Future developments

& meeting evaluation

THE HUMAN VARIOME PROJECT
an NGO official partner of UNESCO
sharing data • reducing disease

Newcastle University Medicine Malaysia

Agilent Trusted Answers

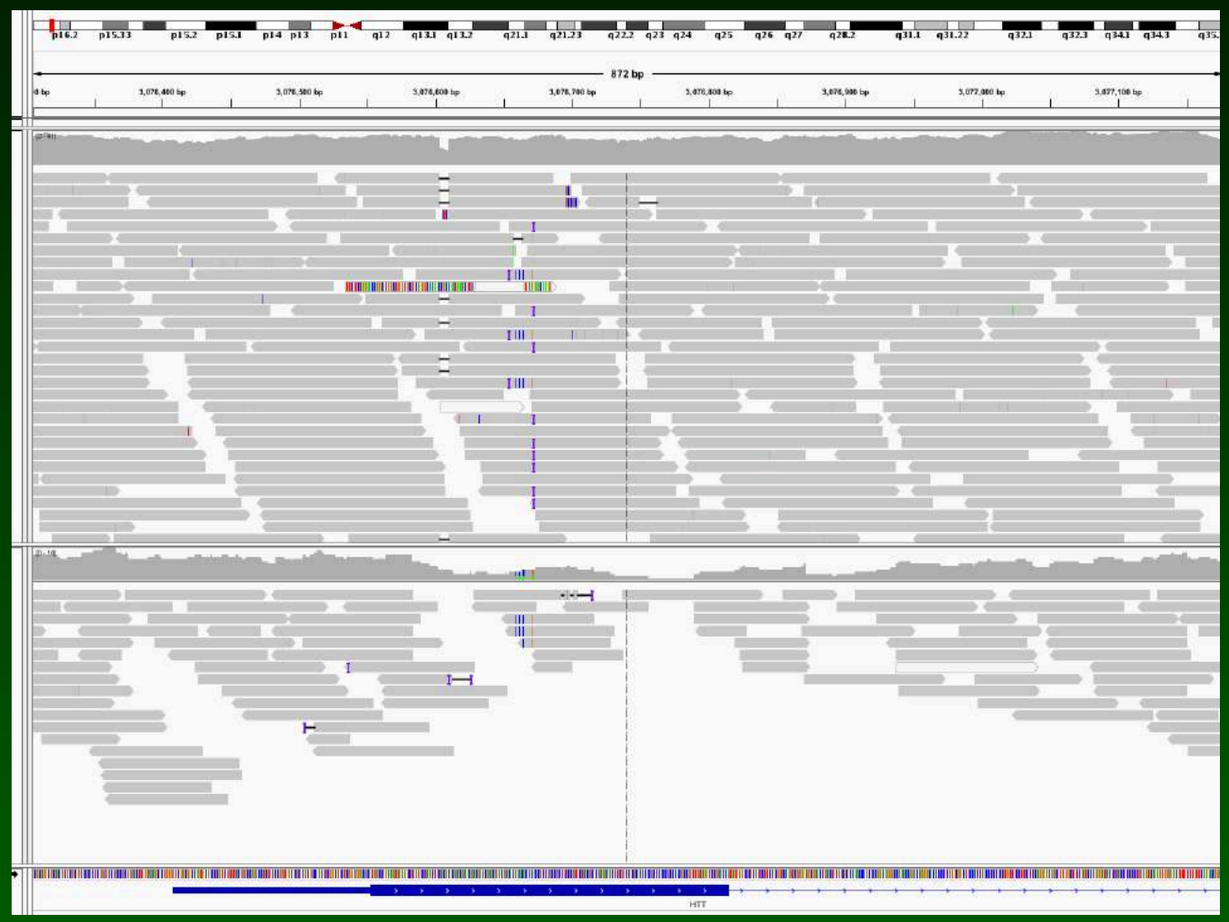
tinyurl.com/ VEPTC-23

Johan den Dunnen

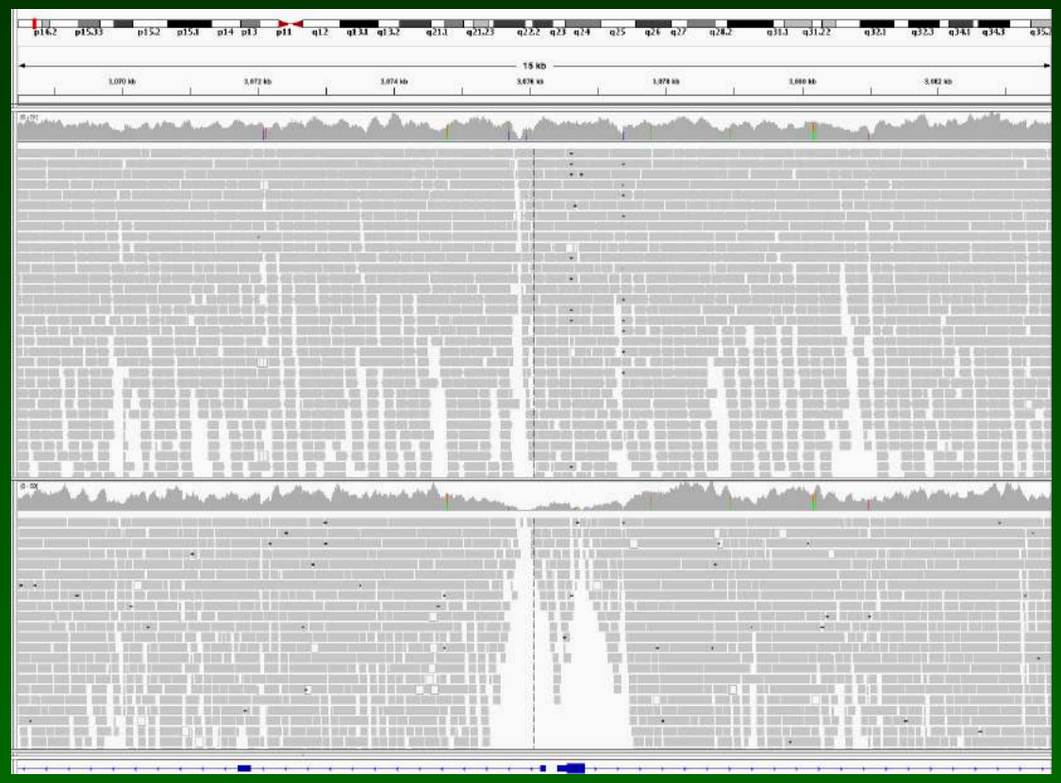
My genome

sequenced it twice

(best way to determine quality)



HTT gene



top: no PCR (2013)
bottom: few cycles (2017)

GC-bias (WGS)

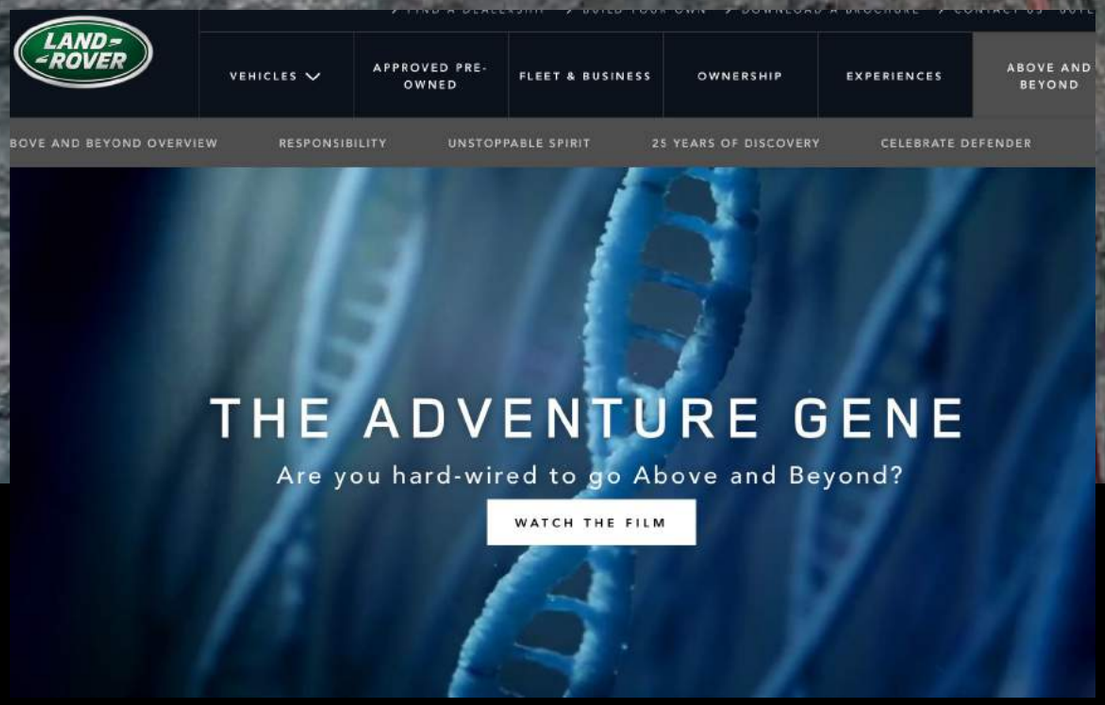
Your genome

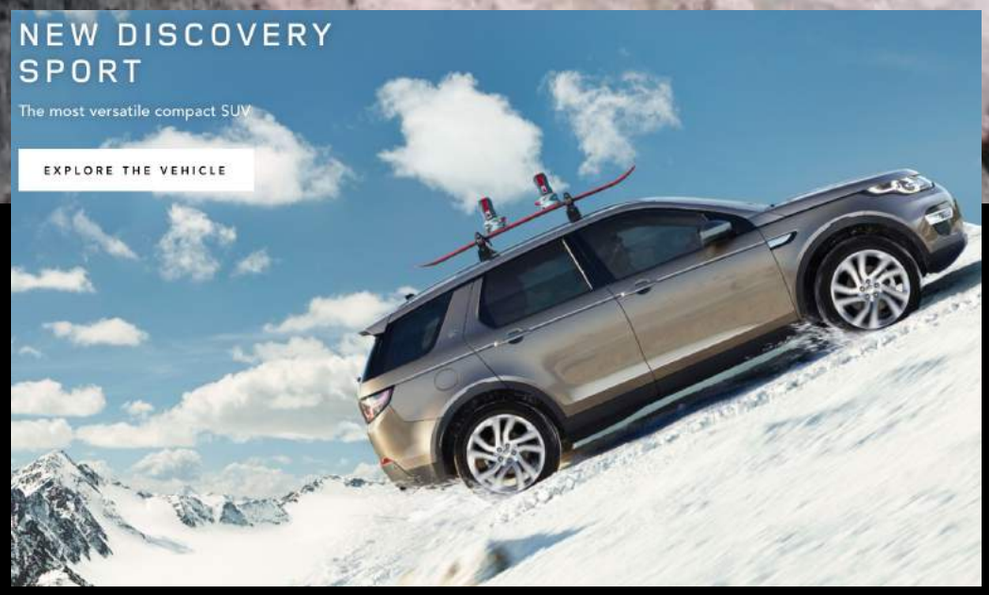
who sequenced their genome ?

who had a DNA test ?

who has the DRD4 7R gene ?

1 in 4 has the
DRD4 7R gene





Commercial DNA test

dante labs

Never worry again

Whole Genome Sequencing (WGS) - Full DNA Analysis

£399

Whole Exome Sequencing (WES) - Sequence all Your Genes

£299

2017

Special offer

maybe offer on Halloween
because it is a scary thing to do ?

...future !?

...your (grand) grand children will not believe you dared to live without knowing your genome,

...nor your partner's genome

Eerst een DNA-test, dan pas bevruchten

Geneeskunde

Een baby zonder ernstige erfelijke ziekte. Stellen die dat willen, kunnen hun DNA op tientallen ziekten laten testen. Nog vóór ze het kind maken.

Wim Köhler 23 september 2016

nrc.nl

...future !?

nowadays nobody would start surgery without an X-ray,

why do we start treatment without knowing the genome ?

Olaf Rieß

... for the hospital

...a patient will not be treated when the basics, the DNA, is not known

...why risk undesired effects from treatment, when these can be determined beforehand ?

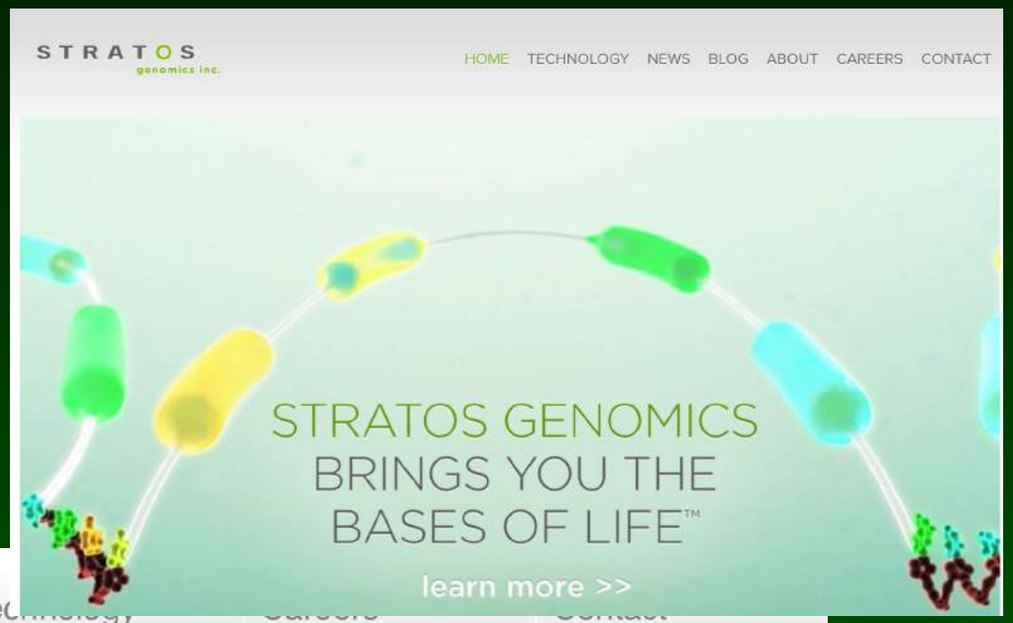
...why risk treating a problem for which the origin lies elsewhere (has a genetic component) ?

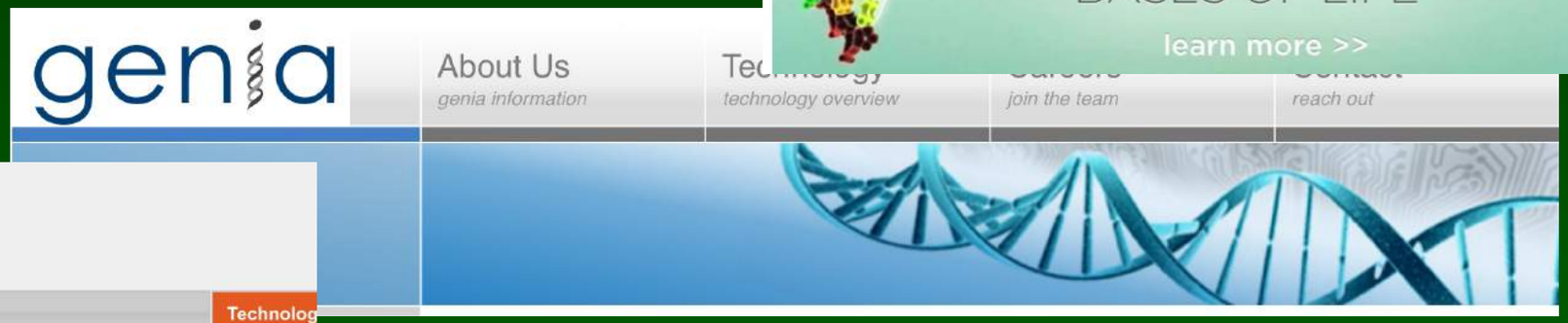
more sequence
longer reads
faster
cheaper

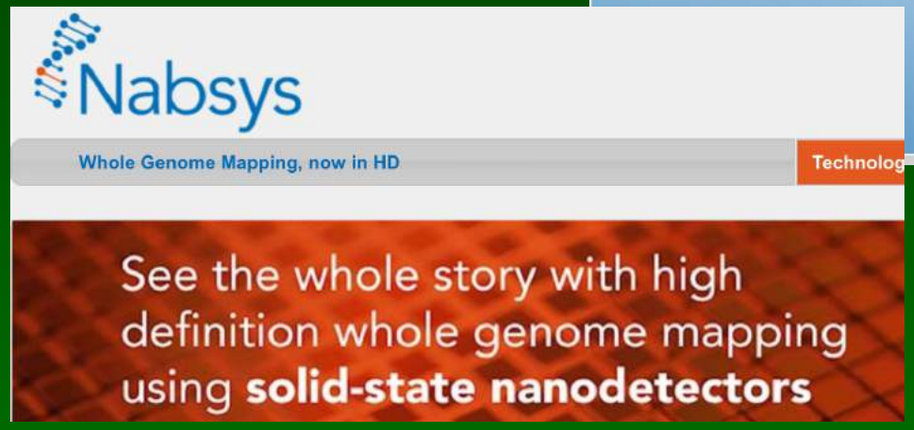
...single molecule
...label-free

Single molecule sequencing

future technology







Future technology

Future technology

twoporeguys

..and then

Oxford NANOPORE Technologies

SmidgION

sequence @home

...everything possible

...all these possibilities,
too many to test

...anything that theoretically can go wrong,
in practice will go wrong once

...incl. bioinformatically

Rare cases ?

- **maybe, ...but**
  - *we go for the simple & obvious*
    - *many options not even considered*
  - *many not detected using exome sequencing*
  - *rare cases difficult to proof*
    - *may require additional experiments and functional proof*

- **recent publications**
  - *intellectual disability, >2100 WES trios*
  - *used statistics to find proof of causality*
  - *several new genes/variants implicated*

Rare cases ?

- **many mono-genic diseases solved**

where are the di-genic diseases ??
I would expect many more

NATURE GENETICS VOLUME 44 | NUMBER 12 | DECEMBER 2012

Digenic inheritance of an *SMCHD1* mutation and an FSHD-permissive D4Z4 allele causes facioscapulohumeral muscular dystrophy type 2

Richard J L F Lemmers[1,13], Rabi Tawil[2,13], Lisa M Petek[3], Judit Balog[1], Gregory J Block[3], Gijs W E Santen[4], Amanda M Amell[3], Patrick J van der Vliet[1], Rowida Almomani[4], Kirsten R Straasheijm[1], Yvonne D Krom[1], Rinse Klooster[1], Yu Sun[1], Johan T den Dunnen[1,4], Quinta Helmer[5], Colleen M Donlin-Smith[2], George W Padberg[6], Baziel G M van Engelen[6], Jessica C de Greef[1,12], Annemieke M Aartsma-Rus[1], Rune R Frants[1], Marianne de Visser[7], Claude Desnuelle[8,9], Sabrina Sacconi[8,9], Galina N Filippova[10], Bert Bakker[4], Michael J Bamshad[3,11], Stephen J Tapscott[10], Daniel G Miller[3,11] & Silvère M van der Maarel[1]

clear phenotype
unsolved FSHD cases

WES analysis several families
shared SMCHD1 variants

Genes

- **20,000 protein coding**
  60,000 total
- **which gene should be in a specific panel**
- **which transcript to use**
  preferred reference transcript

Genomics england

New rare disease gene tool launched
PanelApp

standards for analysis, agreement on what to analyse

Standards

- **annoying, ...but**
  - *we need them*
  - *..and use without errors*
- **variants**
  - *HGVS nomenclature*
- **phenotypes**
  - *Human Phenotype Ontology (HPO)*

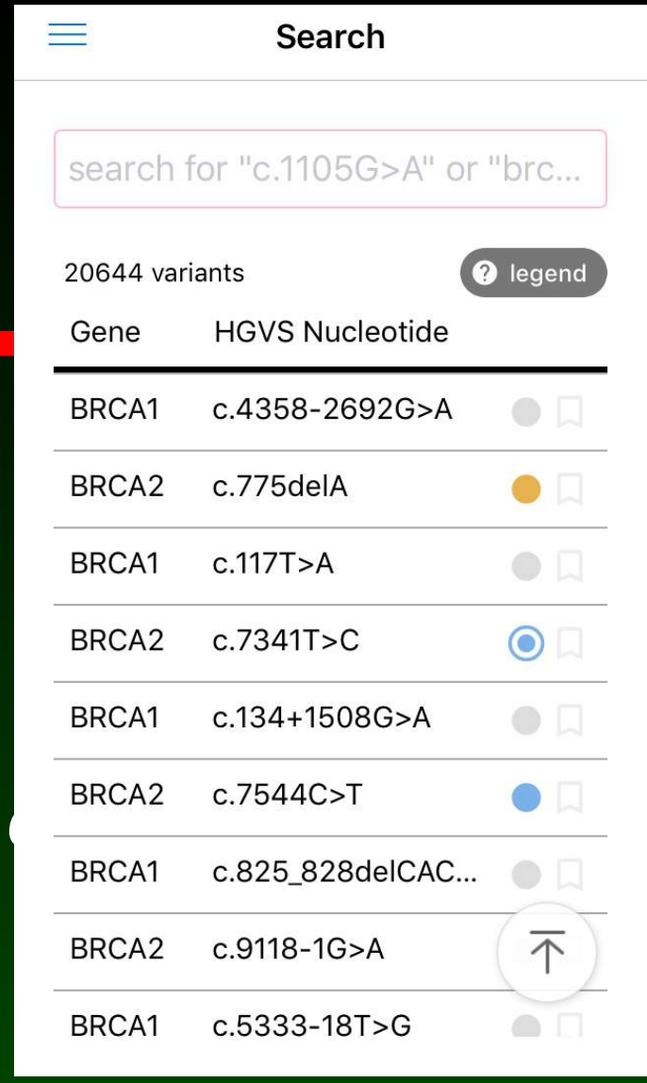
Databases

...all these databases

DNA diagnostics is based on:

SHARING *what we know*
between ***variants in genes***

without sharing, no DNA diagnostics



...now you can give me your data for free

in due time it will become mandatory,
and you have to pay me

Web Images Video Maps News Shopping Gmail more ▾

Google

c.62G>A lovd

Search | Advanced Search | Preferences

Web Show options...

Did you mean: c.62G>A ***loved***

Essayez avec cette orthographe : c.62G>A ***love***

Search unique variants - **LOVD** - Leiden Open Variation Database ...
02, **c.62G**>A, -, r.(?) p.(Arg21Gln), ARG1_00001, -, -, Mitchell 2009, DNA, HRMA ... Powered by **LOVD** v.2.0 Build 18. Enabled modules: showmaxdbi
chromium.liacs.nl/**LOVD**2/variants.php?select_db=ARG1
unique&search_pathogenic_=- - 28k - Cached - Similar p

View unique variants - **LOVD** - Leiden Op
01, 1-**62G**>A (Reported 10 times), -, -, GCK_0003
Leu20Pro, GCK_00063, -. 02, 106C>T (Reported 2
chromium.liacs.nl/**LOVD**2/variants.php?action=vie
Cached - Similar pages
More results from chromium.liacs.nl »

Variants - NGRL, Manchester **LOVD** - Leiden C
NGRL, Manchester **LOVD**. ubiquitin protein ligase E3A (
RNA change. Protein, p.Cys21Tyr (predicted) ...
ngrl.man.ac.uk/**lovd**2/variants.php?select_db=UBE3A&a
0000082%2C0000082%2C21 - Similar pages

Google

c.1A>G LOVD

ALL IMAGES VIDEOS SHOPPING NEWS MAPS BOOKS

Did you mean: c.1A>G ***LOVE***

HBB:c.1A>G - bx.psu.edu).
https://lovd.bx.psu.edu › variants › DNA...

HBB homepage View unique variants Public list of submitters Submit new data
View unique variants · Search unique ... LOVD - Variant listings for HBB. Unhide

All transcript variants in gene FANCA - Global Variome shared LOVD
https://databases.lovd.nl › shared › FANCA

Share

back at the office

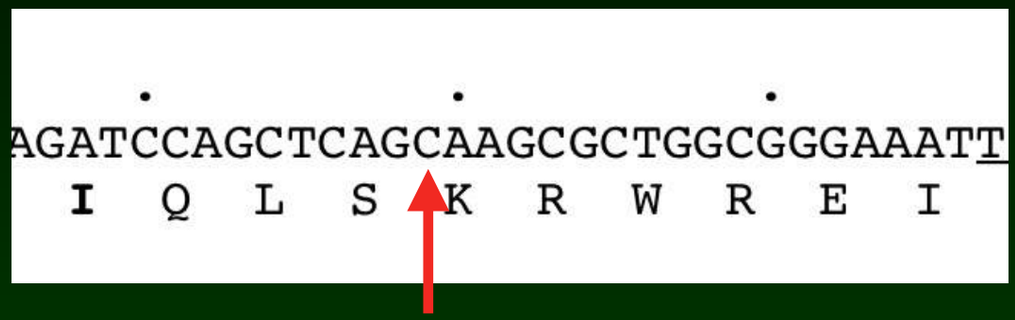
submit ALL variants
(immediately)

or send us your file
for batch submission

for the patients and their families

Share !!

DMD gene



c.5859C>T r.(?) p(Ser1953=)

found in diagnosis

prenatal
at risk family muscular dystrophy
no definite diagnosis

found in diagnosis

WES, trio analysis
male parent
45y, healthy
one of many variants

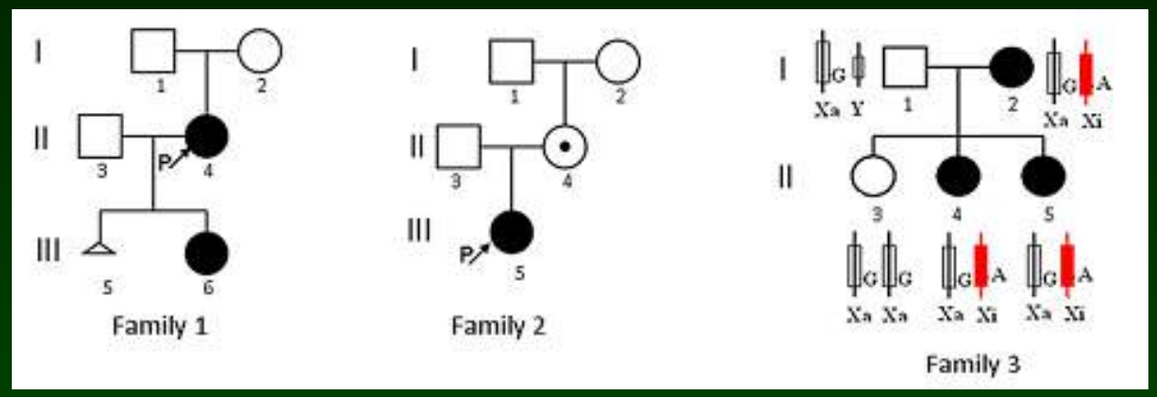
you may have life saving information, did you realize ?

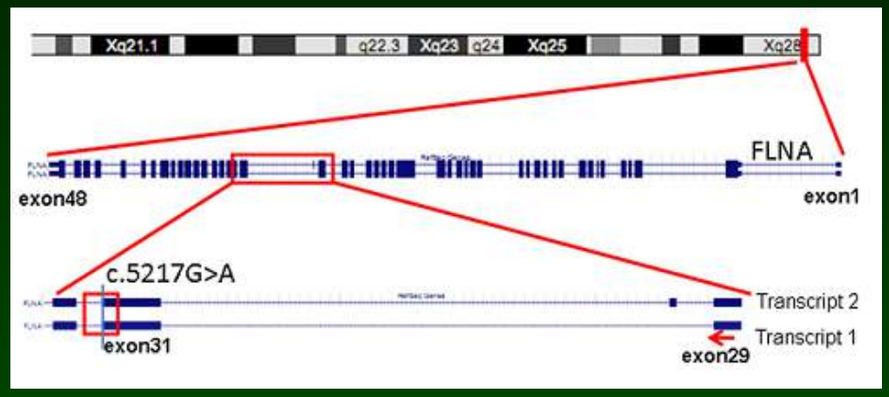
The American Journal of Human Genetics *87*, 146–153, July 9, 2010

REPORT

Terminal Osseous Dysplasia Is Caused by a Single Recurrent Mutation in the *FLNA* Gene

Yu Sun,[1,11] Rowida Almomani,[1,11] Emmelien Aten,[1] Jacopo Celli,[1] Jaap van der Heijden,[1] Hanka Venselaar,[2] Stephen P. Robertson,[3] Anna Baroncini,[4] Brunella Franco,[5,6] Lina Basel-Vanagaite,[7] Emiko Horii,[8] Ricardo Drut,[9] Yavuz Ariyurek,[1,10] Johan T. den Dunnen,[1,10] and Martijn H. Breuning[1,*]





FLNA.lovd.nl

LOVD Leiden Open Variation Database

Mental Retardation database

filamin A, alpha (actin binding protein 280) (FLNA)

Curator: Johan den Dunnen

LOVD v.2.0 Build 29 [Curren

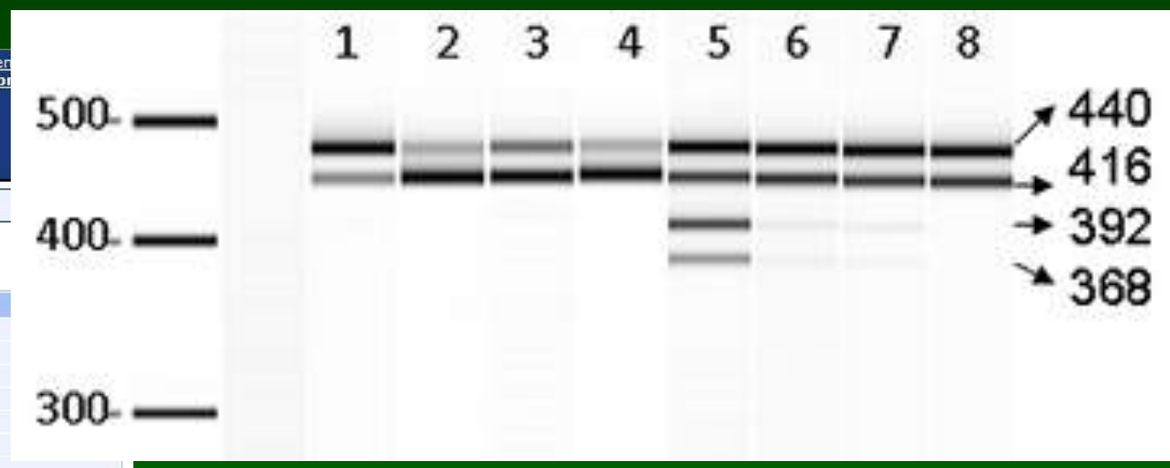
Register as subm

Home | Variants | Submitters | Submit | Documentation

FLNA homepage | Switch gene

LOVD Gene homepage

General information	
Gene name	filamin A, alpha (actin binding protein 280)
Gene symbol	**FLNA**
Chromosome Location	Xq28
Database location	www.LOVD.nl/MR
Curator	Johan den Dunnen
Database reference for citations	Sun et al. 2010, Am J Hum Genet. 87: 146-153
PubMed references	View all (unique) PubMed references in the FLNA database
Date of creation	March 06, 2009
Last update	October 24, 2010
Version	**FLNA101024**
Add sequence variant	Submit a sequence variant
First time submitters	Register here
Reference sequence	coding DNA reference sequence for describing sequence variants
GenBank reference	FLNA_NG_011506.1.gb
Total number of unique DNA variants reported	**84**
Total number of individuals with variant(s)	**289**
Total number of variants reported	**309**



Genomics projects

GoNL
GENOMEoftheNETHERLANDS

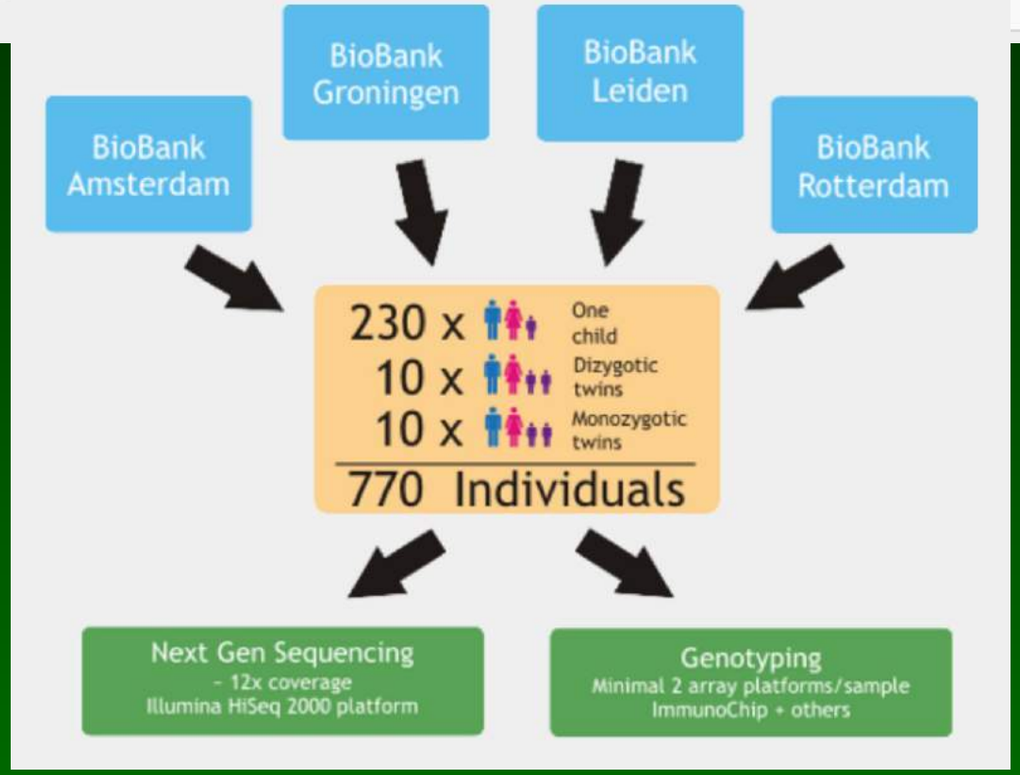
Home | About us | Access to the data | Resources | The GoNL team | Wiki

Ultra-sharp genetic group portrait of the Dutch

Posted on July 15, 2012

News

- SNP calling complete



BBMRI•NL

Adopt a gene !

become a
foster parent
database curator

THE
HUMAN VARIOME
PROJECT
an NGO official partner of UNESCO
sharing data • reducing disease

HGV
HUMAN GENOME
VARIATION SOCIETY

LOVD
Leiden Open Variation Database

claim your child at
gene.LOVD.nl

essential on your CV
...only ~15,000 available

with 7,000,000,000 people
chance 1/400,000

RNA, it exists !

..the neglected molecule

under-appreciated

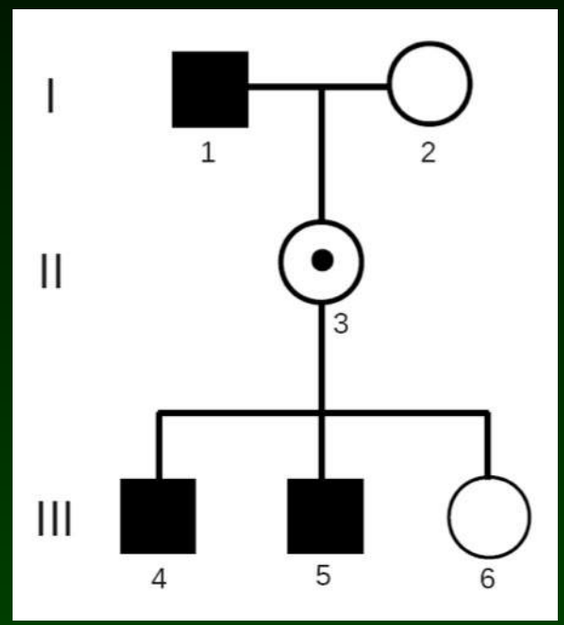
most go blindly DNA > protein

..there is much more

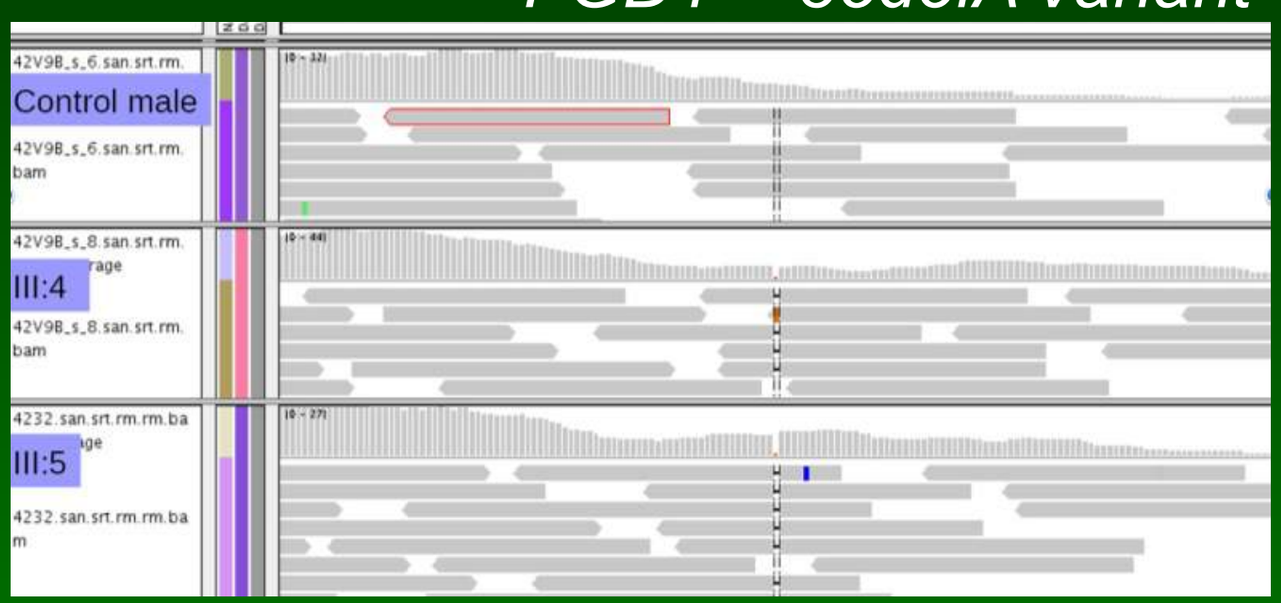
Aarskog-Scott syndrome

- **ASS family**
  FGD1 gene screened
  > no variants

- **whole exome capture**
  no obvious variants
  > thresholds lowered



FGD1 -35delA variant



©Yu Sun
Emmelien Aten

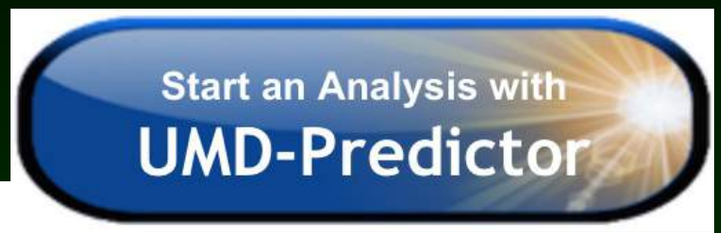
Aarskog-Scott syndrome

- **why FGD1 variant missed ?**
  - *primer on variant site*
    - *allowing amplification in males*
    - *not standard to screen to -50*
- **exome capture**
  - *lower coverage into intron*
  - *variant filtering to -10*
    - *many additional variants, difficult to confirm*
- **few branch site variants**
  - *rare*
  - *easily missed*
  - *difficult to proof*

DNA screen negative: try to analyse RNA !

Predictions

protein predictions



When you ask a prediction tool something it will always give you an result,

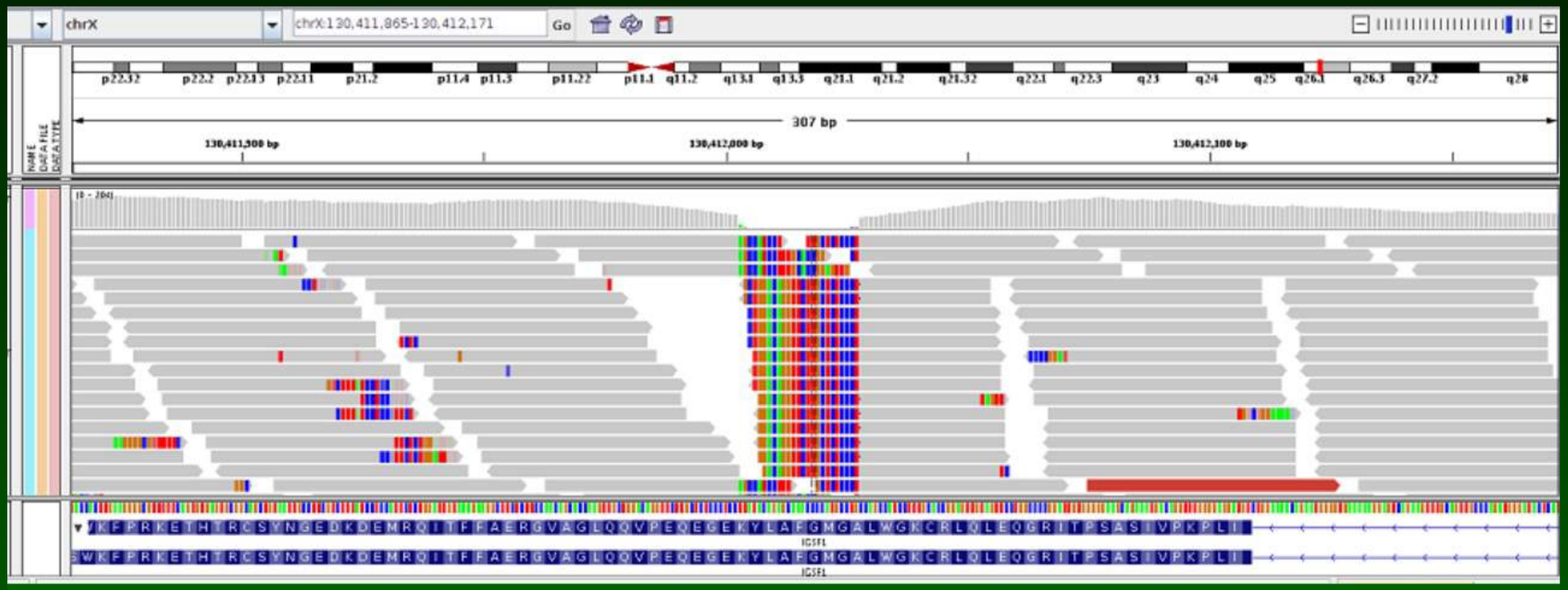
up to you to decide whether to trust the answer

Pipelines

variant missed by software

found by eye

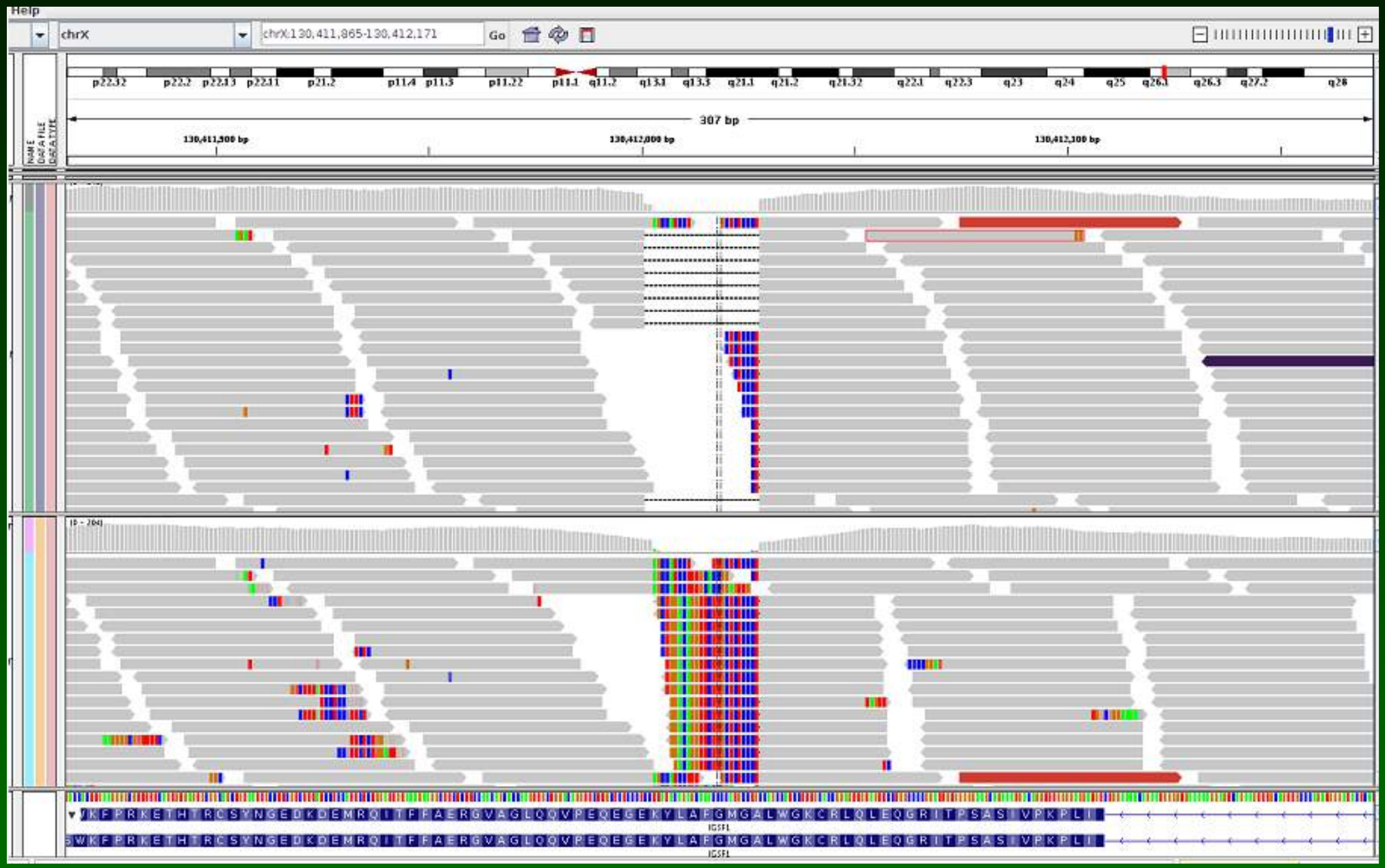
CNV



early WES analysis (2009)

Pipelines

later version



Pipelines

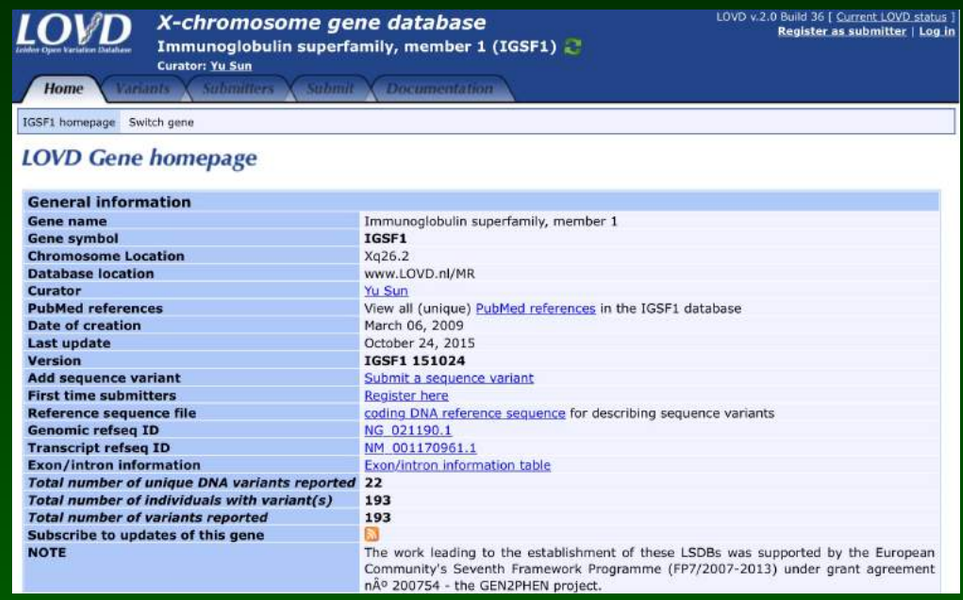
Loss-of-function mutations in *IGSF1* cause an X-linked syndrome of central hypothyroidism and testicular enlargement

Yu Sun[1,20], Beata Bak[2,20], Nadia Schoenmakers[3,20], A S Paul van Trotsenburg[4,20], Wilma Oostdijk[5], Peter Voshol[3], Emma Cambridge[6], Jacqueline K White[6], Paul le Tissier[7,8], S Neda Mousavy Gharavy[7], Juan P Martinez-Barbera[7], Wilhelmina H Stokvis-Brantsma[5], Thomas Vulsma[4], Marlies J Kempers[4,9], Luca Persani[10,11], Irene Campi[10,12], Marco Bonomi[11], Paolo Beck-Peccoz[10,12], Hongdong Zhu[13], Timothy M E Davis[13], Anita C S Hokken-Koelega[14], Daria Gorbenko Del Blanco[14], Jayanti J Rangasami[15], Claudia A L Ruivenkamp[1], Jeroen F J Laros[1], Marjolein Kriek[1], Sarina G Kant[1], Cathy A J Bosch[1], Nienke R Biermasz[16], Natasha M Appelman-Dijkstra[16], Eleonora P Corssmit[16], Guido C J Hovens[16], Alberto M Pereira[16], Johan T den Dunnen[1,17], Michael G Wade[18], Martijn H Breuning[1], Raoul C Hennekam[4], Krishna Chatterjee[3,21], Mehul T Dattani[19,21], Jan M Wit[5,21] & Daniel J Bernard[2,21]

NATURE GENETICS VOLUME 44 | NUMBER 12 | DECEMBER 2012

final evidence came from

mouse *(no phenotype)*
additional families



to check we feed pipeline with an artificial reference sequence and artificial variants

Sequencing

outsources sequencing

focus on development

Genome browsers

wonderful tools, free for everybody
where would we be without them

Bob & Ben,
we like their tool very much

(...we did not ask them to compare the two)

Variant classification

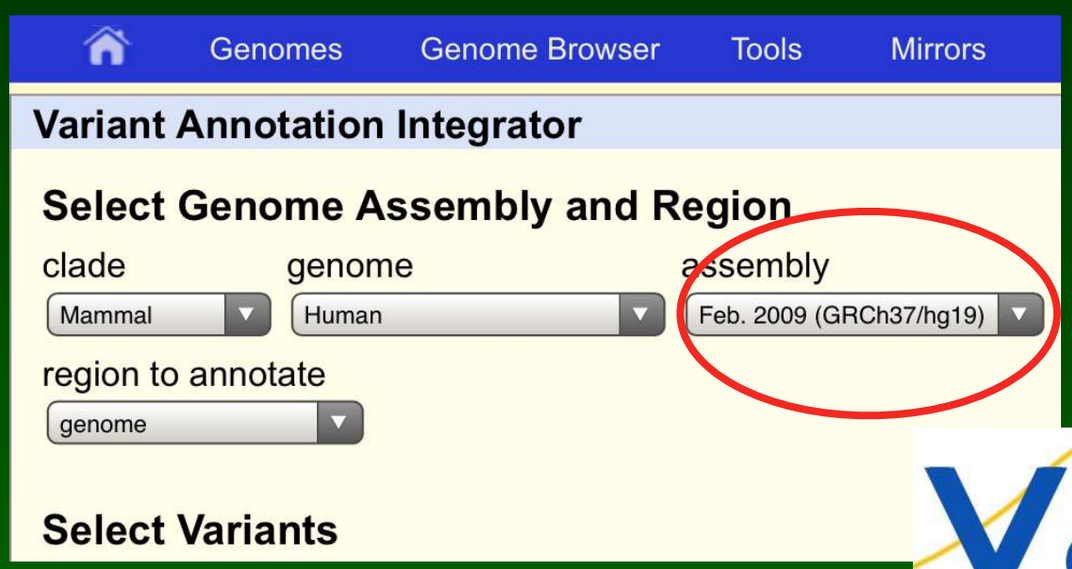
standards for classification

ACMG recommendations

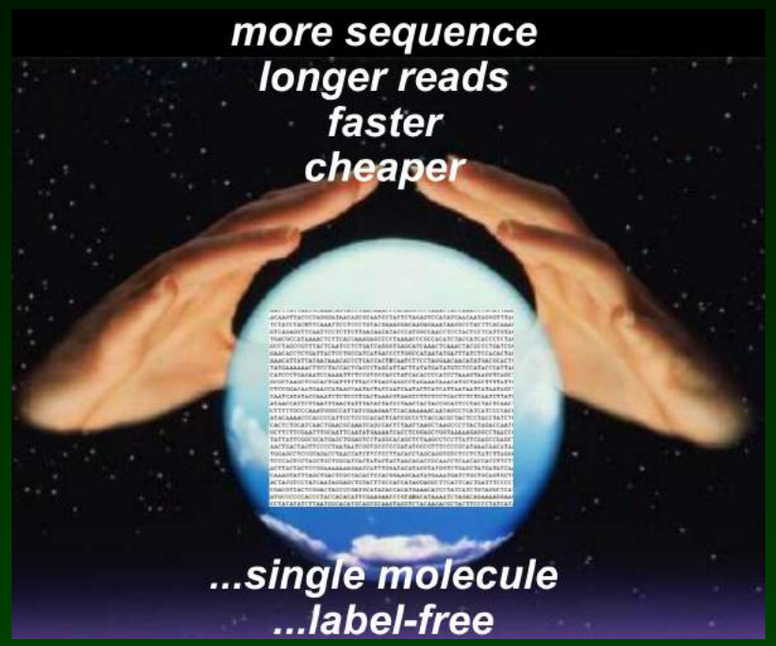
labs start sharing classifications

ACMG:

"beware of variants that may impact splicing"



Future technology



more sequence
longer reads
faster
cheaper

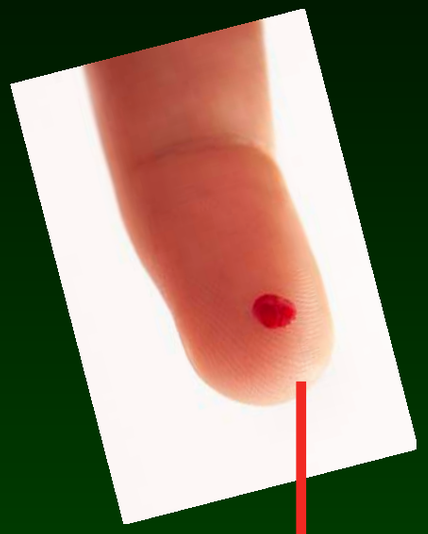
higher coverage
better alignment *(de novo assembly)*
fewer ***& better databases***
improved predictions

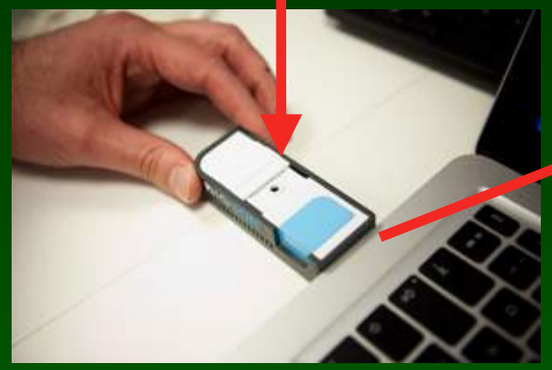
Predictions

...it is good we can not yet trust predictions

(dangerous tools, eventually they will take over your job)

Future VEP





LOVD
Leiden Open Variation Database

FINAL

VeIP

CE

GENOME REPORT

(complete error free)

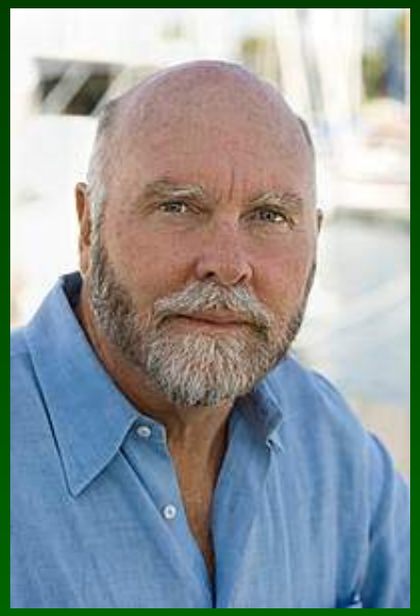
2008

Focus on disease

(individual genomes sequenced)

James Watson

JLupsky, Kim,
GChurch, DTutu, JFlattery,
MSnyder,
….



Craig Venter

Marjolein Kriek

www.BasVanVlijmen.com

A rumour

female DNA finally sequenced

"here the defective gene for parking a car backwards"

From: **Pastafarian ®**

Subject: **re: Scientists claim to understand women**

Nobel Prize for them

27/05/2008 3:15:32 PM

post id: 3604572

Scientists crack women's DNA code

FINALLY, men may be able to understand women, it seems. Dutch scientists said they have mapped the full genetic sequence of an individual woman's DNA for the first time.

Researchers at Leiden University Medical Centre said they had sequenced the genome of one of their researchers, geneticist Marjolein Kriek, and plan to publish it after review.

2008

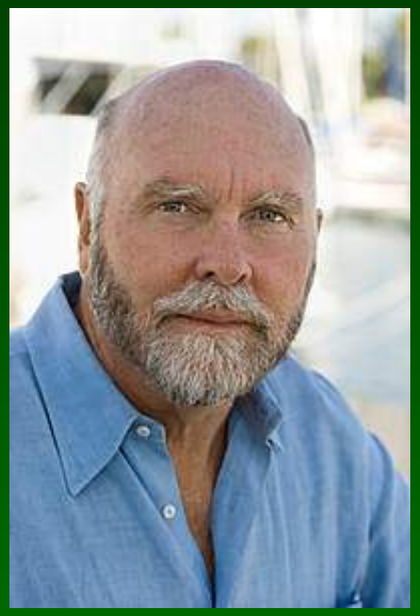
Focus on disease

(individual genomes sequenced)

James Watson

JLupsky, Kim,
GChurch, DTutu, JFlattery,
MSnyder,
….

Marjolein Kriek



Craig Venter

conclusion 'sick' much easier then 'healthy'

Agilent
Trusted Answers

Newcas
Univers
Medicine Ma

Scientific Programme

Prof. Johan T. den Dunnen (Leiden, Nederland) CHAIR
Prof. Chris Baldwin (NUMed, Malaysia) LOCAL ORGANISER
Dr Andreas Laner (Munich, Germany)
Prof. Poh San Lai (NUS, Singapore)

next course ?

- **1998 - ...**
- **2000 - Leeds (UK)**
- **2002 - Montpellier (FR)**
- **2004 - Newcastle (UK)**
- **2006 - Leiden (NL)**
- **2008 - Rotterdam (NL)**

- **2016 - Heraklion (GR)**
- **2017 - Prague (CZ)**
- **2018 - Johor (MY)**
- **2019 - ...**

Evaluation

- how was the course ?
- topics missing ?
- format ?
  length
  demos