the variant genomes behind the variant humans

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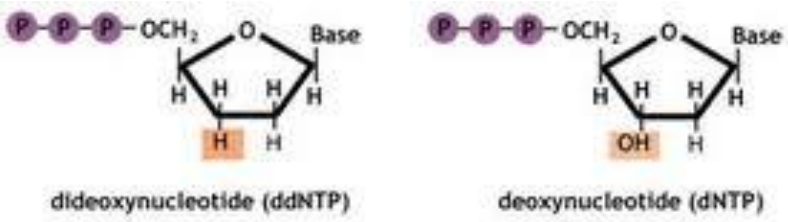
*James*Watson *Francis*Crick
1953

Sanger method to read DNA



Frederick Sanger
Nobel prices 1958 and 1980
born August 13 1918,
died November 19 2013

Science March 7, 1986:

«to read the entire human genome»

Renato Dulbecco

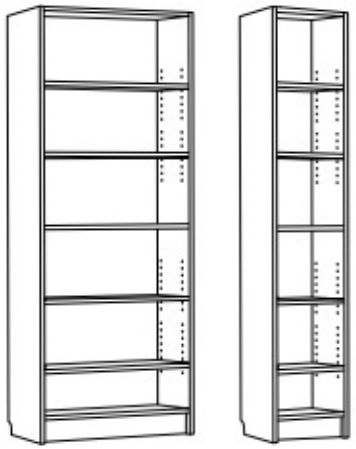
Nobel Price for Medicine1975

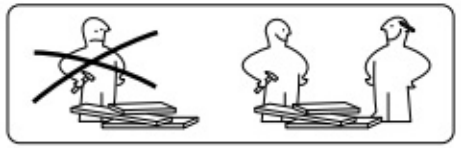
Catanzaro, 22 febbraio 1914 – La Jolla, 19 febbraio 2012

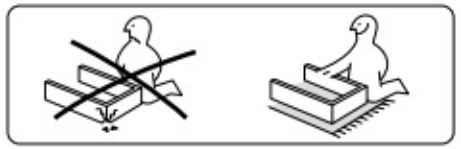
Human Genome Project

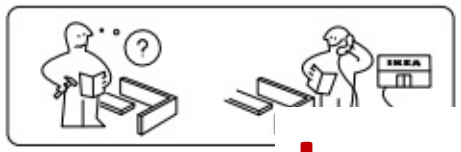
- 3 billions of dollars
- 13 years (1988-2001)

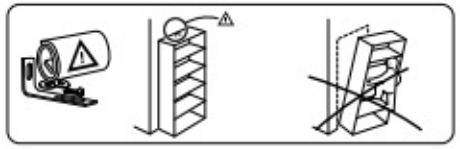
BILLY

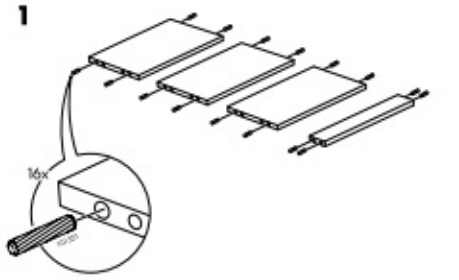


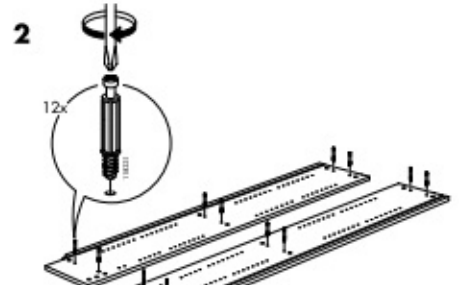




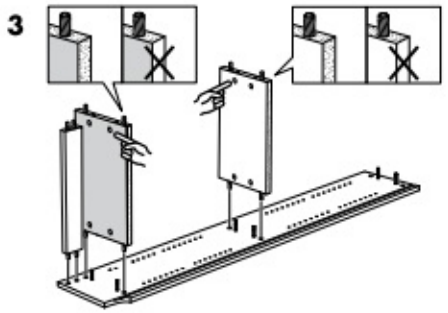


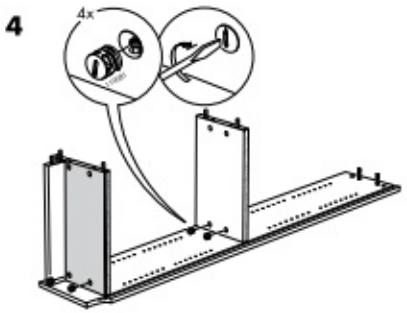


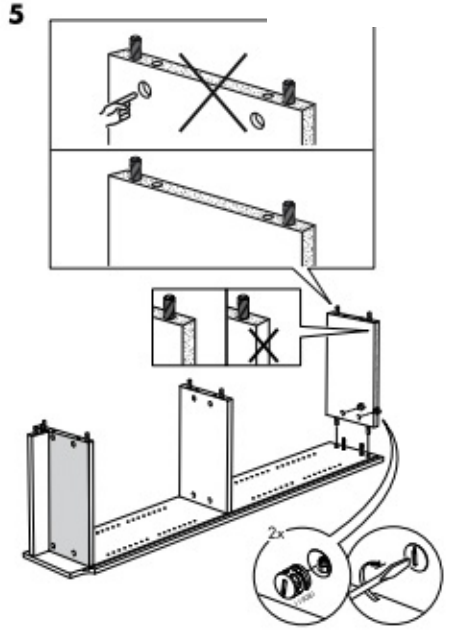


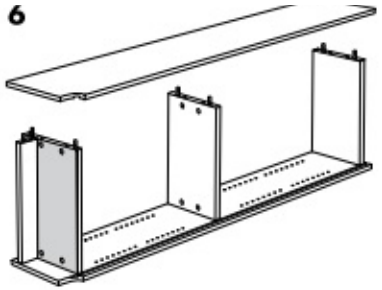


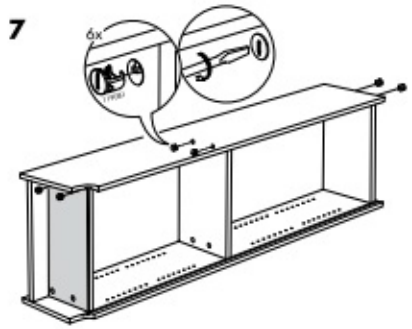
human assembly instructions

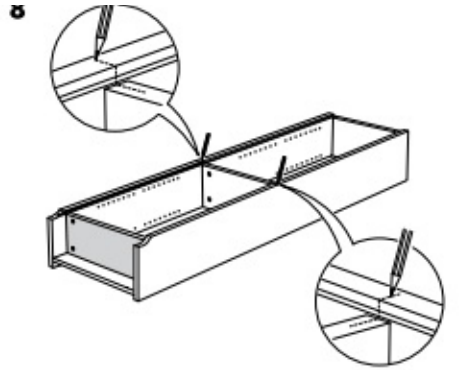


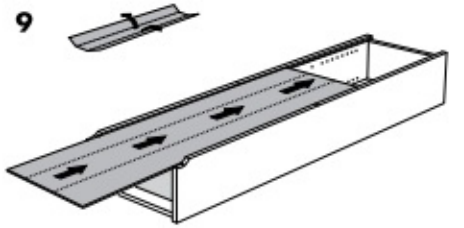












use, function and repair instructions

planned obsolescence

all the cells in our body have the same DNA

Maternal mitochondrial DNA 16.500 bp

Maternal nuclear DNA 3.070.000.000 bp

nucleus

Paternal nuclear DNA 3.070.000.000 or 2.970.000.000 bp

2002

96-capillary 3730xl DNA Analyzer

2,100,000 bp/day

= 476 days / billion DNA bp

2,000,000$/ billion DNA bp

2008

Genome Analyzer II

4,000,000,000 bp/7 days

= 42 hours/ billion DNA bp

350$/ billion DNA bp

2017

NovaSeq6000

6,000,000,000,000 bp/40 hours

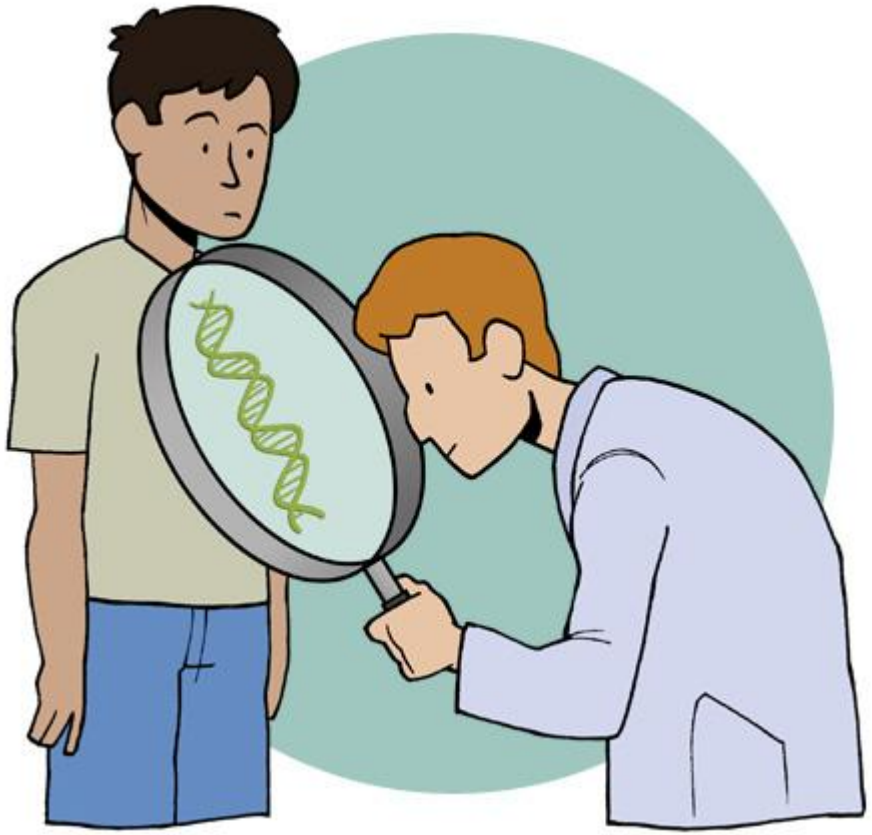
= 40 seconds/ billion DNA bp

7$/ billion DNA bp

from the human genome to the genomes of humans

The individual genome
next generation sequencing

4.4 Millions
DNA variations
compared to the
reference genome

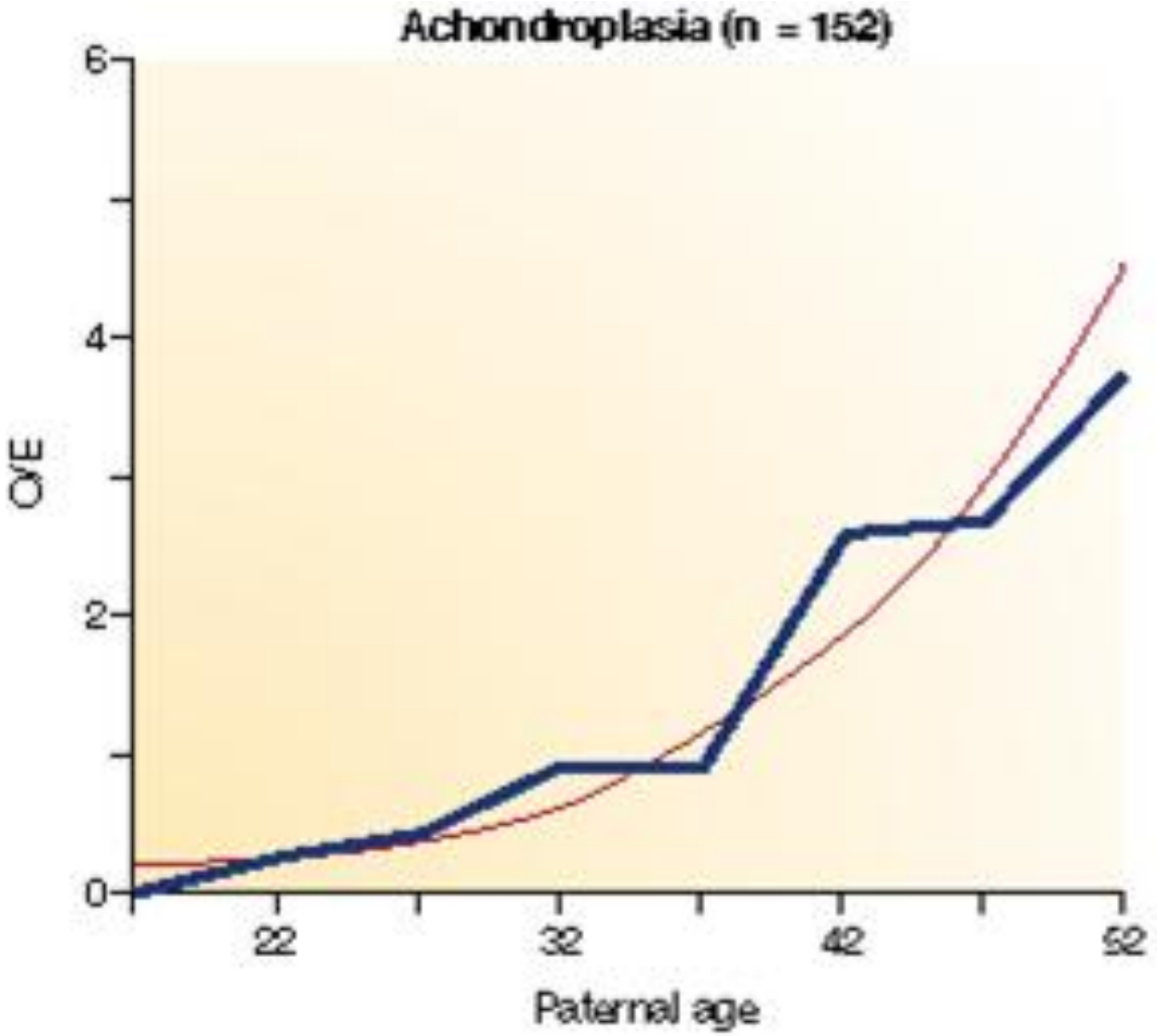


errors in copying DNA

insertional mutagenesis viral DNA

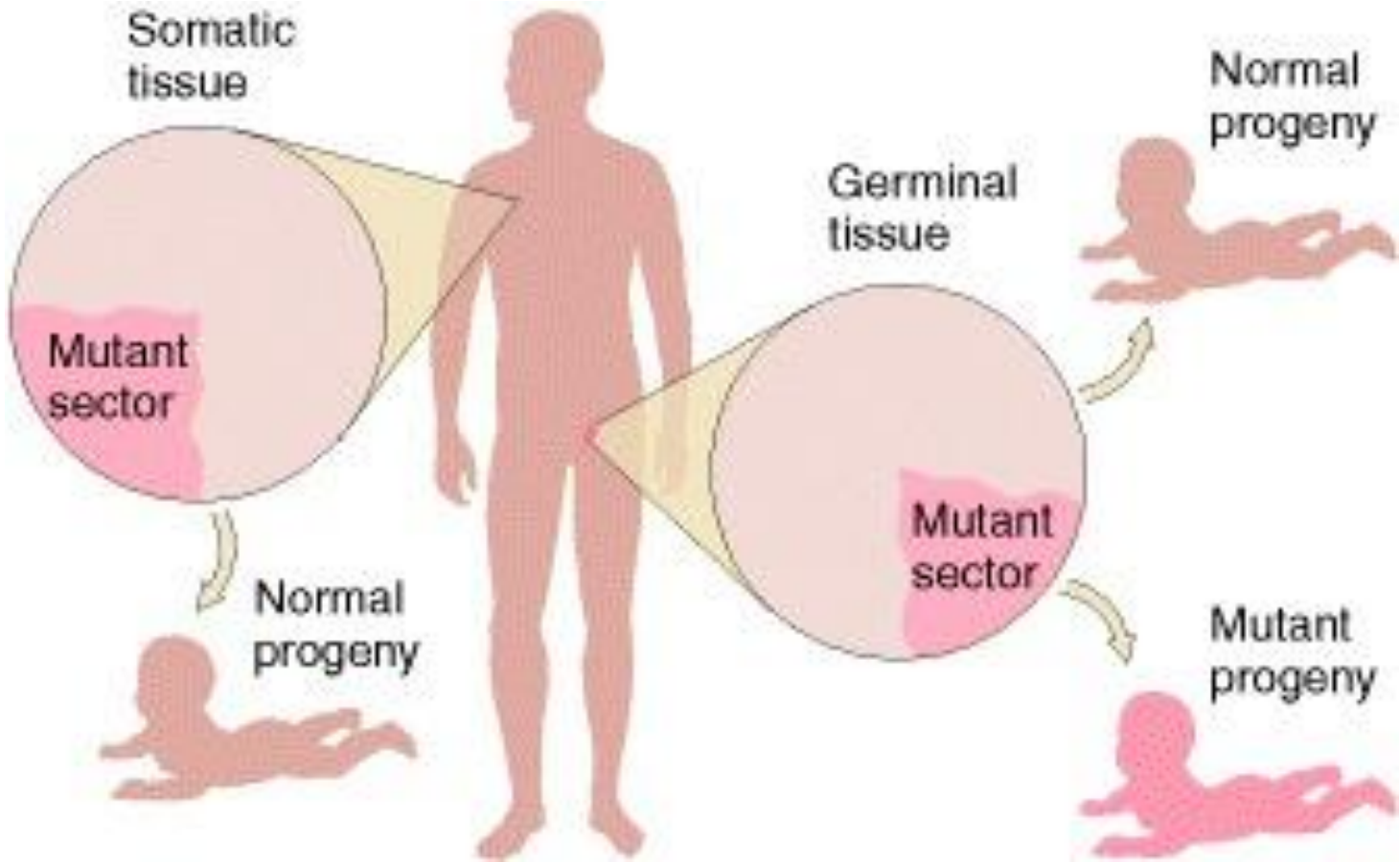
corrupted DNA (aging)

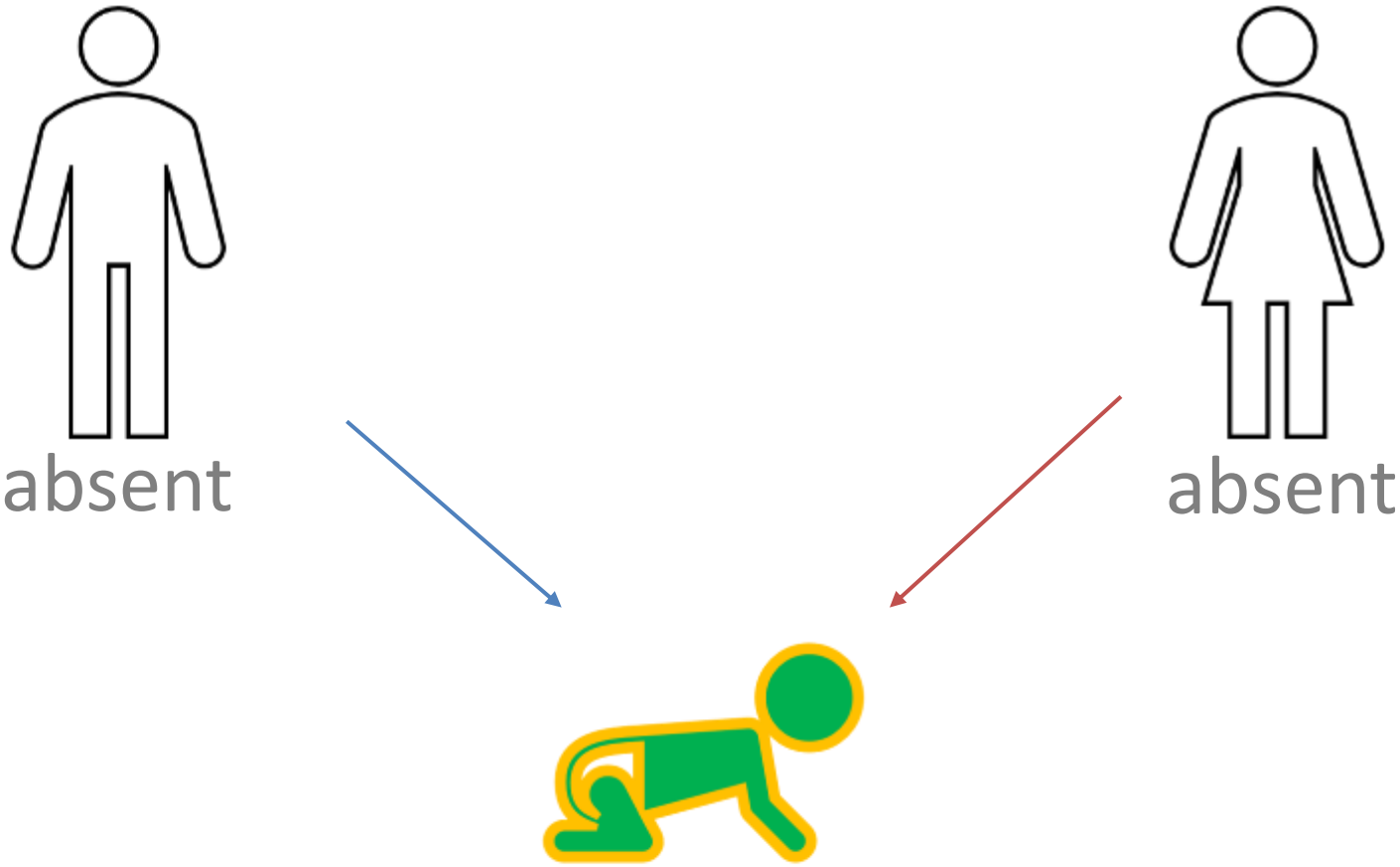
relative frequency of *de novo* achondroplasia for different paternal ages



the number of male germ-cell divisions

Age	Chromosome replications
15	35
20	150
30	380
40	610
50	840


Somatic tissue
Mutant sector
Normal progeny
Germinal tissue
Normal progeny
Mutant sector
Mutant progeny



one *de novo* mutation

errors are the source of human variability

>4,000,000 small variations

changing single letters

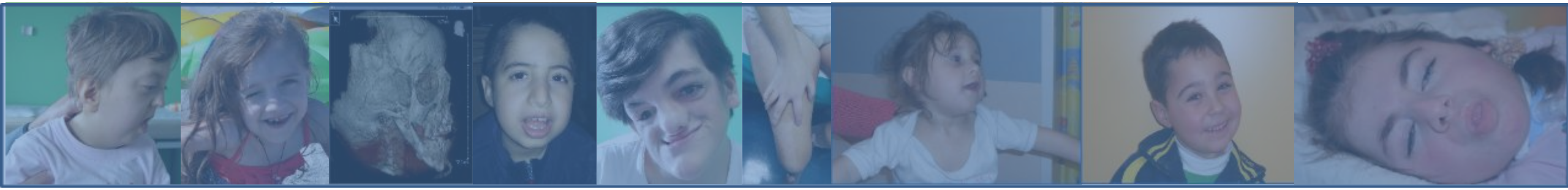
‘We know what we are, but know not what we may be’

‘We know what we **c**are, but know not what we may be’

>12,000 structural variations

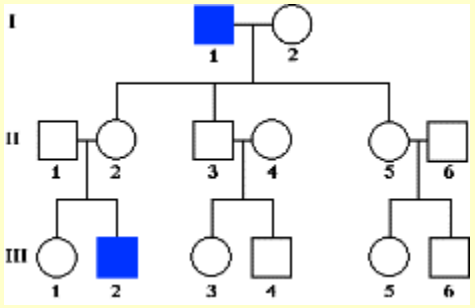
changing chapters/books

There is a continuous spectrum of phenotypic effects of DNA variations, from adaptive traits to embryonic lethality



Telethon Undiagnosed Program

Patient expectations: accessibility, diagnosis, sharing, communication



may be a new genetic disease?

clinical check up

sequencing and matching

data sharing validation

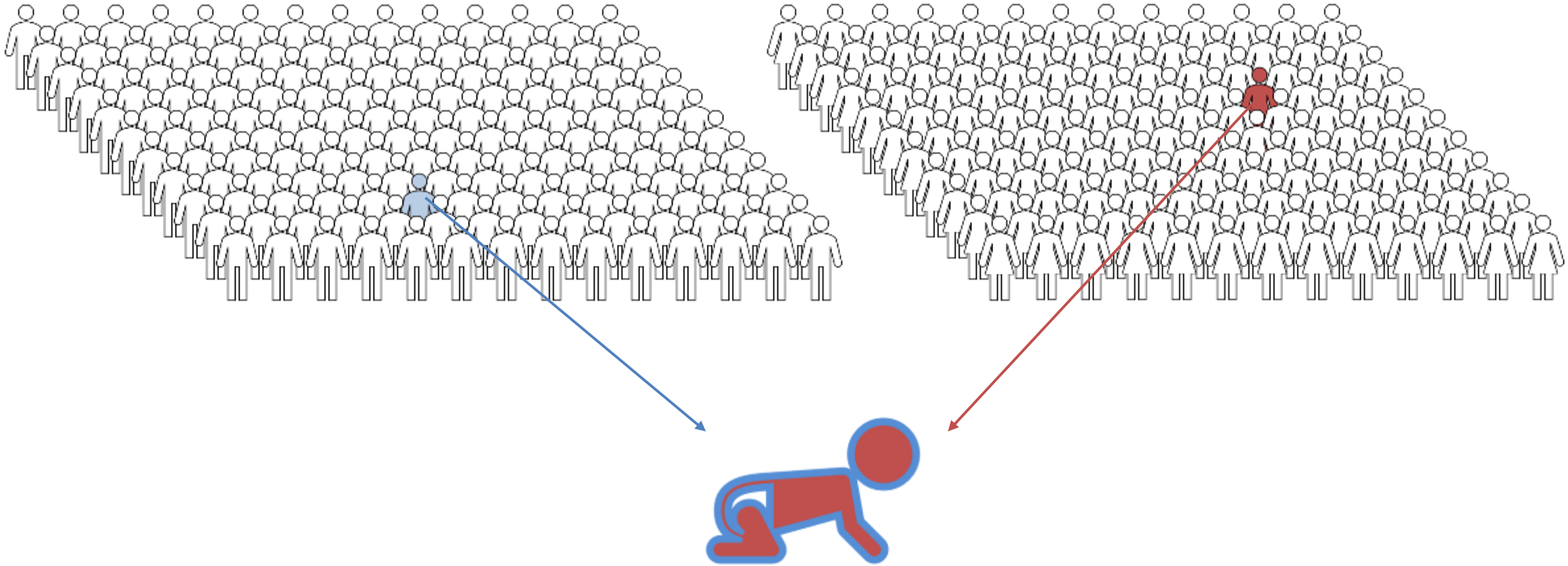
genetic disease is well known and patients receive diagnosis

genetic disease can be diagnosed in specific centers

diagnosis of a mutation in a disease gene

return of results and counselling

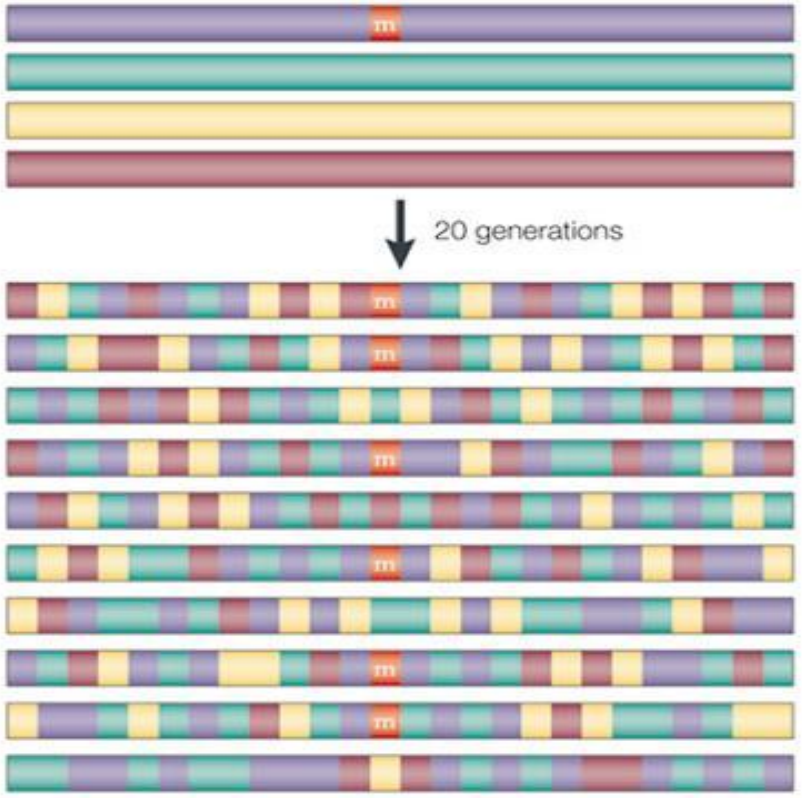
heterozygous healthy carriers

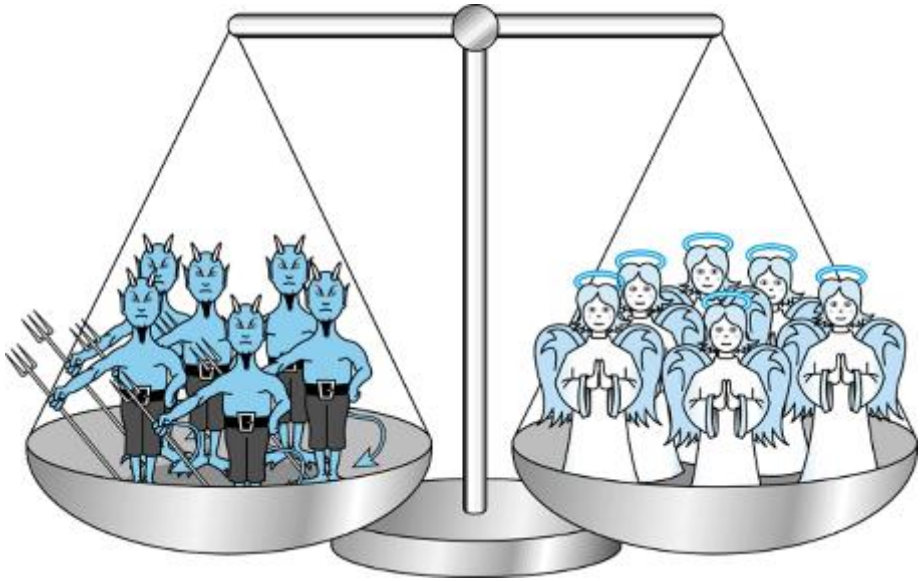


two mutations in the same gene
40-50% intellectual disability

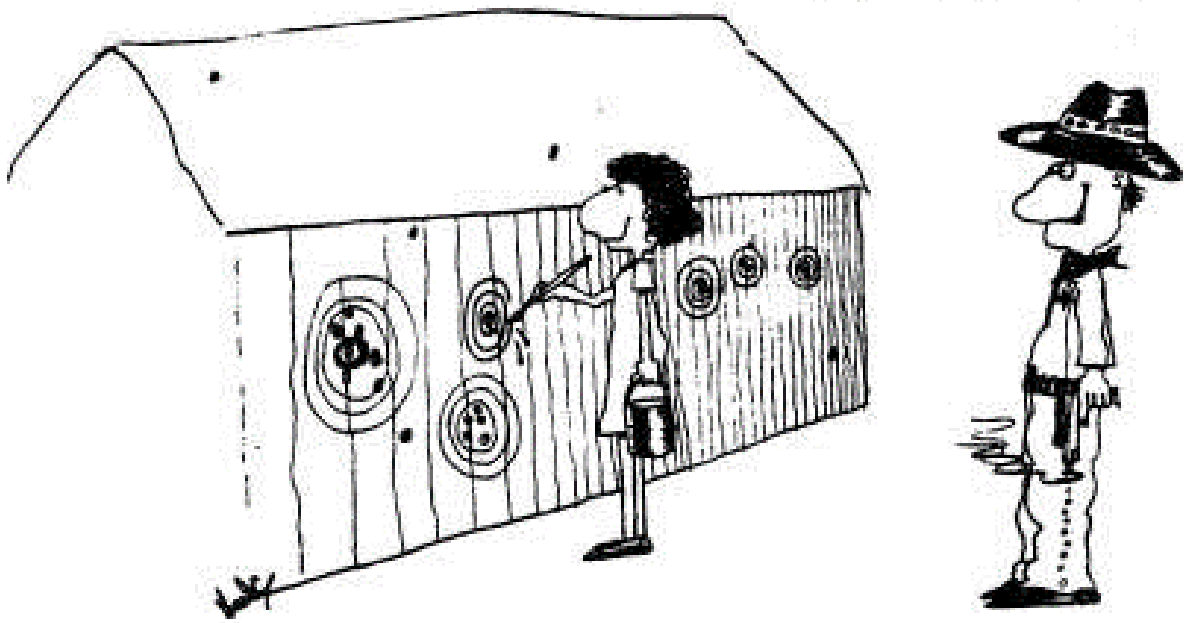
You can follow one DNA variant out of 4 Millions, but you cannot forget all the other agonist and antagonist variations

billions of genomes data are required to solve part of the association





The Texas Sharpshooter Fallacy



It arises when a person has a large amount of data at disposal, but only focuses on a small subset of that data

catechol-O-methyltransferase (COMT) gene

Val158 alleles may be associated with an advantage in the processing of aversive stimuli (warrior strategy)

Met158 alleles may be associated with an advantage in memory and attention tasks (worrier strategy)

This gene has 949 different variants and 45 copy number variants

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Family may provide evolution clue

Five siblings from Turkey who walk on all fours could provide science with an insight into human evolution, researchers have said.

The siblings may have reverted to an ancient form of locomotion (Image: Passionate Productions/BBC)

The four sisters and one brother could yield clues to why our ancestors made the transition from four-legged to two-legged animals, says a UK expert.

But Professor Nicholas Humphrey rejects the idea that there is a "gene" for bipedalism, or upright walking.

A BBC documentary about the family will be shown on Friday 17 March.

Professor Humphrey, from the London School of Economics (LSE), says that our own species' transition to walking on two feet must have been a more complex process that involved many changes to the skeleton and to the human genetic make-up.

However, a German group says a genetic abnormality does seem to be involved in the siblings' gait.

Coordination problem

BBC NEWS: VIDEO AND AUDIO

See the siblings walking on their hands and feet

VIDEO

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THE FAMILY THAT WALKS ON ALL FOURS

A family of adult human quadrupeds found living in a remote part of Turkey sparks a fierce scientific debate. A Turkish neuroscientist believes they are evolutionary throwbacks. A German geneticist believes they could hold vital clues about how man became bipeds. But are they right?

Guided by Professor Nick Humphrey and other top experts, the film weaves the scientific evidence with an intimate portrait of the family's life.

The Family That Walks On All Fours first aired in the UK on BBC2 in March 2006. The NOVA version of the film appeared on PBS in the US in November. The film has also been broadcast in 30 other countries. See the NOVA website for the US trailer

autosomal recessive cerebellar ataxia, mental retardation, and dysequilibrium syndrome-2 with homozygous **p.P856L**

Research

Homozygosity mapping and targeted genomic sequencing reveal the gene responsible for cerebellar hypoplasia and quadrupedal locomotion in a consanguineous kindred

Suleyman Gulsuner,[1] Ayse Begum Tekinay,[2] Katja Doerschner,[3,4] Huseyin Boyaci,[3,4] Kaya Bilguvar,[5,6,7] Hilal Unal,[2] Aslihan Ors,[4] O. Emre Onat,[1] Ergin Atalar,[4,8] A. Nazli Basak,[9] Haluk Topaloglu,[10] Tulay Kansu,[11] Meliha Tan,[12] Uner Tan,[13] Murat Gunel,[5,6,7] and Tayfun Ozcelik[1,2,14]

[1]*Department of Molecular Biology and Genetics, Faculty of Science, Bilkent University, Ankara 06800, Turkey;* [2]*Institute of Materials Science and Nanotechnology, Bilkent University, Ankara 06800, Turkey;* [3]*Department of Psychology, Faculty of Economics, Administrative and Social Sciences, Bilkent University, Ankara 06800, Turkey;* [4]*National Research Center for Magnetic Resonance, Bilkent University, Ankara 06800 Turkey;* [5]*Department of Neurosurgery, Yale University School of Medicine, New Haven, Connecticut 06510, USA;* [6]*Department of Neurobiology, Yale University School of Medicine, New Haven, Connecticut 06510, USA;* [7]*Department of Genetics, Center for Human Genetics and Genomics and Program on Neurogenetics, Yale University School of Medicine, New Haven, Connecticut 06510, USA;* [8]*Department of Electrical and Electronics Engineering, Faculty of Engineering, Bilkent University, Ankara 06800, Turkey;* [9]*NDAL Laboratory, School of Arts and Sciences, Bogazici University, Istanbul 34342, Turkey;* [10]*Department of Pediatric Neurology, Ihsan Dogramaci Children's Hospital, Ankara 06100, Turkey;* [11]*Department of Neurology, Hacettepe University Faculty of Medicine, Ankara 06100, Turkey;* [12]*Department of Neurology, Baskent University Faculty of Medicine, Ankara 06490, Turkey;* [13]*Department of Physiology, Cukurova University Faculty of Medicine, Adana 01330, Turkey*

The biological basis for the development of the cerebro-cerebellar structures required for posture and gait in humans is poorly understood. We investigated a large consanguineous family from Turkey exhibiting an extremely rare phenotype associated with quadrupedal locomotion, mental retardation, and cerebro-cerebellar hypoplasia, linked to a 7.1-Mb region of homozygosity on chromosome 17p13.1–13.3. Diffusion weighted imaging and fiber tractography of the patients' brains revealed morphological abnormalities in the cerebellum and corpus callosum, in particular atrophy of superior, middle, and inferior peduncles of the cerebellum. Structural magnetic resonance imaging showed additional morphometric abnormalities in several cortical areas, including the corpus callosum, precentral gyrus, and Brodmann areas BA6, BA44, and BA45. Targeted sequencing of the entire homozygous region in three affected individuals and two obligate carriers uncovered a private missense mutation, WDR81 p.P856L, which cosegregated with the condition in the extended family. The mutation lies in a highly conserved region of WDR81, flanked by an N-terminal BEACH domain and C-terminal WD40 beta-propeller domains. WDR81 is predicted to be a transmembrane protein. It is highly expressed in the cerebellum and corpus callosum, in particular in the Purkinje cell layer of the cerebellum. *WDR81* represents the third gene, after *VLDLR* and *CA8*, implicated in quadrupedal locomotion in humans.

[Supplemental material is available for this article.]

Uner Tan Syndrome : reverse evolution

long range information, phasing, structural variant detection
and copy number determination

10X GENOMICS

illumina

PCR-free WGS of trios