of father’s age to disease risk

Augustine Kong¹, Michael L. Frigge¹, Gisli Masson¹, Soren Besenbacher¹,², Patrick Sulem¹, Gisli Magnusson¹.

*Kong et al. Nature 2011*

Human Genetics Nijmegen
Four questions

• Should we offer prenatal diagnosis to everyone?

• Should boys freeze their sperm at 17?
Can our genes predict personality and behaviour?
Nature versus Nurture
Nature versus Nurture

Women programmed for four-year love affairs

John Harlow
Social Affairs Editor

FORGET the seven-year itch: relationships are genetically programmed to self-destruct after four years, according to new research by a leading anthropologist.

PSYCHOLOGICAL SCIENCE

Research Report

GENETIC INFLUENCE ON RISK OF DIVORCE

Matt McGue and David T. Lykken
Department of Psychology, University of Minnesota
A family that I studied 20 years ago
Clinical description

-X-LINKED MILD LEARNING PROBLEMS
-FEMALE CARRIERS NORMAL

-ABNORMAL BEHAVIOUR
  - AGRESSIVE OUTBURSTS
  - EXHIBITIONISM
  - (ATTEMPTED) RAPE
  - ARSON
Abnormal Behavior Associated with a Point Mutation in the Structural Gene for Monoamine Oxidase A

H. G. Brunner,* M. Nelen, X. O. Breakefield, H. H. Ropers, B. A. van Oost

SCIENCE • VOL. 262 • 22 OCTOBER 1993
EVIDENCE FOR A POSSIBLE AGGRESSION GENE

SCIENCE    July 1993
缺少單氧酶可能導致侵略行為

MAO A DEFICIENCY

男性暴力行兇，就是單一系統責任嗎？
MAOA deficiency is unlikely to explain any specific behaviour in society

* MAOA deficiency is rare

* Behavioural phenotype is non-specific

* Behaviour is modified by other (environmental) factors, also in this family
Nature vs Nurture
We all have variants

- ~20,000 exonic variants
  - Excluding known variants (dbSNP+ inhouse) ~200
    - Silent ~ 60
    - Nonsense/frameshift ~ 40
    - Missense ~ 95
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Remember this?

The story continues
Guess what?

1/3 of all males has a variant in MAOA

If this has any effect at all, it must be really small...
“Inside the Warrior Gene.”

The weekend mommy blog:

Very early yesterday morning, I was wide awake and watching a documentary on the National Geographic channel, entitled “Inside the Warrior Gene.”

Now knowing who does and doesn't have the Warrior Gene is not easy as people might think it is.

**Guess what?**
None of the prizefighters nor the leader of a biker group had the Warrior Gene.

But all three Buddhist monks had the Warrior Gene.
The weekend mommy blog:

None of the prizefighters nor the leader of a biker group had the Warrior Gene.

But all three Buddhist monks had the Warrior Gene.
The Get Out of Jail Free gene

The sentence of one killer in Italy has been reduced as he possesses a ‘violent gene’. Can DNA be used as a defence?
The evidence on one gene, known as MAO-A proved particularly persuasive for the judge.

The Bayout trial is thought to be the first time that violent genes have been invoked to amend a sentence. It shows that the controversial field of behavioural genetics is having a dramatic effect in courtrooms today.
A question

Should we allow genetic information in the court room?
Four questions

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