What are good drug targets and how to find them?

Mathematical and Computational Biology in Drug Discovery (MCBDD), Module I

Dr. Jitao David Zhang, February - March 2025

Outline

- Always write down numbers and possibilities for inference.
- We review biological foundations of target identification.
- Genetics doubles the success rate of target identification.

Exercise of *inference* (I)

I have three pills and two hamsters. The pills are optically identical. The two hamsters are also optically identical, though there are subtle differences such that:

1. Pill A makes both hamsters sleep.
2. Pill B makes neither animal sleep.
3. Pill C makes one animal sleep but not the other.

Now I pick a pill, feed it to one hamster, and the hamster falls asleep. What's the probability that the same pill makes the other animal sleep, too?

Exercise of *inference* (II)

The company *Fränzi and Friends* developed a new quick test at home for SARS-Cov-2, which is pending regulatory agency's review. The test has been shown to have a sensitivity of 99% and a specificity of 99%.

Suppose that Fred uses the test by *Fränzi and Friends* and the test was positive. Assume that 5% of the population is in fact infected. Was is your guess about the probability that Fred is indeed infected?

Ground truth

Prediction	Positive	Negative
Positive	True Positive (TP)	False Positive (FP)
Negative	False Negative (FN)	True Negative (TN)

Sensitivity=TP/(TP+FN)
Specificity=TN/(FP+TN)

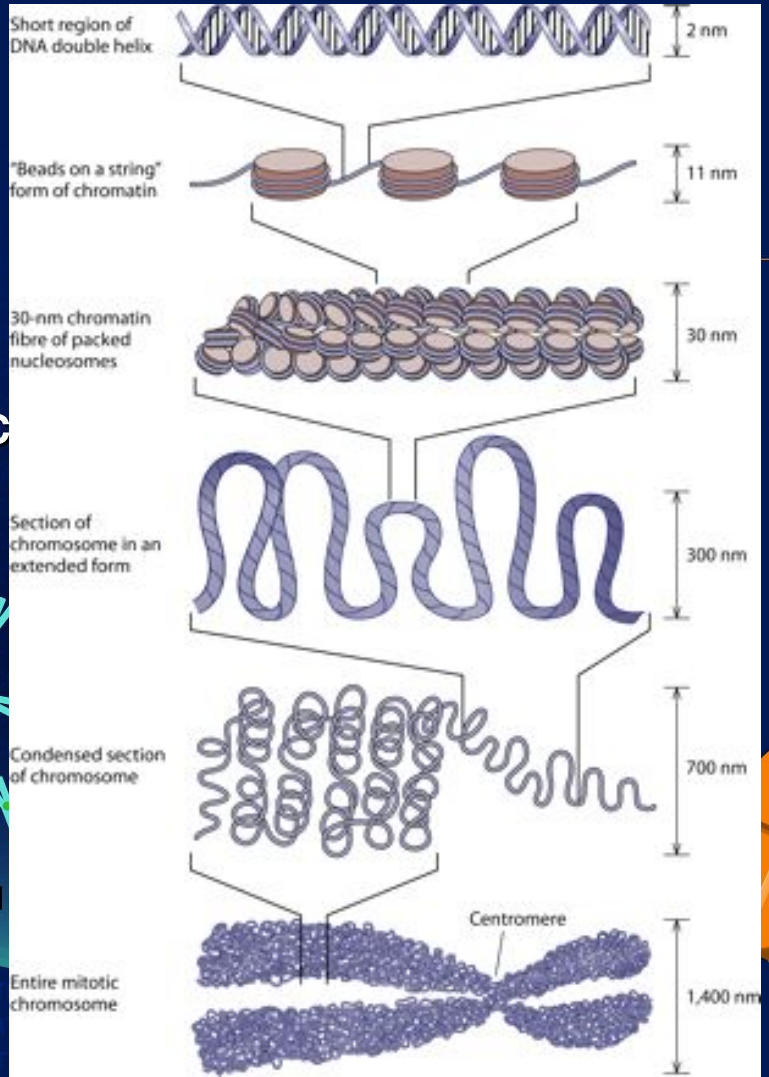
Example

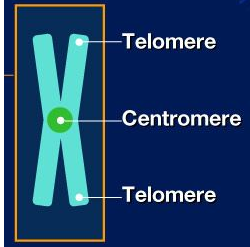
Hidden truth

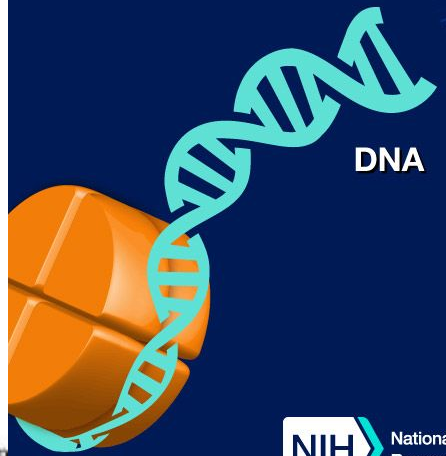
Diagnosis	Healthy	Disease
Healthy	45	5
Disease	10	40

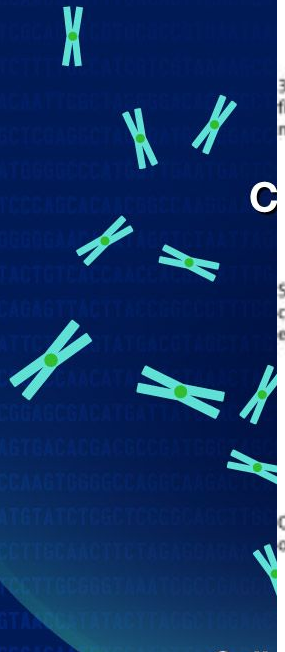
Sensitivity=45/(45+10)=81.8%
Specificity=40/(5+40)=88.9%

Chromosome



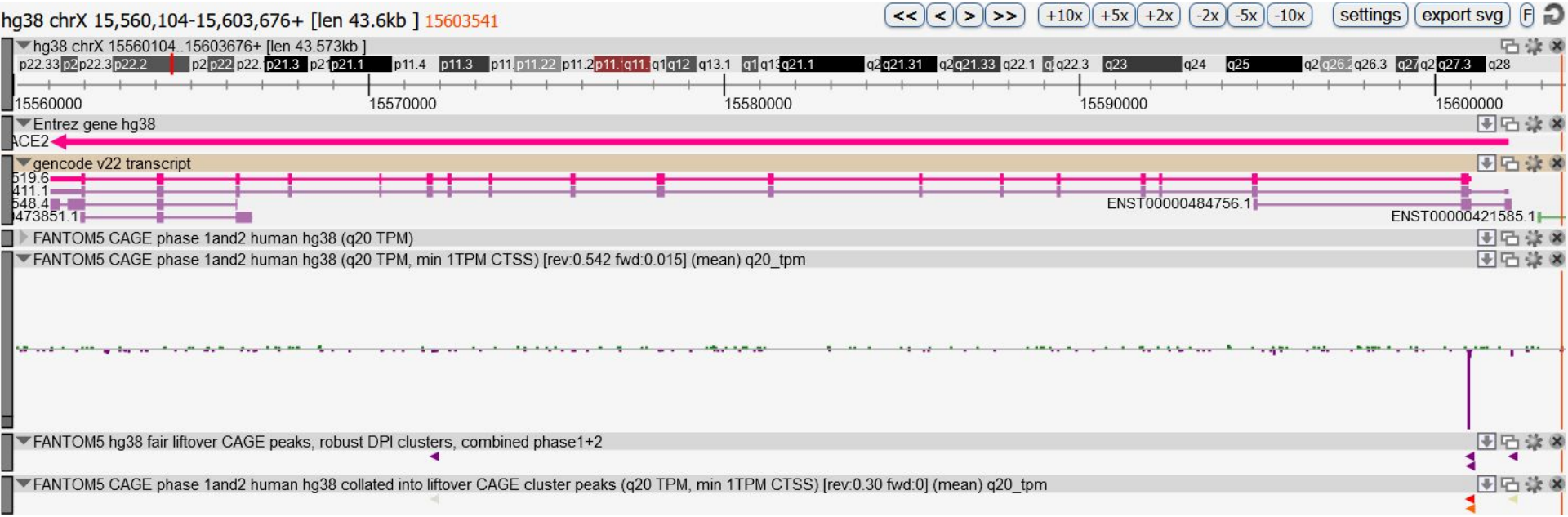






NIH National Human Genome Research Institute

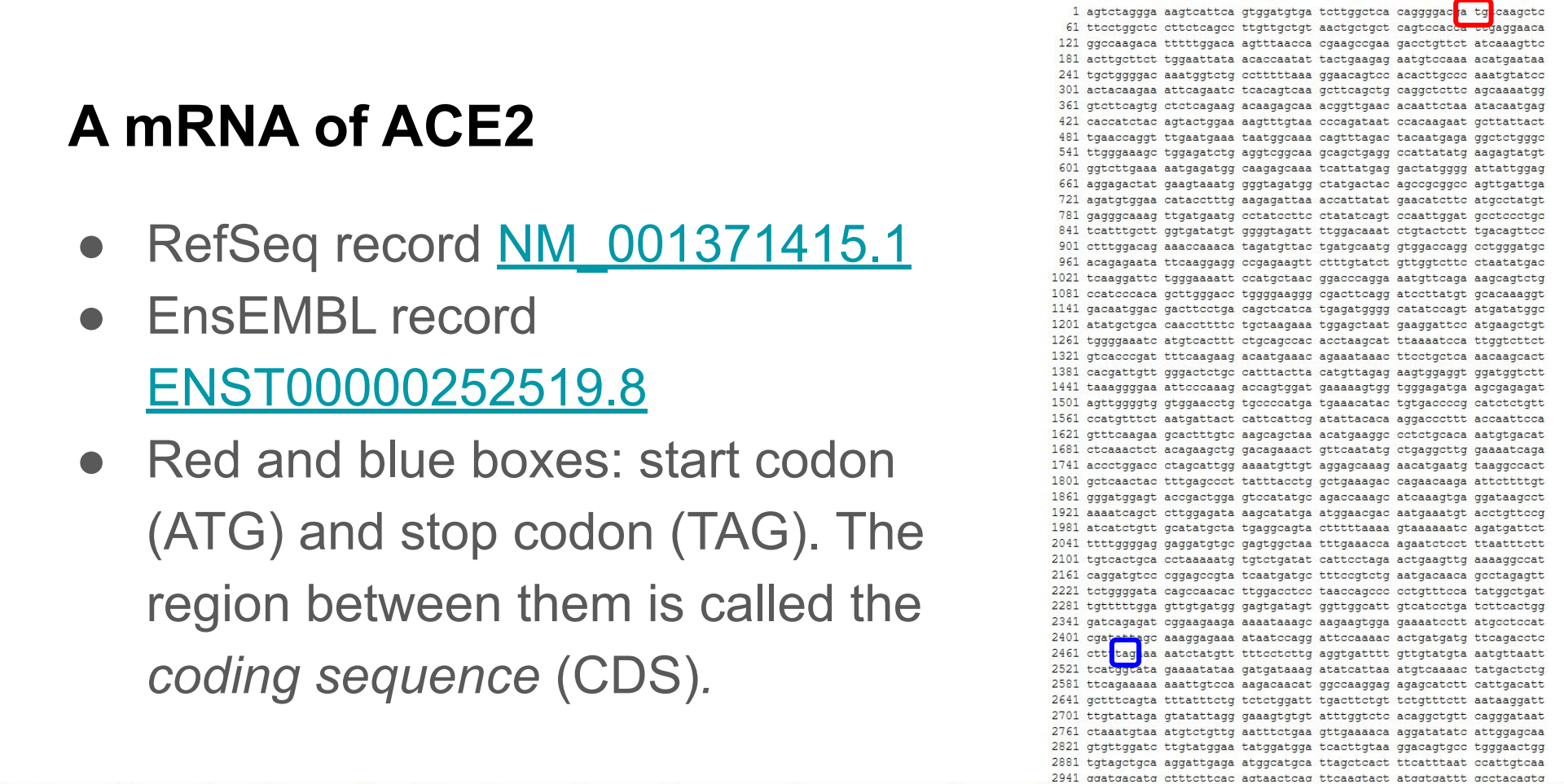
Gene structure and gene expression



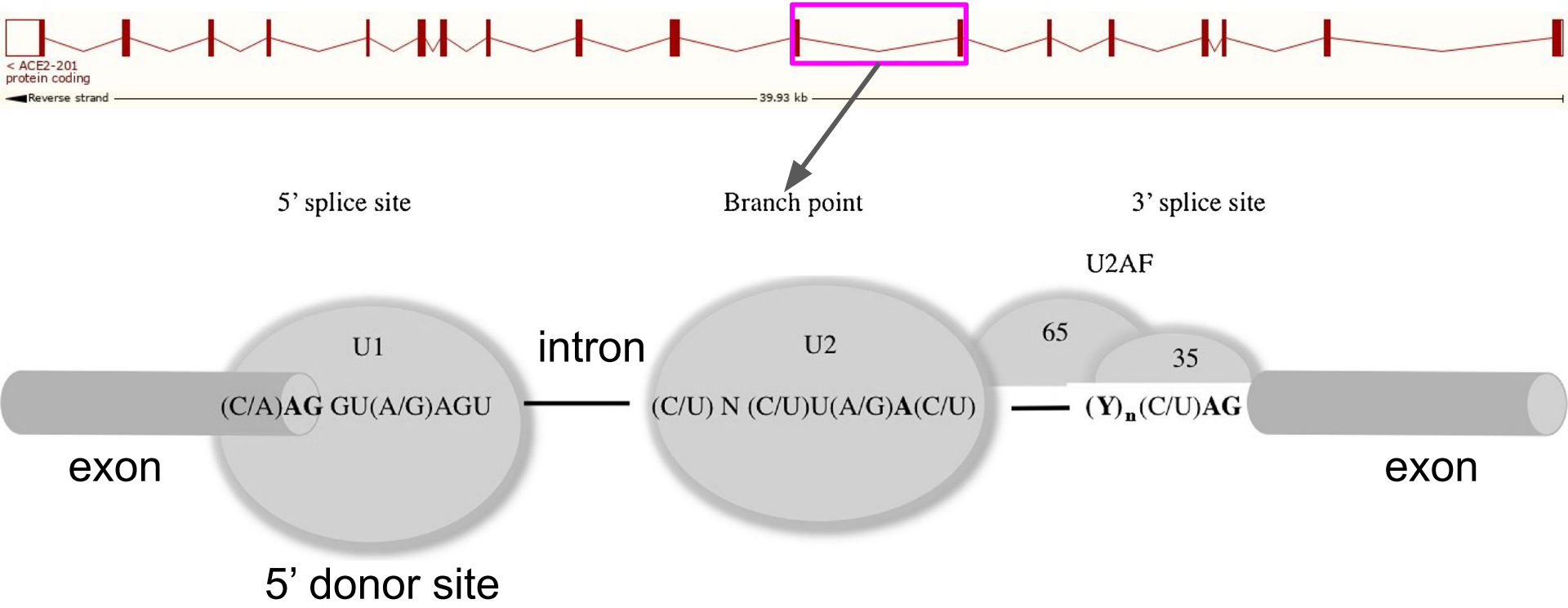
ACE2 viewed in [FANTOM5/ZENBU]

A mRNA of ACE2

- RefSeq record NM_001371415.1
- EnsEMBL record ENST00000252519.8
- Red and blue boxes: start codon (ATG) and stop codon (TAG). The region between them is called the *coding sequence* (CDS).



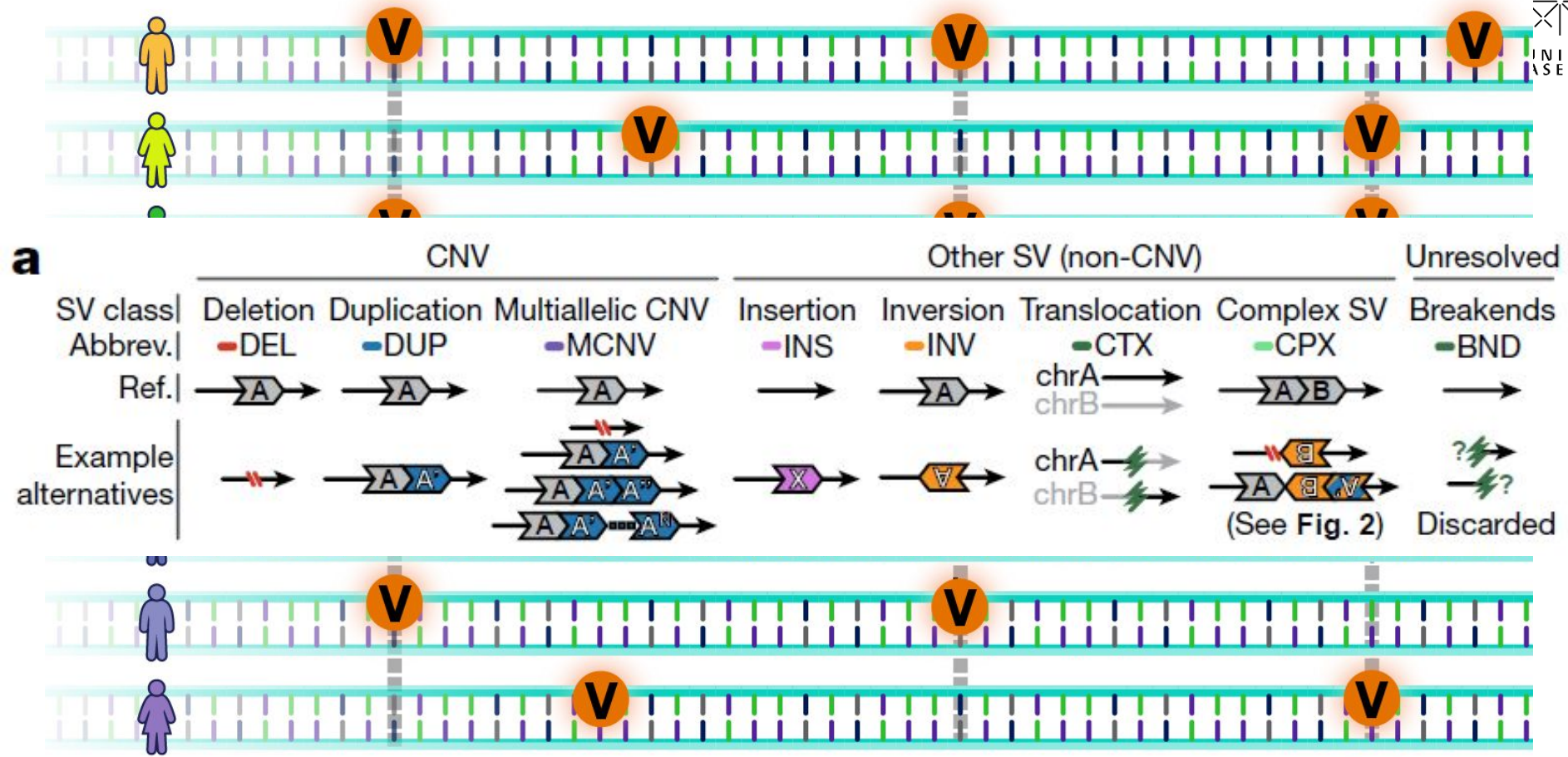
The splicing code



Person one

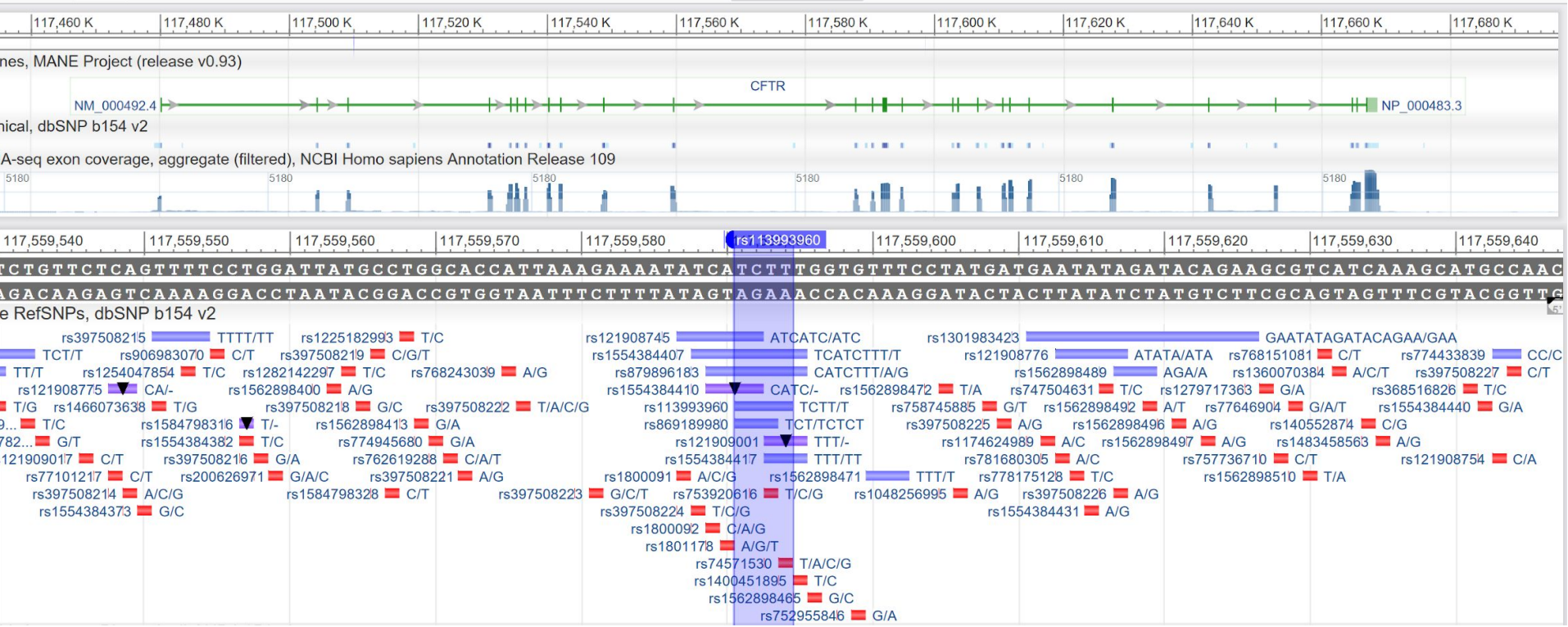
A G A C G C T

Variant ID	Source	HGVS Consequence	VEP Annotation	LoF Curation	Clinical Significance	Flags	Allele Count
17-7579817-C-T	E	c.74+22G>A	intron		Likely benign		1
17-7579831-C-T	E	c.74+8G>A	splice region		Likely benign		1
17-7579924-G-A	E G	c.-12C>T	5' UTR		Likely benign		7
17-7579932-G-C	E	c.-20C>G	5' UTR		Likely benign		2
17-7578142-C-A	E G	c.672+35G>T	intron		not provided		9
17-7577142-C-A	E	p.Gly266Ter	stop gained		Pathogenic		1
17-7578188-C-A	E	p.Glu221Ter	stop gained		Pathogenic		1
17-7578263-G-A	E	p.Arg196Ter	stop gained		Pathogenic		1
17-7576928-TAGGAA...	E	c.920-14_920-3delTGC...	splice region		Uncertain significance		2
17-7578171-C-A	E G	c.672+6G>T	splice region		Uncertain significance		2
17-7578171-C-T	E	c.672+6G>A	splice region		Uncertain significance		1
17-7579934-C-T	G	c.-22G>A	5' UTR		Uncertain significance		1
17-7565206-T-A	G	c.*51A>T †	3' UTR				1
17-7565222-C-T	G	c.*35G>A †	3' UTR				1


a
CNV
Other SV (non-CNV)
Unresolved
SV class
Deletion
Duplication
Multiallelic CNV
Insertion
Inversion
Translocation
Complex SV
Breakends
Abbrev.
DEL
DUP
MCNV
INS
INV
CTX
CPX
BND
Ref.
chrA
chrB
Example alternatives
(See Fig. 2)
Discarded

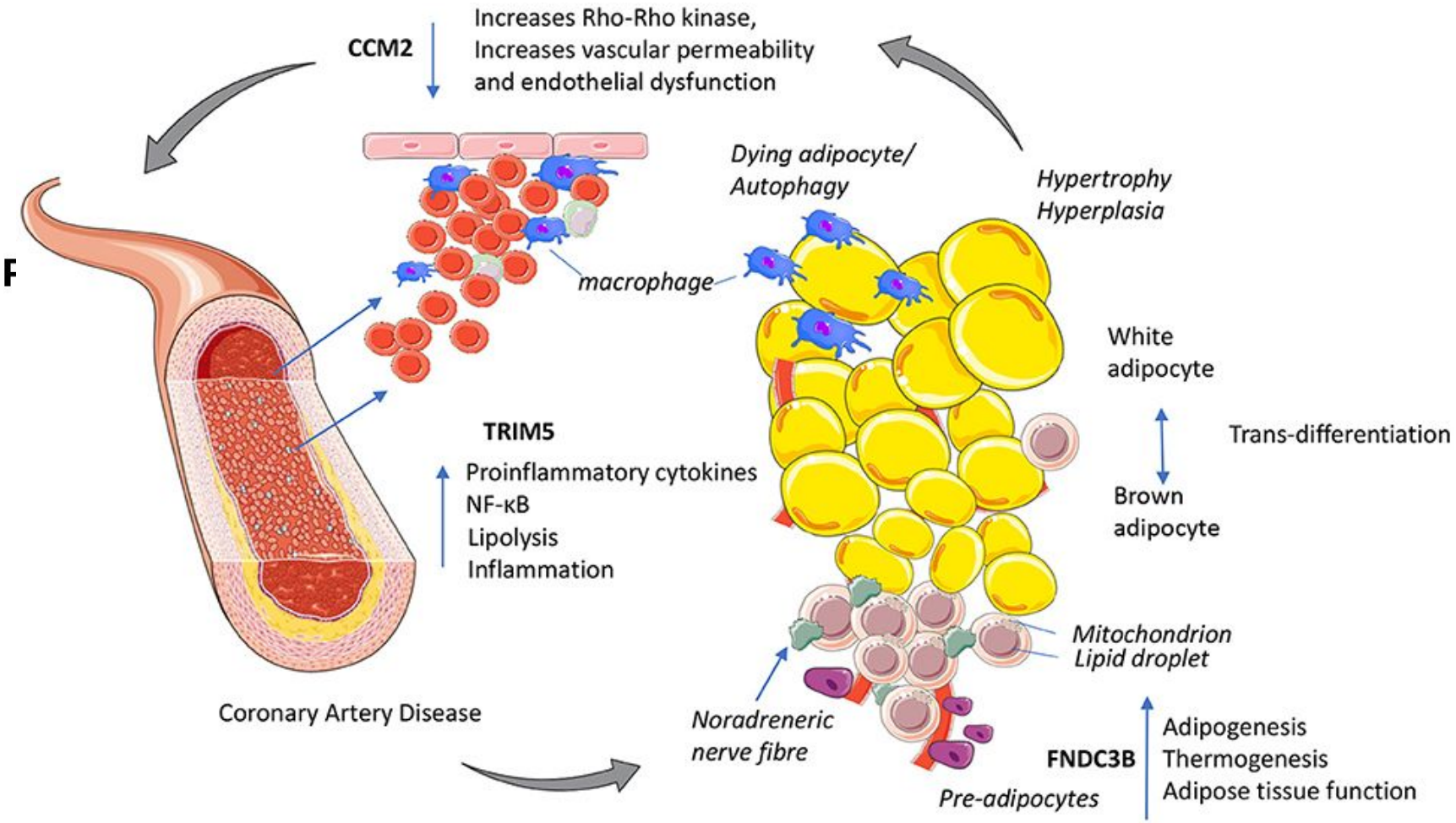
Example of monogenic disease

Cystic fibrosis



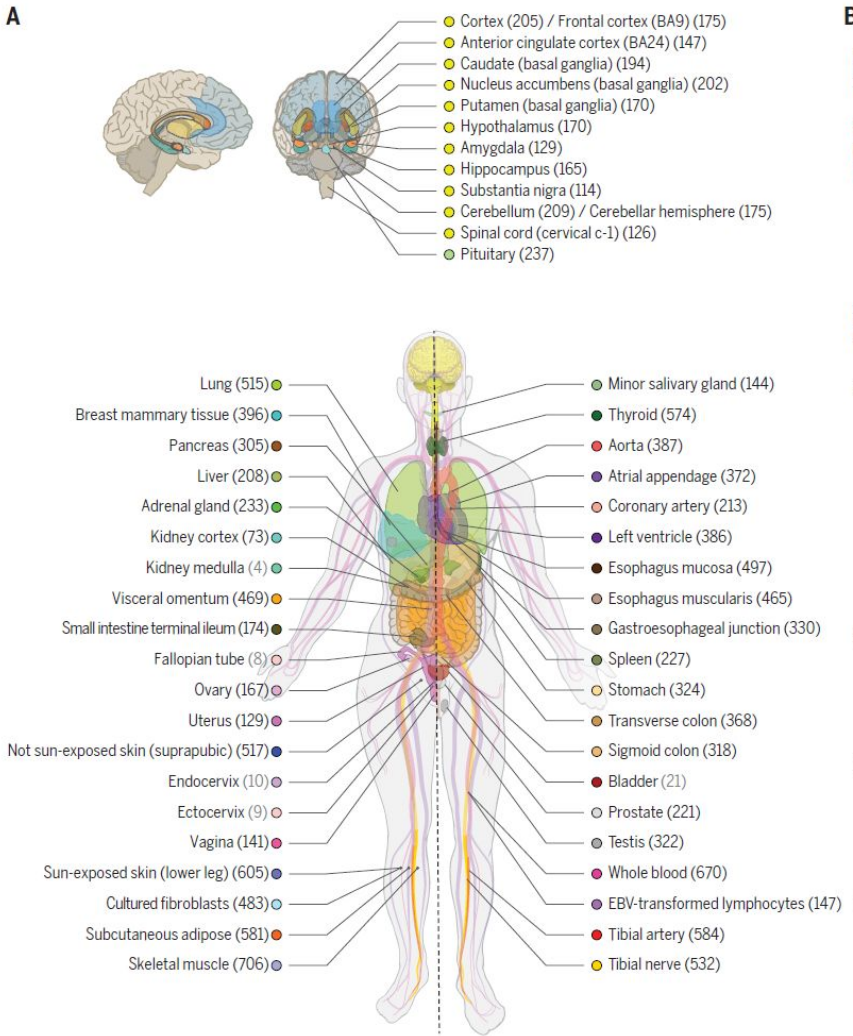
The *CFTR* gene (Chr 7), and rs113993960 (F508del), the most common cause of cystic fibrosis (CF). Read more about CFTR modulator therapies (*CF Foundation*), and a deep coverage by Sarah Zhang (*Atlantic*).

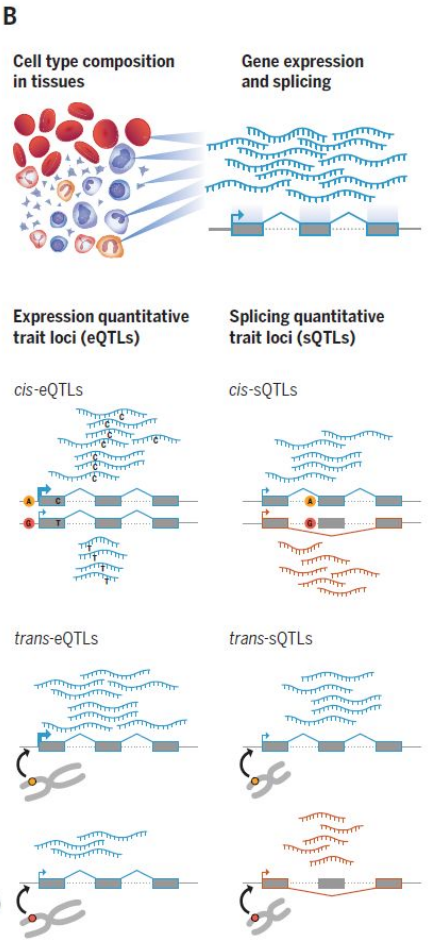
Example of complex disease



Dna Se

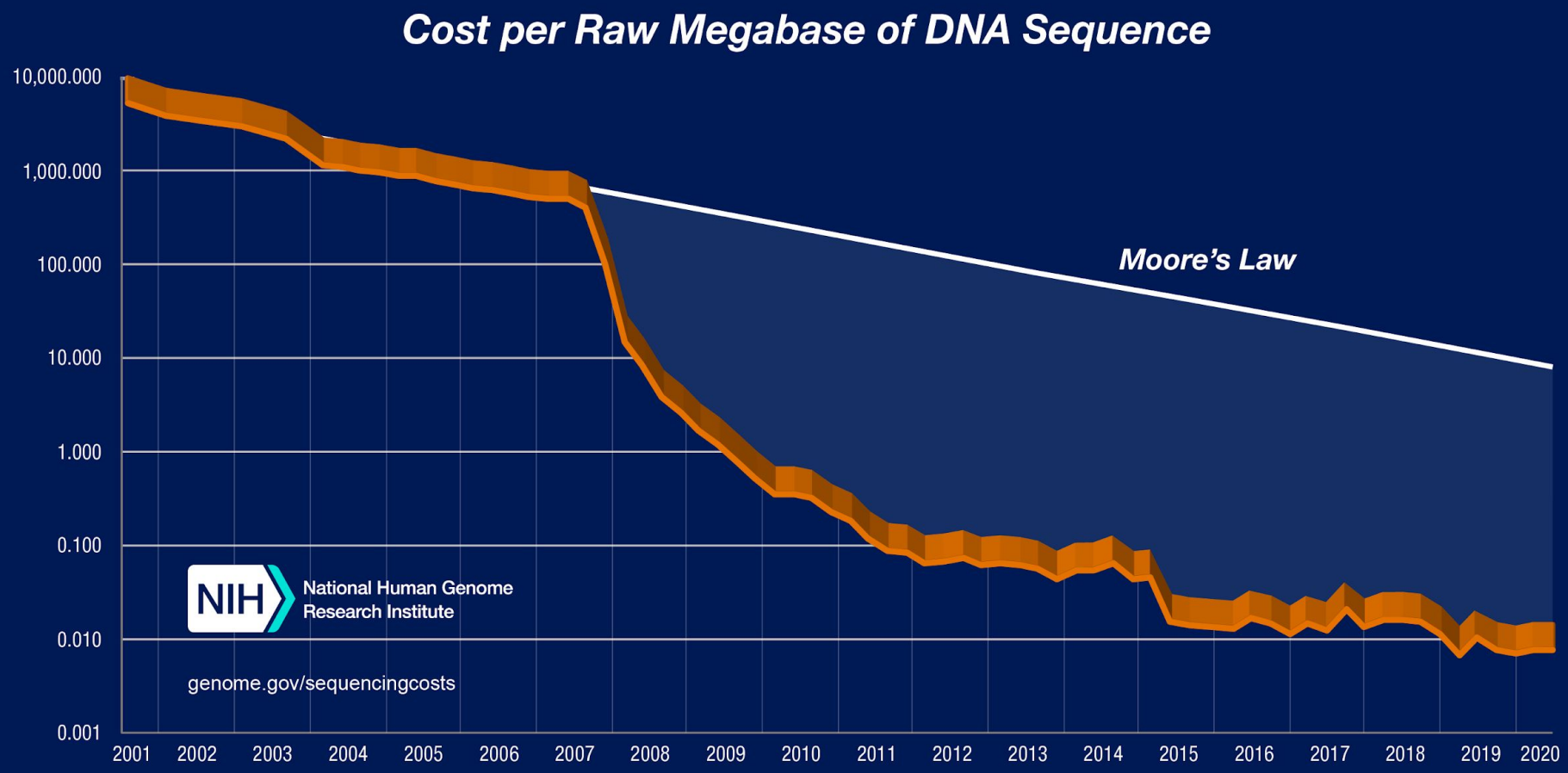
FACT SHEETS
genome.gov





GTEx (v8)

National Human Genome Research Institute


Cost per Raw Megabase of DNA Sequence
10,000.000
1,000.000
100.000
10.000
1.000
0.100
0.010
0.001
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
2001
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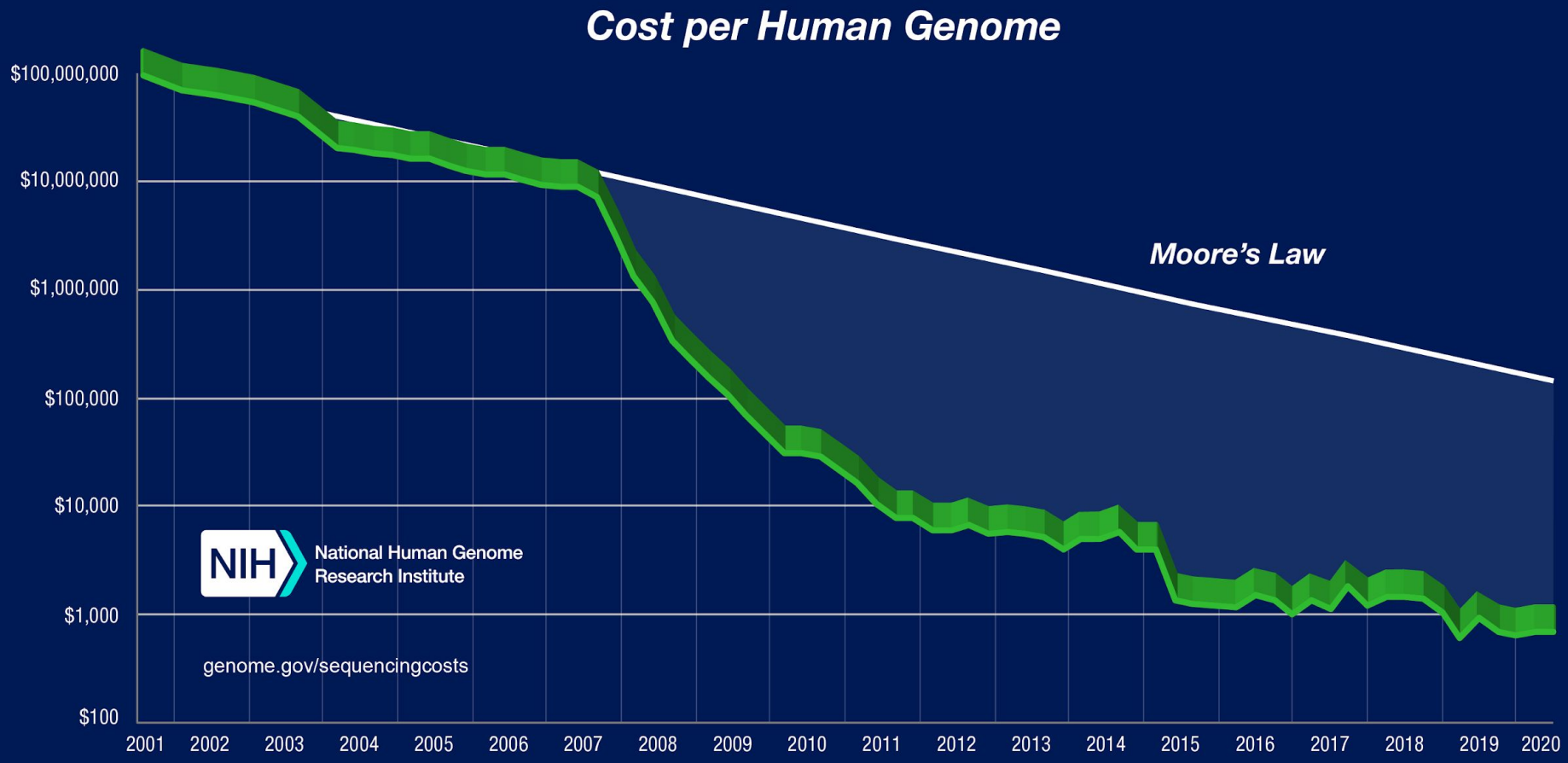
Cost per Human Genome
$100,000,000
$10,000,000
$1,000,000
$100,000
$10,000
$1,000
$100
Moore's Law
NIH
National Human Genome Research Institute
genome.gov/sequencingcosts
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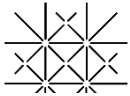
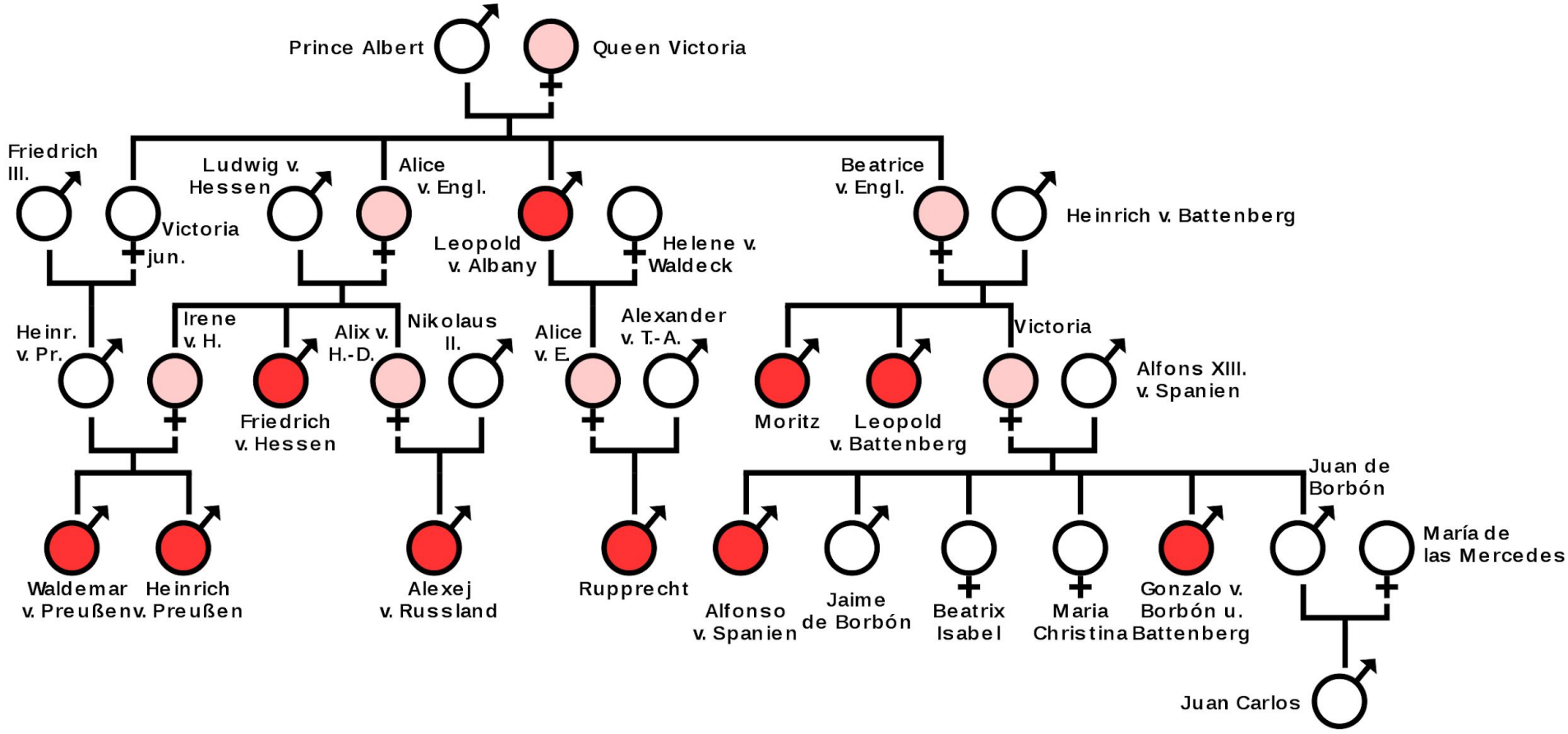
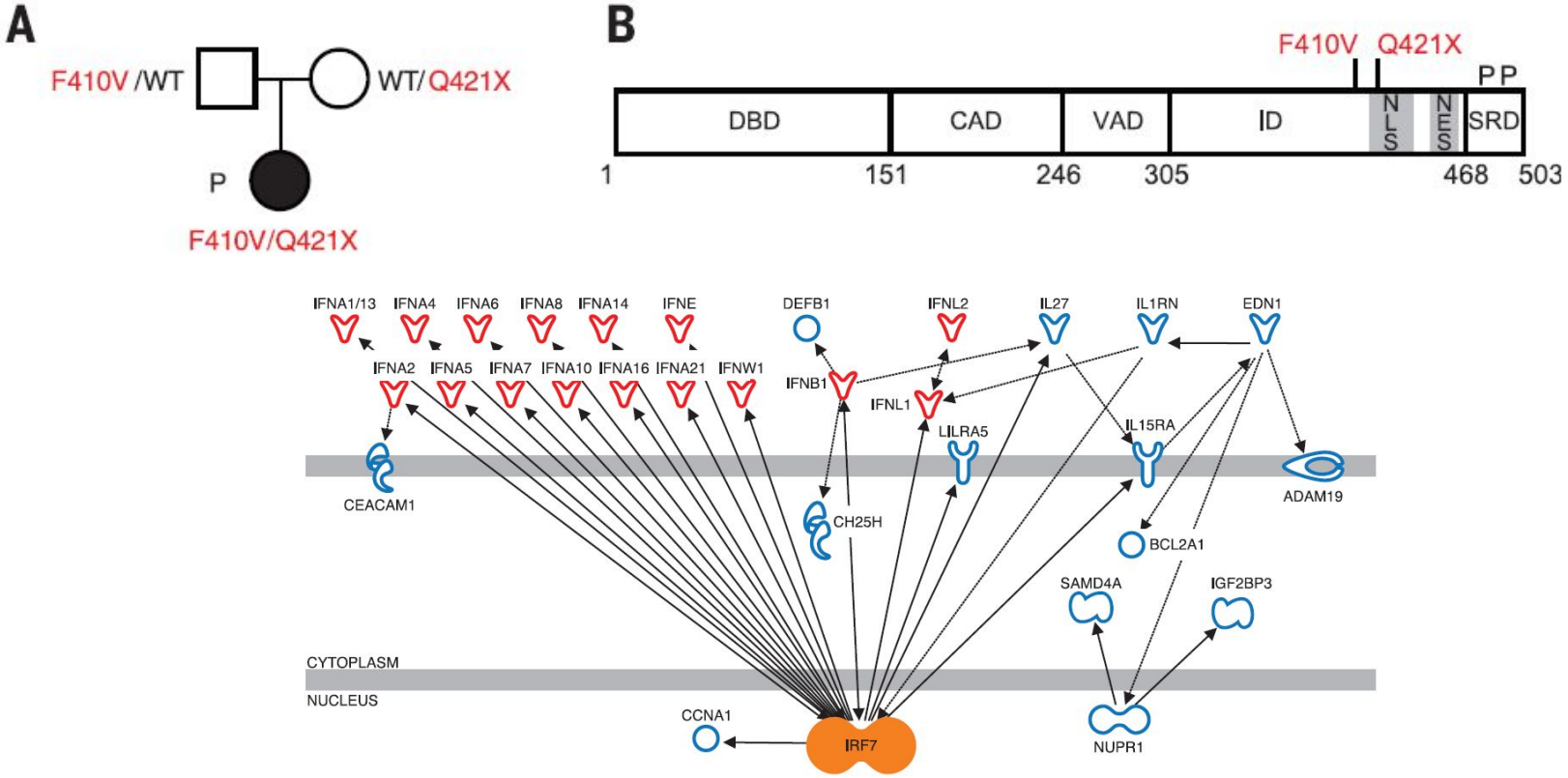
Haemophilia in the descendants of Queen Victoria





Prussia (1889-1945) | Prussia (1900-1904) | of Russia (1904-1918) | Teck (1907-1928) | Asturias (1907-1938) | Spain (1914-1934)

Life-threatening influenza infection in human IRF7 deficiency detected by trio sequencing



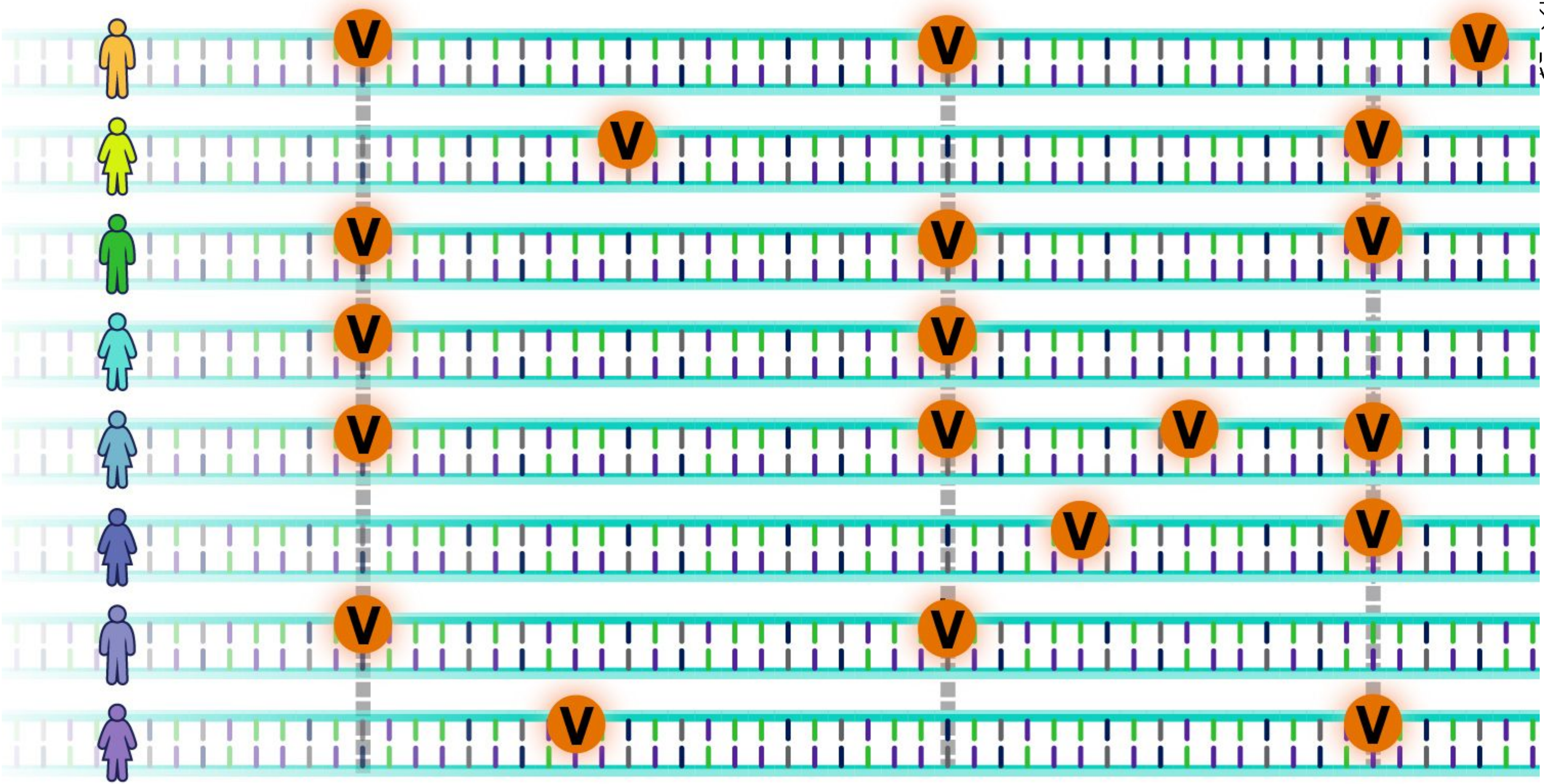
Genome biology in one screenshot

ACE2 viewed in [NCBI Genome Browser]

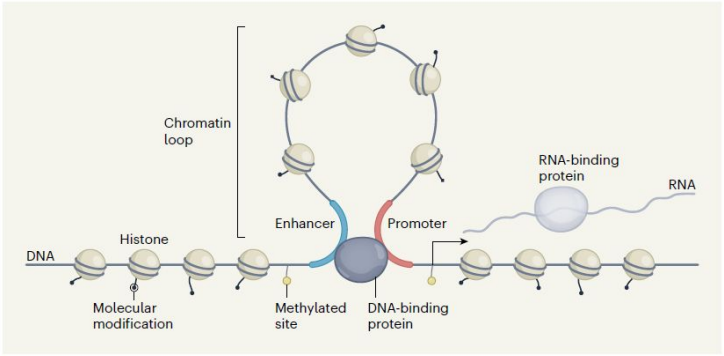
The Human Genome and Variations

Gene Structure and gene expression

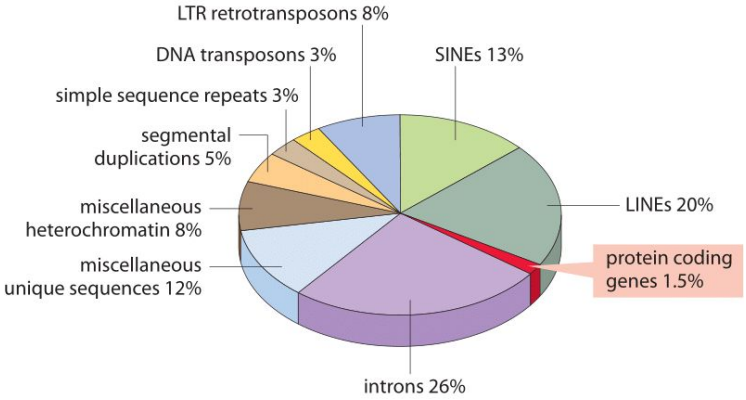
DNA and RNA sequencing

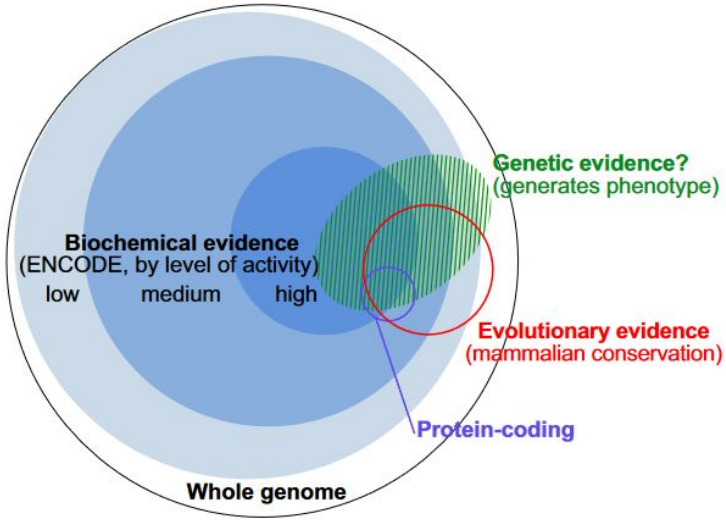

V

Much of the genome is junk, some is regulatory



main components of the human genome

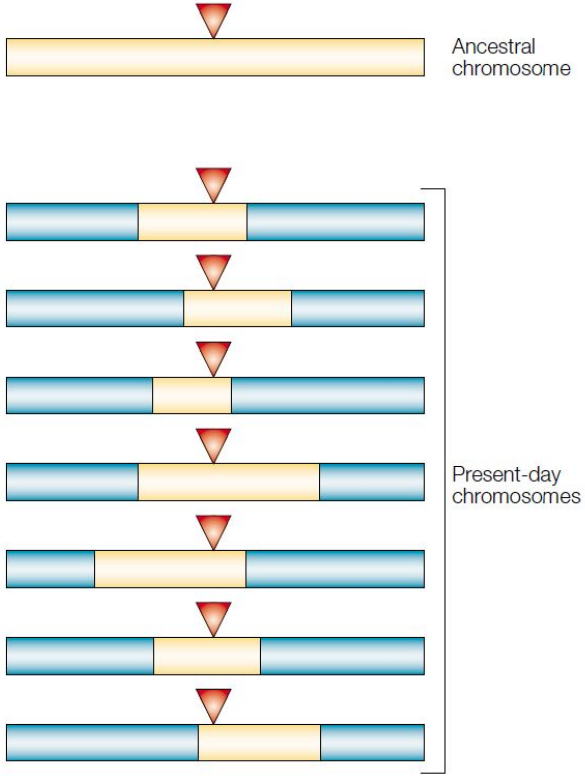




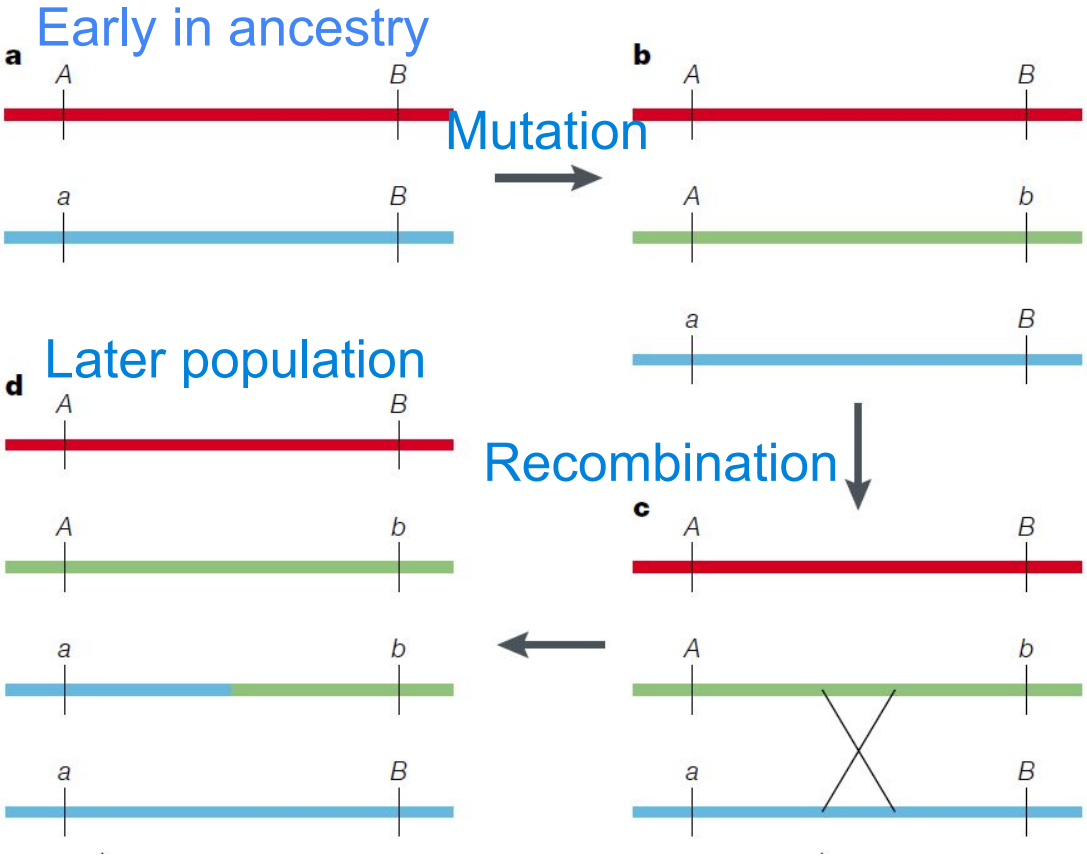
1. Gregory, T. R. Synergy between sequence and size in Large-scale genomics. Nat Rev Genet 6, 699–708 (2005).
2. Kellis, M. et al. Defining functional DNA elements in the human genome. Proceedings of the National Academy of Sciences 111, 6131–6138 (2014).

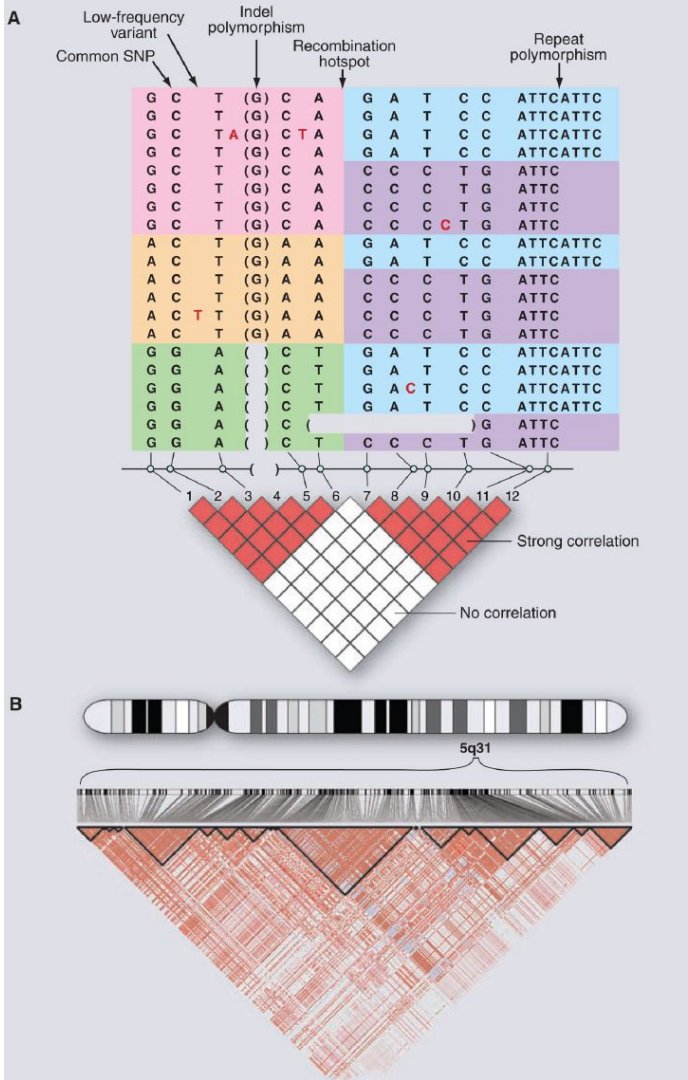
Linkage Disequilibrium in human genome

Particular alleles (single gene copies) at neighbouring loci tend to be co-inherited. For tightly linked loci, this might lead to associations between alleles in the population. This property is known as linkage disequilibrium (LD).



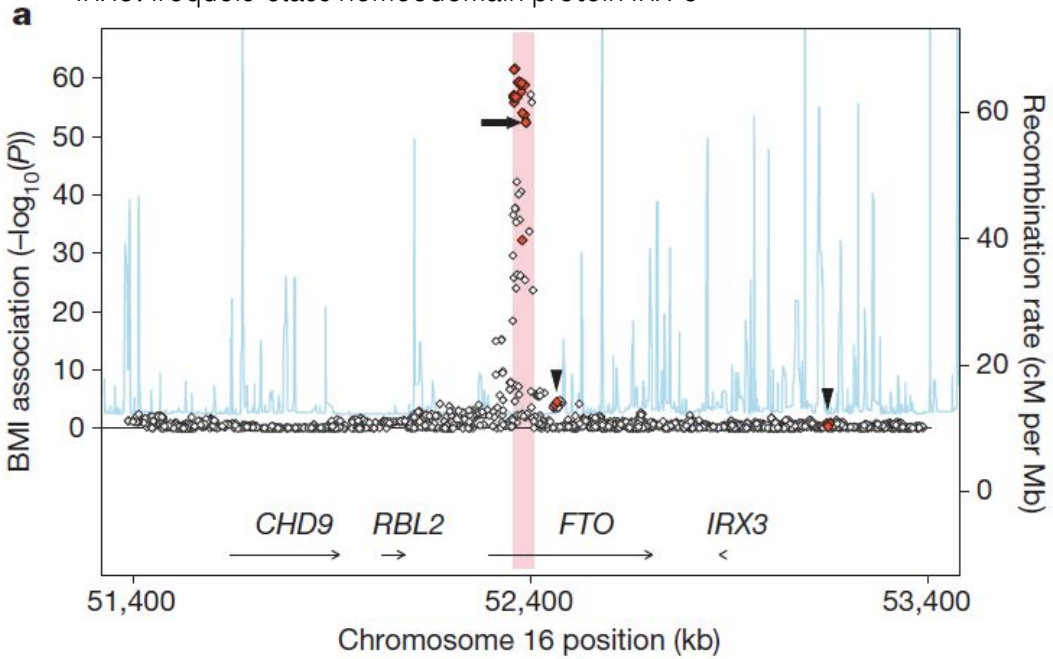
Population genetics helps with disease mapping

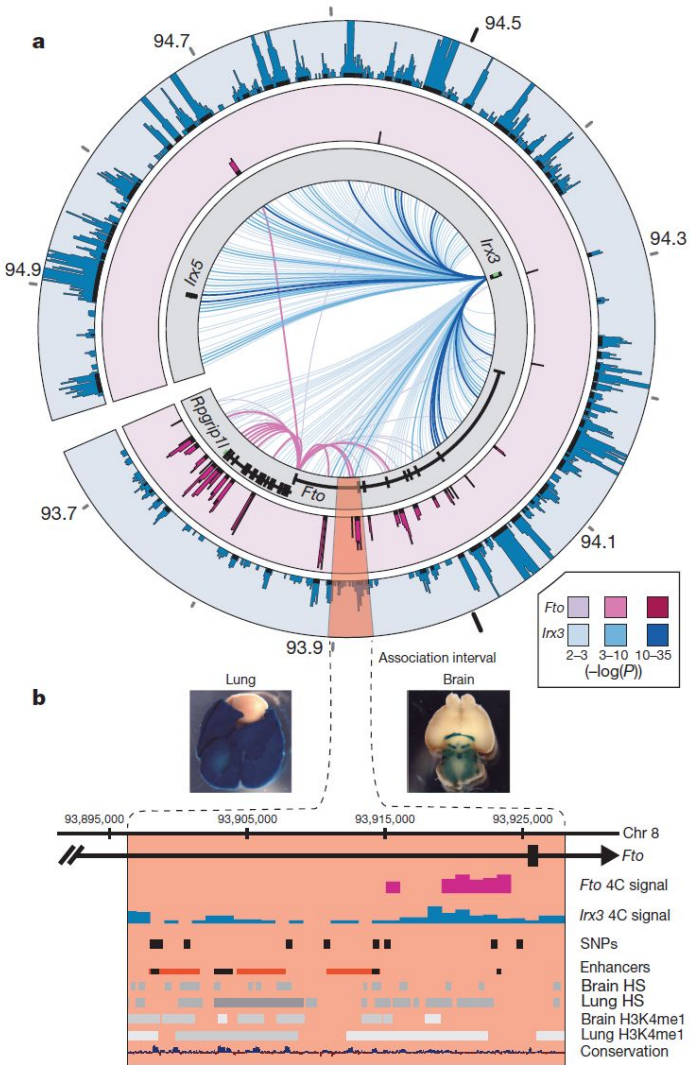




Is FTO a good target for obesity?

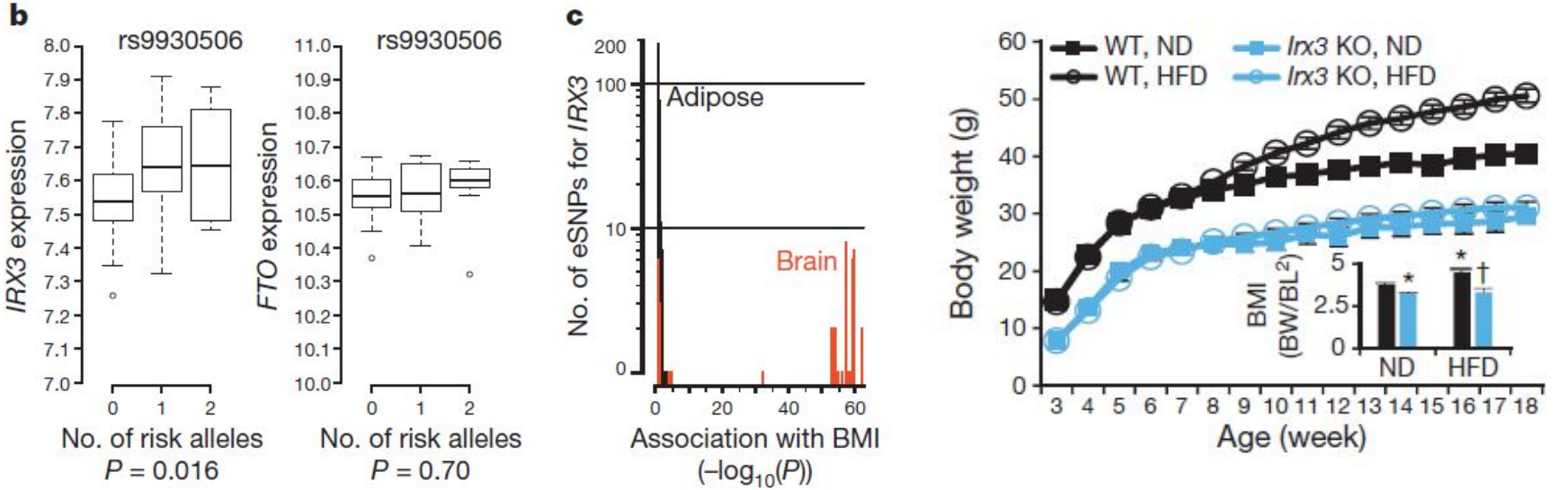
FTO: fat mass and obesity-associated gene, which hosts rs9930506
IRX3: Iroquois-class homeodomain protein IRX-3





Smemo, S. et al. Obesity-associated variants within FTO form long-range functional connections with IRX3. Nature 507, 371–375 (2014).

SNPs in *FTO* gene interacts with promoter of *IRX3*, the knockout of which reduces body weight



End of the first lecture on 28.02.25

Genetics helps to find drug targets

The hypothesis: genes that are associated with disease-associated traits are more likely to be a valid drug target for an indication with similar phenotypes than genes that are not associated. The more causal the association, the more likely.

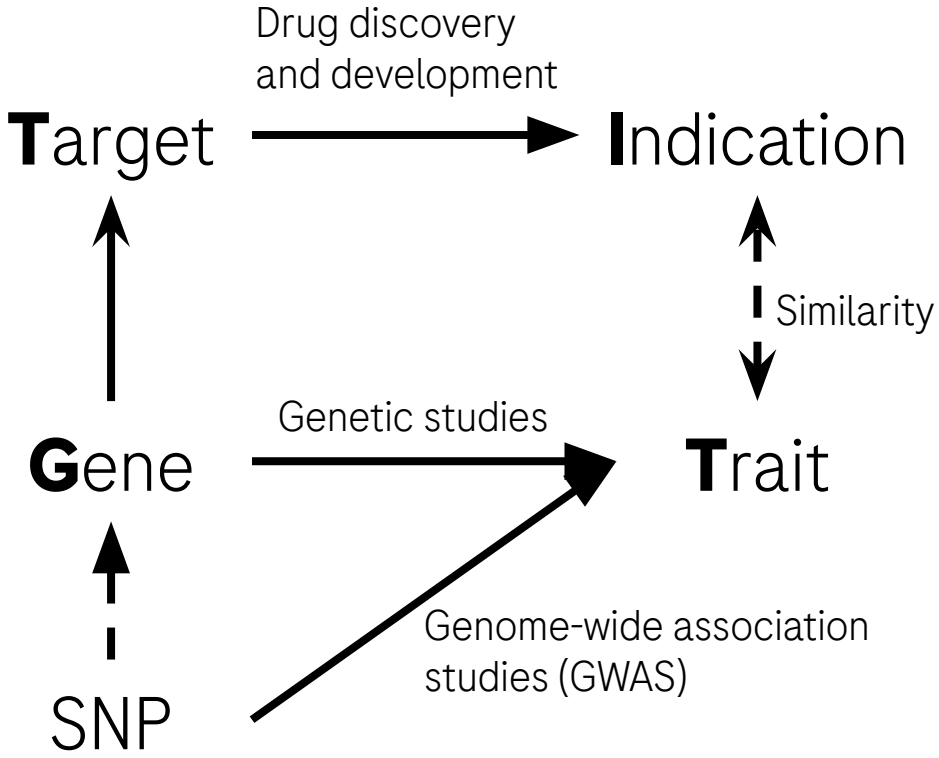


Illustration of the definition of genetic support for drug target

drug programs

gene	indication MeSH ID	indication MeSH term	phase
ABCC8	D000070642	Brain injury, traumatic	Phase II
ABCC8	D003924	Diabetes Mellitus, Type 2	Launched
FFAR1	D003924	Diabetes Mellitus, Type 2	Phase III
IL1R1	D003924	Diabetes Mellitus, Type 2	Phase II

similarity = 1.0

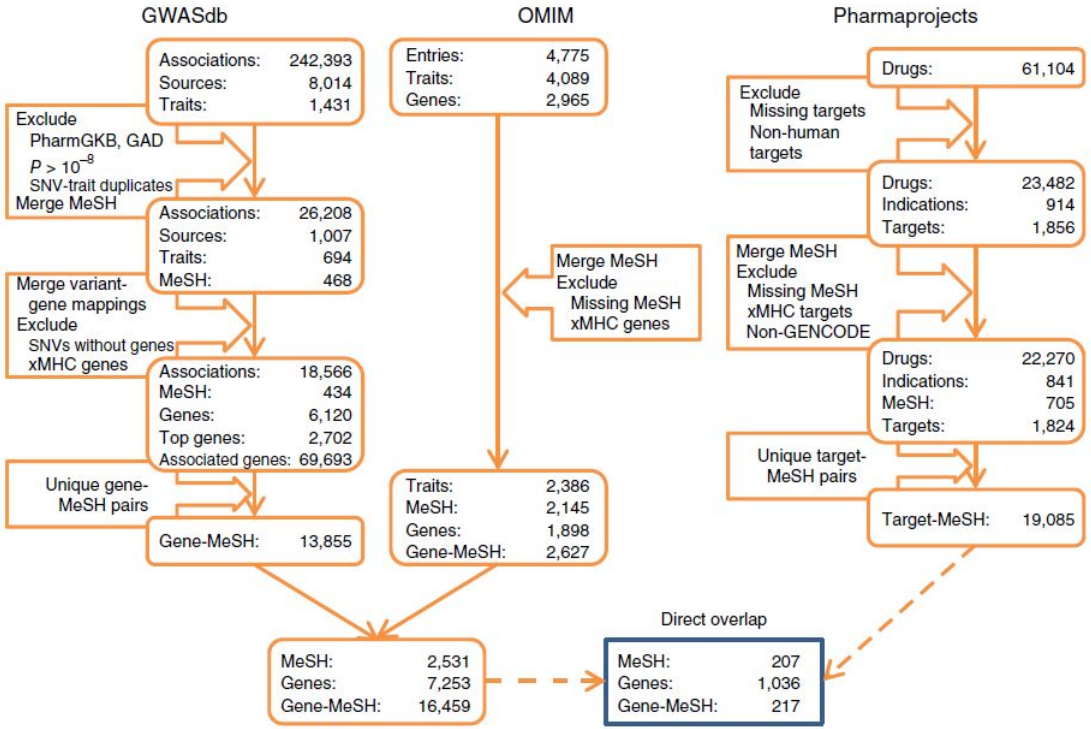
human genetic associations

gene	association MeSH ID	association MeSH term	source
ABCC8	D003924	Diabetes Mellitus, Type 2	OTG
ABCC8	D003924	Diabetes Mellitus, Type 2	OMIM
ABCC8	D007003	Hypoglycemia	OMIM
ABCC8	D000428	Alcohol Drinking	Genebass
IL1R1	D015212	Inflammatory Bowel Diseases	OTG

- MeSH: Medical Subject Headings (NIH)
- OTG: Open Targets Genetics, with an example of ABCC8
- OMIM: Online Mendelian Inheritance in Man
- Genebass: Gene(exome)-based association studies, with an example of ABCC8

Minikel, Eric Vallabh, Jeffery L. Painter, Coco Chengliang Dong, and Matthew R. Nelson. 2024. “Refining the Impact of Genetic Evidence on Clinical Success.” Nature 629 (8012): 624–29. https://doi.org/10.1038/s41586-024-07316-0.

Impact of genetics on target identification: a factor of ~2 estimated by Nelson *et al.*



Disease ← Gene ← Drug

GWASdb: a database for human genetic variants identified by genome-wide association studies (Li et al., 2012, now almost obsolete). Alternatives include the GWAS Catalog (NHGRI-EBI).

Pharmaprojects: commercial tool to track and analyse global drug R&D landscape (the CITELINE company).

Nelson, Matthew R. et al. 2015. "The Support of Human Genetic Evidence for Approved Drug Indications." Nature Genetics 47 (8): 856–60. https://doi.org/10.1038/ng.3314.

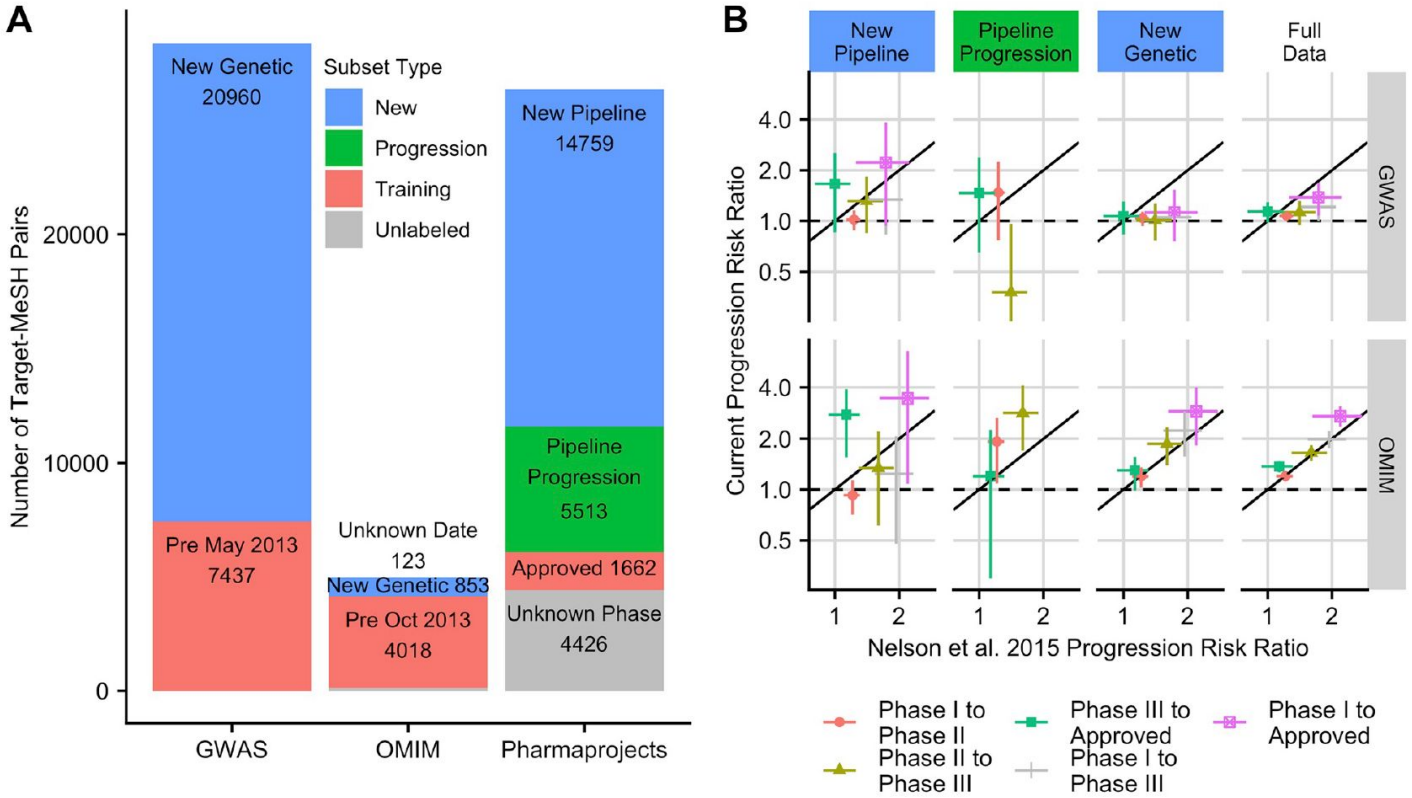
Nelson *et al.* inferred that genetic support offers an likelihood ratio ~2

Table 1 The relative value of genetic support for the probability that a target-indication pair progresses along the drug development pipeline, based on historical drug trial information

	p(progress|genetic support)/(progress|no genetic support)		
Progression	GWASdb and OMIM	GWASdb	OMIM
Phase I to phase II	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.2 (1.1–1.3)
Phase II to phase III	1.5 (1.3–1.7)	1.4 (1.2–1.7)	1.6 (1.3–1.9)
Phase III to approval	1.1 (1.0–1.2)	1.0 (0.8–1.2)	1.1 (0.9–1.3)
Phase I to phase III	1.8 (1.5–2.1)	1.8 (1.4–2.1)	1.9 (1.5–2.3)
Phase I to approval	2.0 (1.6–2.4)	1.8 (1.3–2.3)	2.2 (1.6–2.8)

Values give the ratio of the probability of a target-indication pair progressing given genetic support to the probability of progressing without genetic support; 95% confidence intervals are given in parentheses.

Follow-up study by King *et al.*, 2019: benefits more than 2 fold when causal evidences are strong



King, Emily A., J. Wade Davis, and Jacob F. Degner. 2019. “Are Drug Targets with Genetic Support Twice as Likely to Be Approved? Revised Estimates of the Impact of Genetic Support for Drug Mechanisms on the Probability of Drug Approval.” PLOS Genetics 15 (12): e1008489. https://doi.org/10.1371/journal.pgen.1008489.

Genes with *biologically understandable* genetic association are more likely to be good targets

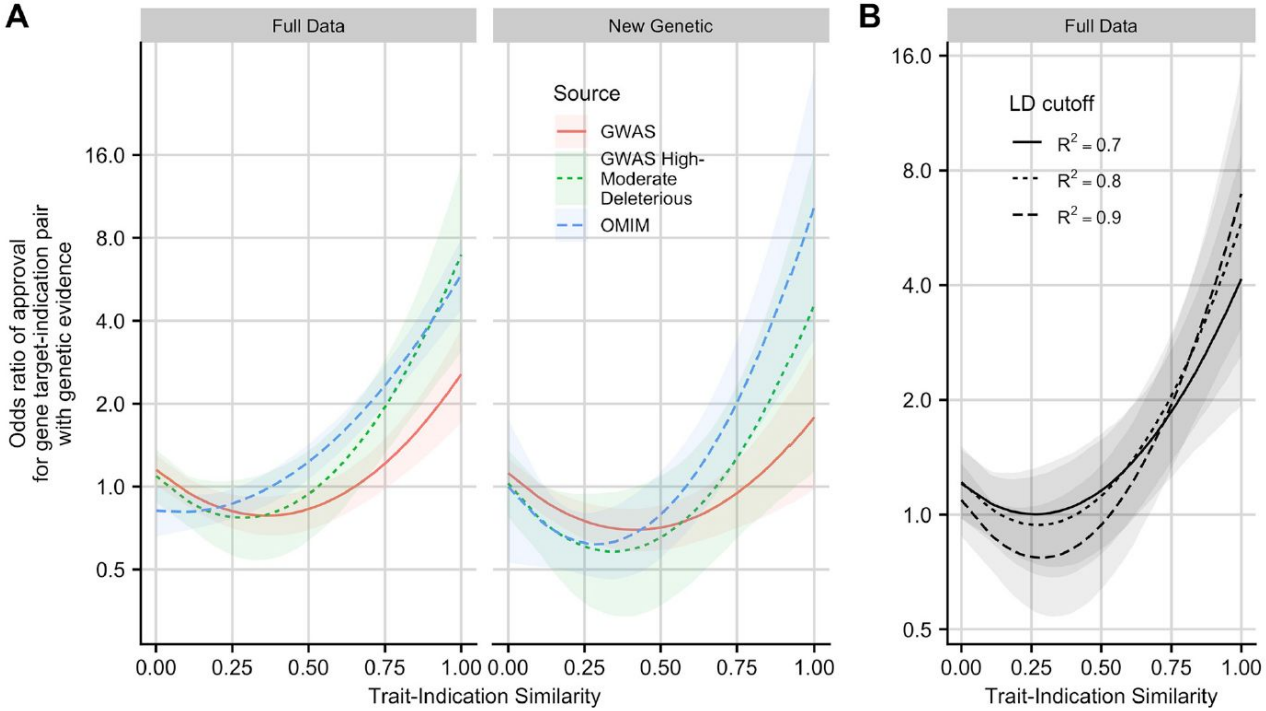
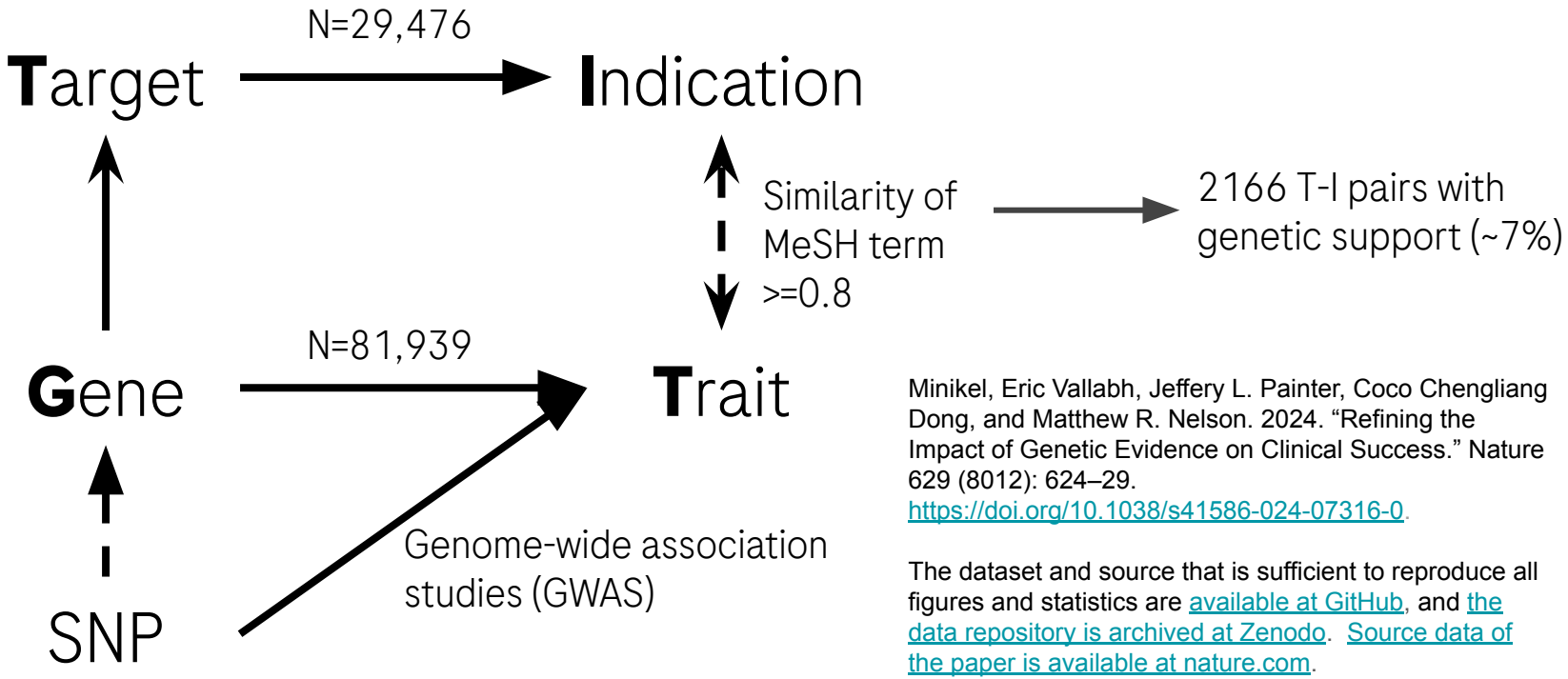


Fig 2. Estimated odds ratio of gene target-indication pair attaining approval, as a function of similarity between drug indication and the most similar trait associated with the target. A: Left: All genetic associations. Right: Only genetic associations reported after 2013 download. B: Effect of LD expansion threshold R^2 on the estimated approval odds ratio of a drug gene target-indication pair supported by a GWAS high-moderate deleterious variant. Posterior median and pointwise 95% credible interval from Bayesian logistic regression.

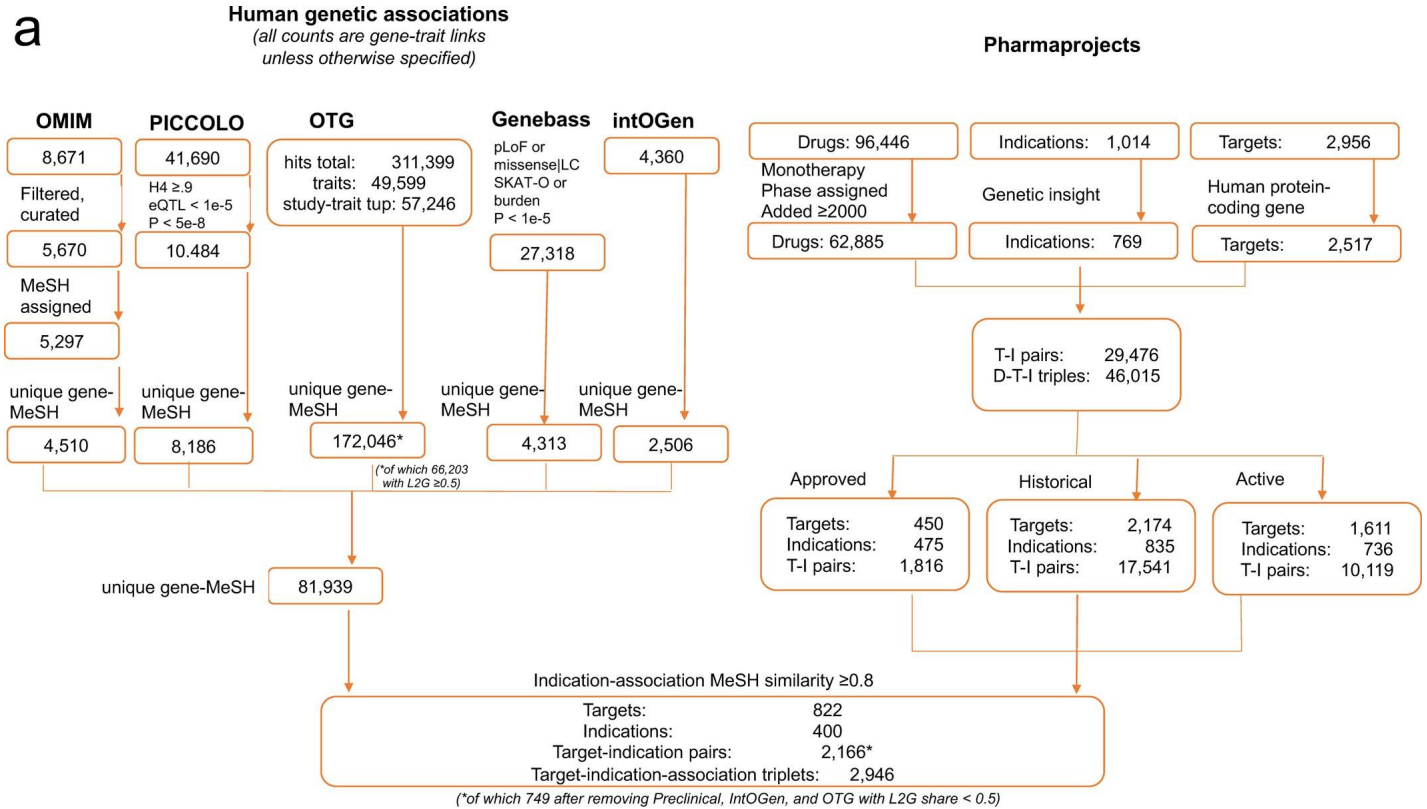
Follow-follow-up study Minikel *et al.* 2024



Minikel, Eric Vallabh, Jeffery L. Painter, Coco Chengliang Dong, and Matthew R. Nelson. 2024. “Refining the Impact of Genetic Evidence on Clinical Success.” Nature 629 (8012): 624–29. https://doi.org/10.1038/s41586-024-07316-0.

The dataset and source that is sufficient to reproduce all figures and statistics are available at GitHub, and the data repository is archived at Zenodo. Source data of the paper is available at nature.com.

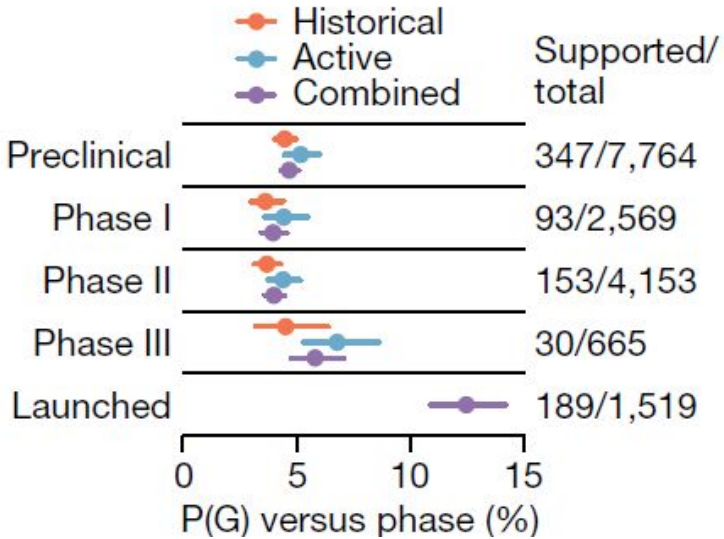
Data processing schematic



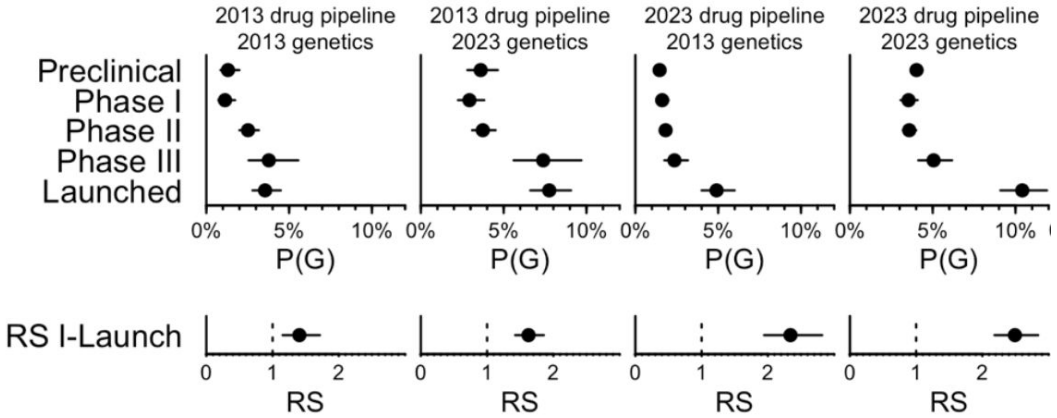
PICCOLO: a GWAS-hits database with gene considering putative causality (GSK).

intOgen: somatic mutations, genes and pathways involved in tumor formation (tumorigenesis). (Barcelona Biomedical Genomics Lab)

Follow-follow-up study Minikel *et al.* 2023

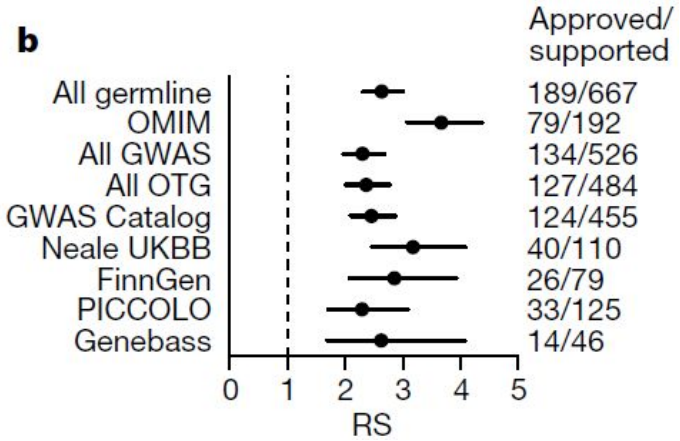


P(G): target-indication pairs with genetic support. Supported/Total: in the unit of target-indication pairs. Error bars represent 95% confidence interval.

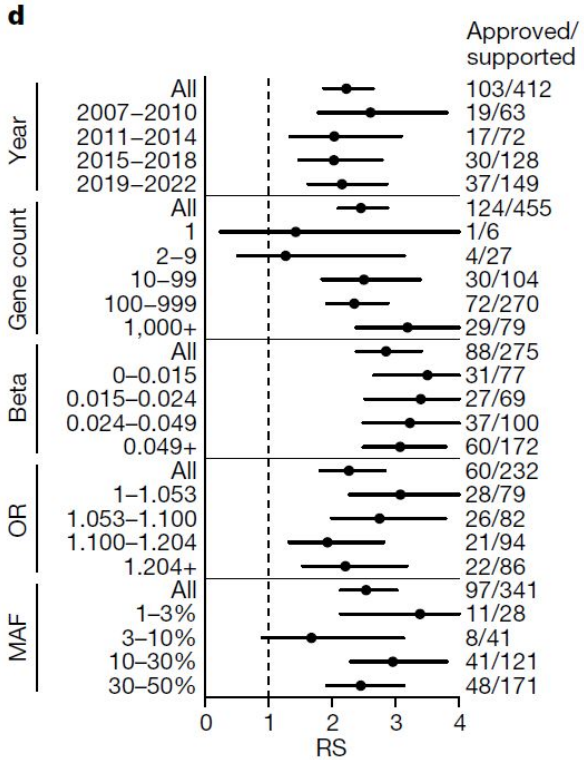


Accumulation of genetic data leads to more targets with genetic support, though only 5-10% target-indication pairs with genetic evidence are exploited. RS=relative success.

The probability of success for drug mechanisms with genetic support is estimated 2.6 times greater than those without



Sensitivity of phase I-launch relative success (RS) to source of human genetic information. *GWAS Catalog*, *Neale UKBB*, and FinnGen are subsets of OTG. Approved/supported: number of T-I pairs that were launched/number of those with support from each source.



Year: in which a target-indication pair got first support

Gene count: number of genes associated with the trait that is similar to an indication.

Beta: effect size of an quantitative trait.

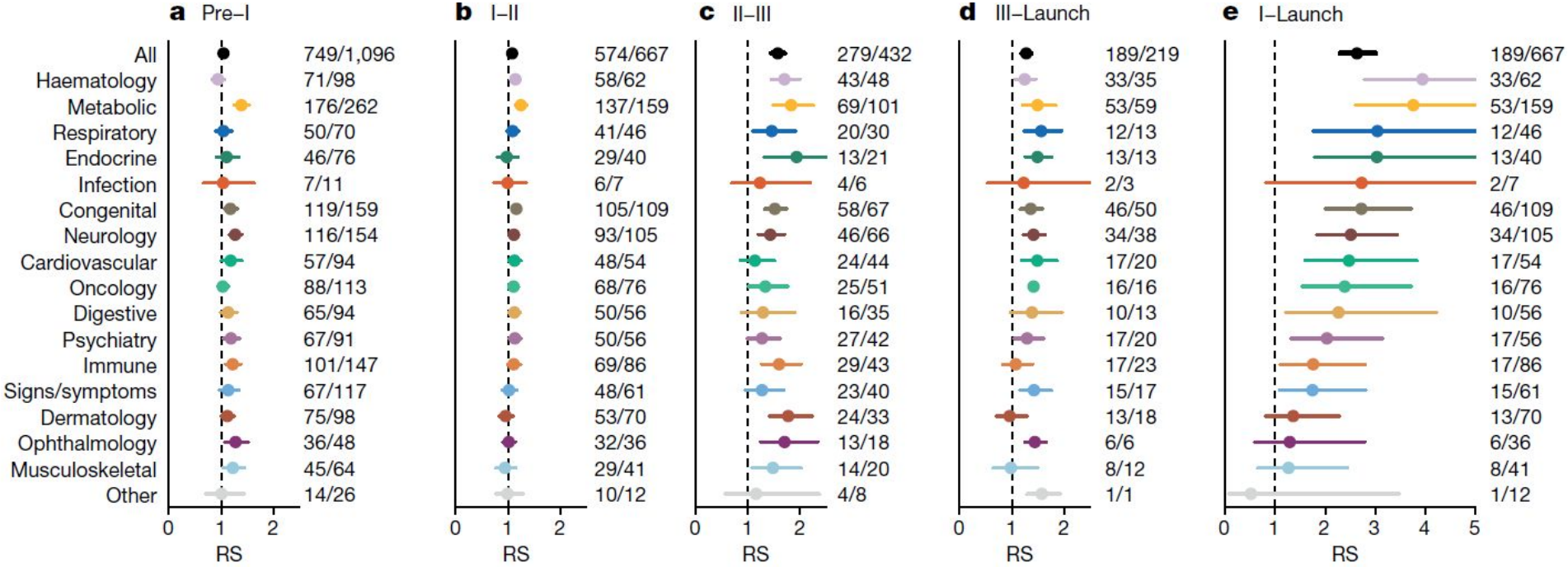
Odds ratio: effect size of a binary trait.

MAF: minor allele frequency

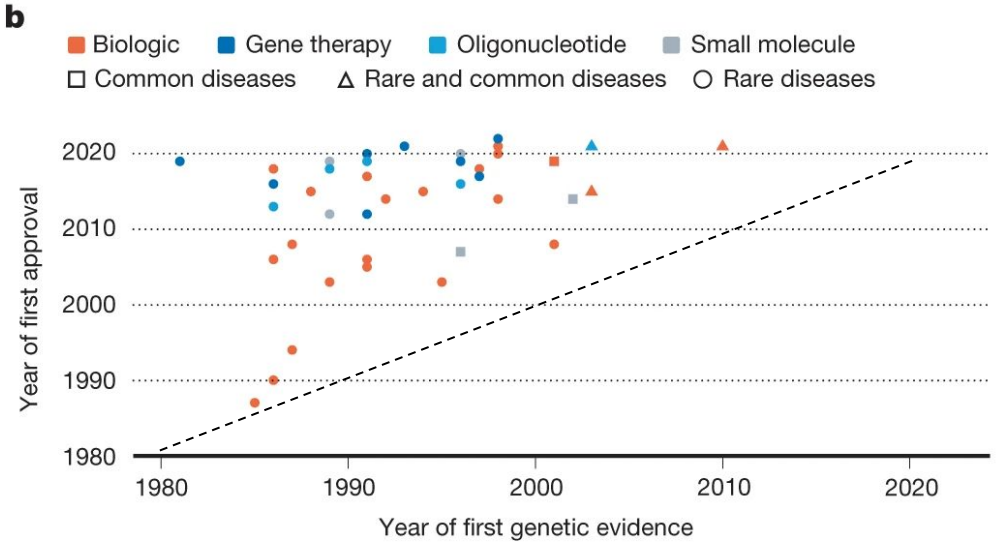
Genetically supported T-I pairs across diseases and target classes

	All genes	Predicted Ab tractable	Predicted SM tractable	Rhodopsin-like GPCRs	Nuclear receptors	Enzymes	Ion channels	Kinases
All areas	719/34,190 **2.1%**	588/17,811 **3.3%**	614/12,391 **5%**	46/508 **9.1%**	22/245 **9%**	116/2,278 **5.1%**	33/714 **4.6%**	135/1,134 **12%**
Haematology	42/4,794 **0.88%**	35/2,409 **1.5%**	37/1,698 **2.2%**	2/87 **2.3%**	0/30 **0%**	8/276 **2.9%**	0/58 **0%**	4/156 **2.6%**
Metabolic	116/6,819 **1.7%**	94/3,594 **2.6%**	95/2,487 **3.8%**	8/90 **8.9%**	10/51 **20%**	14/471 **3%**	2/98 **2%**	3/185 **1.6%**
Respiratory	24/884 **2.7%**	23/480 **4.8%**	12/318 **3.8%**	2/9 **22%**	0/5 **0%**	2/51 **3.9%**	1/26 **3.8%**	0/13 **0%**
Endocrine	35/2,676 **1.3%**	31/1,327 **2.3%**	31/922 **3.4%**	7/53 **13%**	2/32 **6.2%**	1/187 **0.53%**	2/53 **3.8%**	3/80 **3.8%**
Infection	3/234 **1.3%**	3/138 **2.2%**	1/88 **1.1%**	0/4 **0%**	0/2 **0%**	0/13 **0%**	0/7 **0%**	0/2 **0%**
Congenital	87/4,488 **1.9%**	65/2,444 **2.7%**	63/1,697 **3.7%**	2/46 **4.3%**	2/28 **7.1%**	15/296 **5.1%**	1/103 **0.97%**	2/114 **1.8%**
Neurology	81/3,481 **2.3%**	70/1,911 **3.7%**	65/1,212 **5.4%**	8/53 **15%**	0/13 **0%**	10/198 **5.1%**	14/133 **11%**	3/86 **3.5%**
Cardiovascular	39/2,681 **1.5%**	37/1,436 **2.6%**	36/952 **3.8%**	3/43 **7%**	1/17 **5.9%**	10/212 **4.7%**	10/97 **10%**	1/90 **1.1%**
Oncology	295/4,304 **6.9%**	227/2,088 **11%**	277/1,975 **14%**	6/37 **16%**	4/25 **16%**	62/419 **15%**	0/56 **0%**	109/250 **44%**
Digestive	38/2,309 **1.6%**	30/1,252 **2.4%**	26/802 **3.2%**	3/47 **6.4%**	3/21 **14%**	6/129 **4.7%**	1/24 **4.2%**	4/71 **5.6%**
Psychiatry	40/2,382 **1.7%**	38/1,300 **2.9%**	39/786 **5%**	14/53 **26%**	0/18 **0%**	4/131 **3.1%**	6/84 **7.1%**	0/74 **0%**
Immune	66/2,406 **2.7%**	59/1,301 **4.5%**	37/855 **4.3%**	4/40 **10%**	0/7 **0%**	10/125 **8%**	0/26 **0%**	5/79 **6.3%**
Signs/symptoms	47/3,629 **1.3%**	41/1,897 **2.2%**	41/1,200 **3.4%**	7/70 **10%**	4/30 **13%**	4/206 **1.9%**	12/124 **9.7%**	3/107 **2.8%**
Dermatology	49/2,217 **2.2%**	43/1,183 **3.6%**	32/731 **4.4%**	2/24 **8.3%**	0/6 **0%**	7/131 **5.3%**	0/28 **0%**	6/71 **8.5%**
Ophthalmology	23/2,044 **1.1%**	18/1,153 **1.6%**	15/626 **2.4%**	1/19 **5.3%**	1/18 **5.6%**	3/108 **2.8%**	2/54 **3.7%**	0/61 **0%**
Musculoskeletal	30/1,620 **1.9%**	27/887 **3%**	22/539 **4.1%**	1/15 **6.7%**	2/6 **33%**	2/91 **2.2%**	1/31 **3.2%**	4/54 **7.4%**
Other	7/1,513 **0.46%**	6/761 **0.79%**	5/487 **1%**	0/24 **0%**	1/11 **9.1%**	0/93 **0%**	0/35 **0%**	1/41 **2.4%**

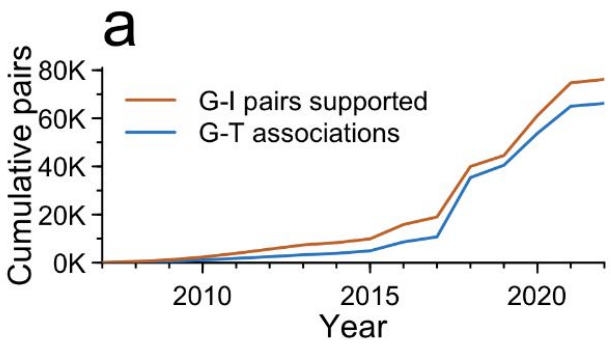
Benefits of genetics-supported targets vary by disease and clinical development phase

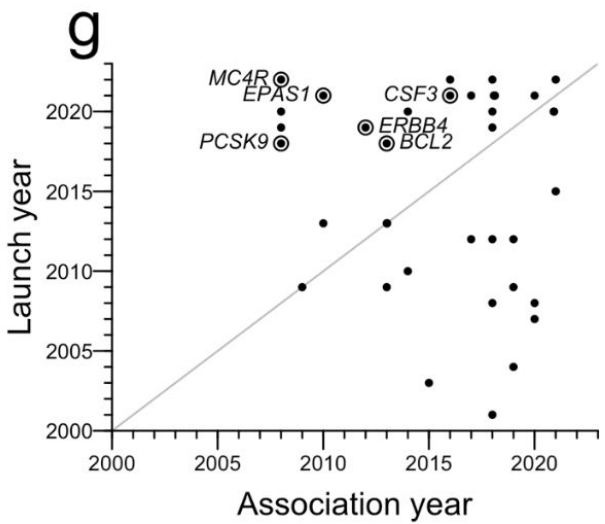


Much genetic support nowadays is found retrospectively



Trajanoska, K. et al. From target discovery to clinical drug development with human genetics. Nature 620, 737–745 (2023).

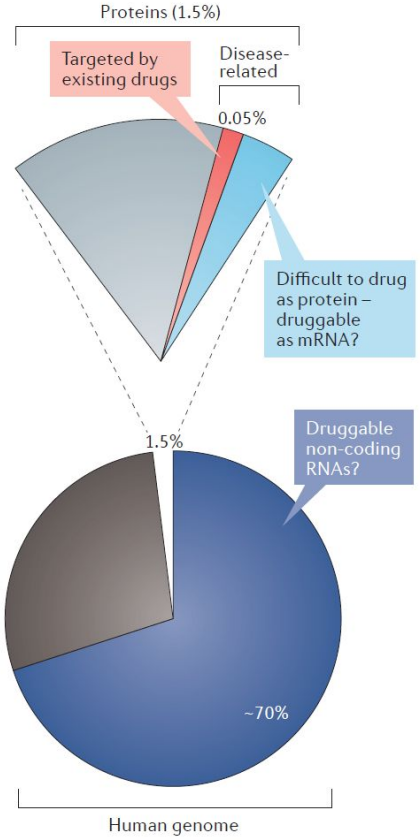


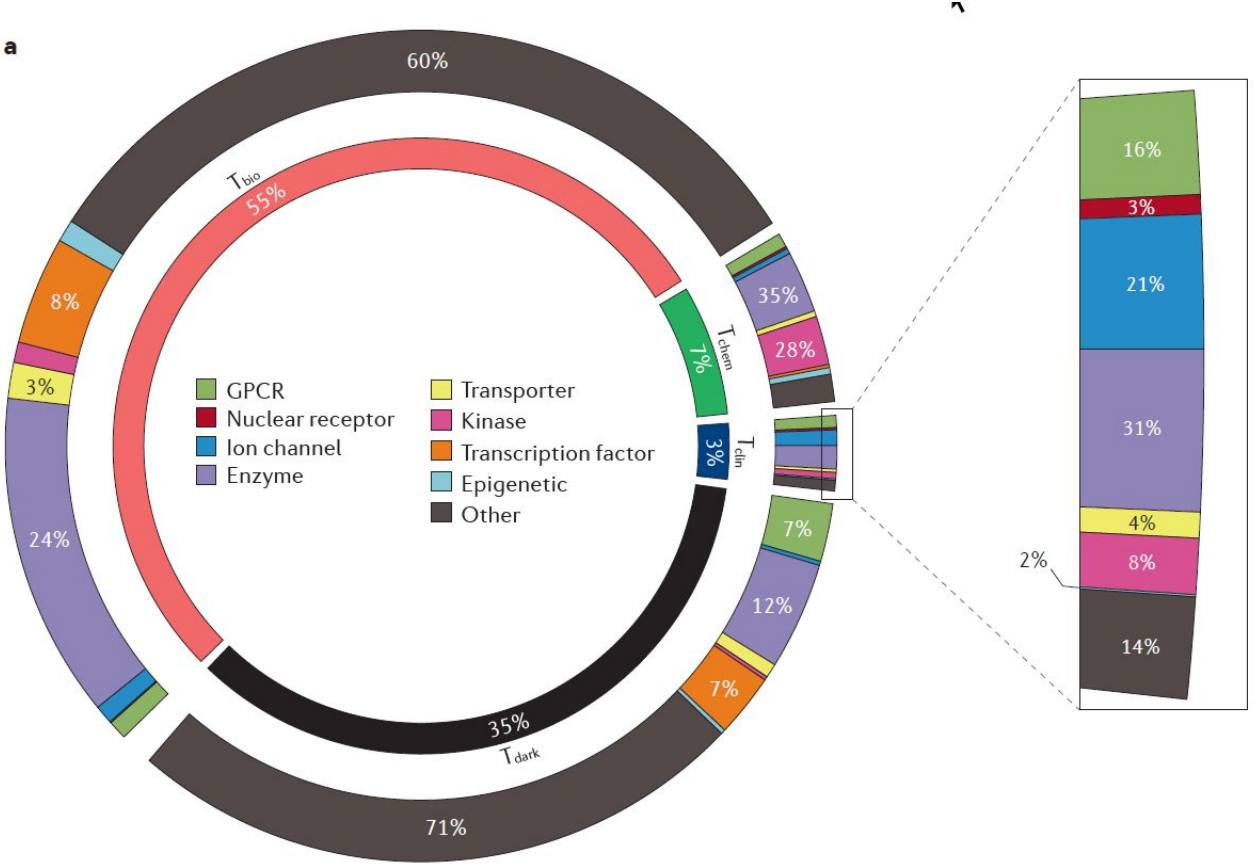


Discussions

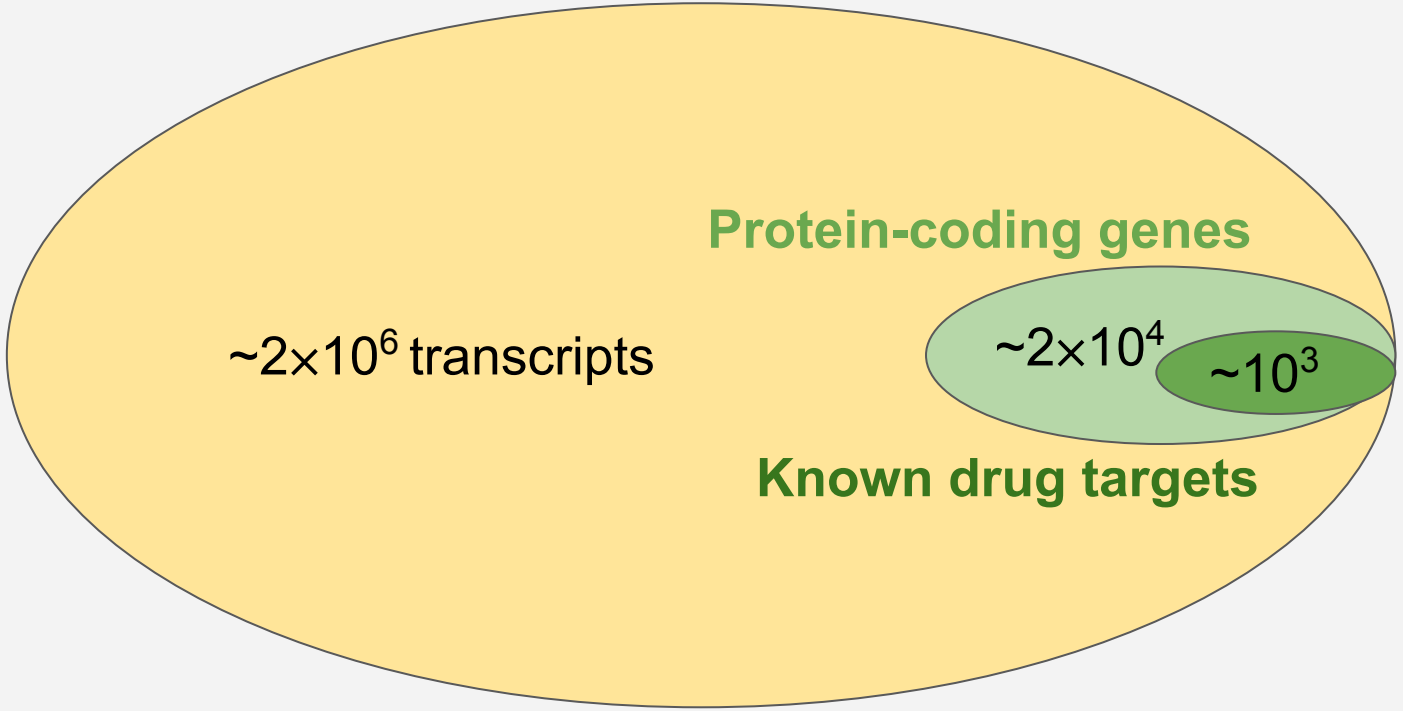
- What practical consequences do the findings that genetics increase target-indication success rates by about two fold?
- What other evidences can we use to increase the likelihood that a gene is a good drug target?
- What are the challenges?

Challenge #1: little experience for much of the genome



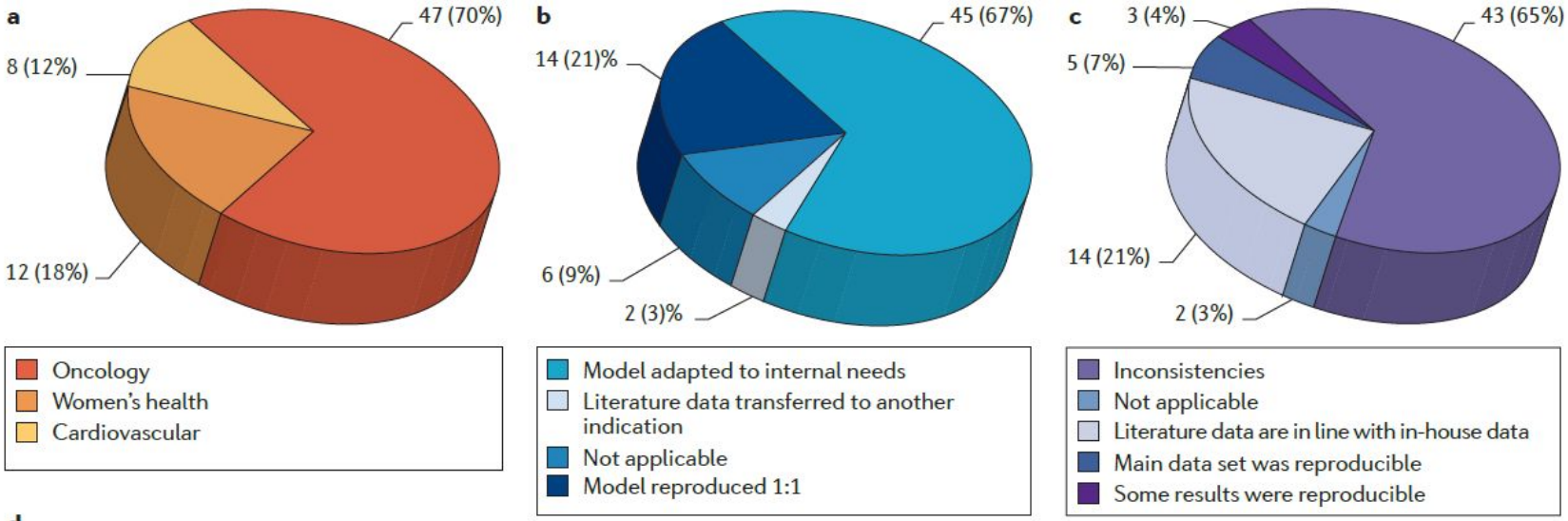


Protein, RNA, or DNA as target?



~3×10^9 DNA bases from maternal and paternal each

Challenge #2: Lack of reproducibility



d

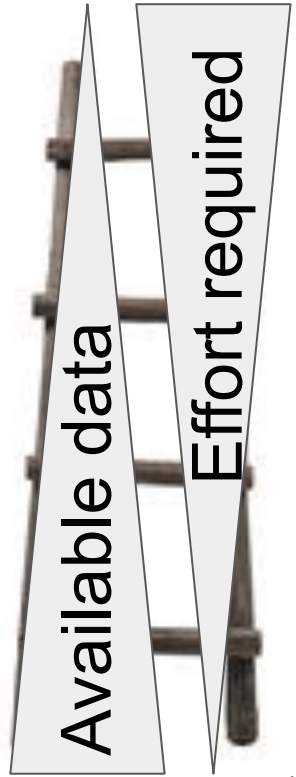
	Model reproduced 1:1	Model adapted to internal needs (cell line, assays)	Literature data transferred to another indication	Not applicable
In-house data in line with published results	1 (7%)	12 (86%)	0	1 (7%)
Inconsistencies that led to project termination	11 (26%)	26 (60%)	2 (5%)	4 (9%)

Challenge #3: The Target Ladder

3. [**Real-world test**] What would happen if we inhibit the activity of the kinase domain in the *WKN3* gene in patients with Alzheimer's Disease?

2. [**Intervention**] What would happen to human cells or to a rat model if we inhibit the activity of the kinase domain in the *WKN3* gene?

1. [**Association**] What are the evolutionary conservation, sequence, expression profile, expression regulation patterns, … of the *WKN3* gene?



Conclusions

- Genomics and genetics offer unprecedented opportunities and challenges for target identification and assessment;
- Target identification and assessment involves knowledge integration and experimental validation;
- A central task of mathematical and computational biology in drug discovery is to perform inference, i.e. using information to reduce uncertainty.

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Offline activity of Module I: submission link (submission deadline: March 14th, 2025)

Offline activity of Module I (Part 1)

Read Refining the Impact of Genetic Evidence on Clinical Success by Minikel *et al.* Report what surprises you most, and submit any questions you may have about the analysis.

Offline activity of Module I (Part 2)

Task 1: The company Fränzi and Friends developed a 2nd-generation quick test at home for SARS-Cov-2, which is pending regulatory agency's review. The test has been shown to have a sensitivity of 99.5% and a specificity of 99.5%. Suppose that Fred uses the test by Fränzi and Friends and the test was positive. Assume that 5% of the population is in fact infected. Was is your guess about the probability that Fred is indeed infected?

Task 2: Please share a piece of code that visualizes the probability that Fred is indeed infected as the dependent variable, with the infection prevalence (5% in the example above, which takes any real-number value between 0.001% to 50%) and the specificity (99% in the example above, which takes values 99%, 99.9%,99.99%, and 99.999%) as independent variables. For simplicity, we fix the sensitivity at 99%. Visualize the results if possible, and use integers to check and explain your results. Use any programming language that you prefer. Please put your code in GitHub or GitLab or other code-hosting service and paste the link below.

Task 3: What are your interpretations of the results?

Backup

An example of complementary views

We want to work on hepatocarcinoma (liver cancer) and have the following information about a potential target X:

- X is a receptor expressing on the surface of most cell types;
- Upon binding ligands, X activates innate immune response;
- Gene sequence of X is conserved in primates but *not* in rodents;
- Protein X interacts with protein Y, which is essential, namely Y knockout causes lethal embryos;
- Asian population has a unique genetic variant in the non-coding region of *X*;

Discussion: what are the consequences of having these information?

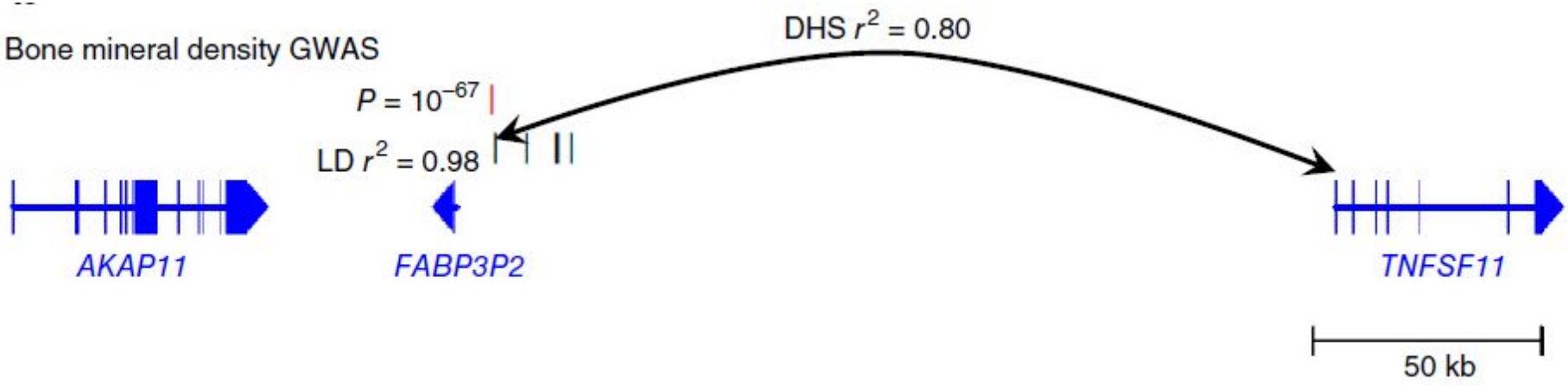
Questions from courses

- Why I recommended the GOT-IT paper? How can academia and industry work together towards good targets?
- Did sequencing cost always follow the Moore's law?
- What happens if there are ATGs (AUGs in RNA) in 5'-untranslated region?
  - In some cases, there are alternative start codons;
  - However, in most cases, the ATGs in 5'-untranslated region seem to be always ignored by the translational machinery. A study (Rogozin, Bioinformatics, 2001) suggested that those AUGs may ensure low basal expression and generate regulatory elements.
- Which target level (gene or protein) is more useful for the target identification? In the lecture, gene-level approach seems not so promising.
- Is blue eyeness a marker of Neanderthalian origin? *The story of OAC2*

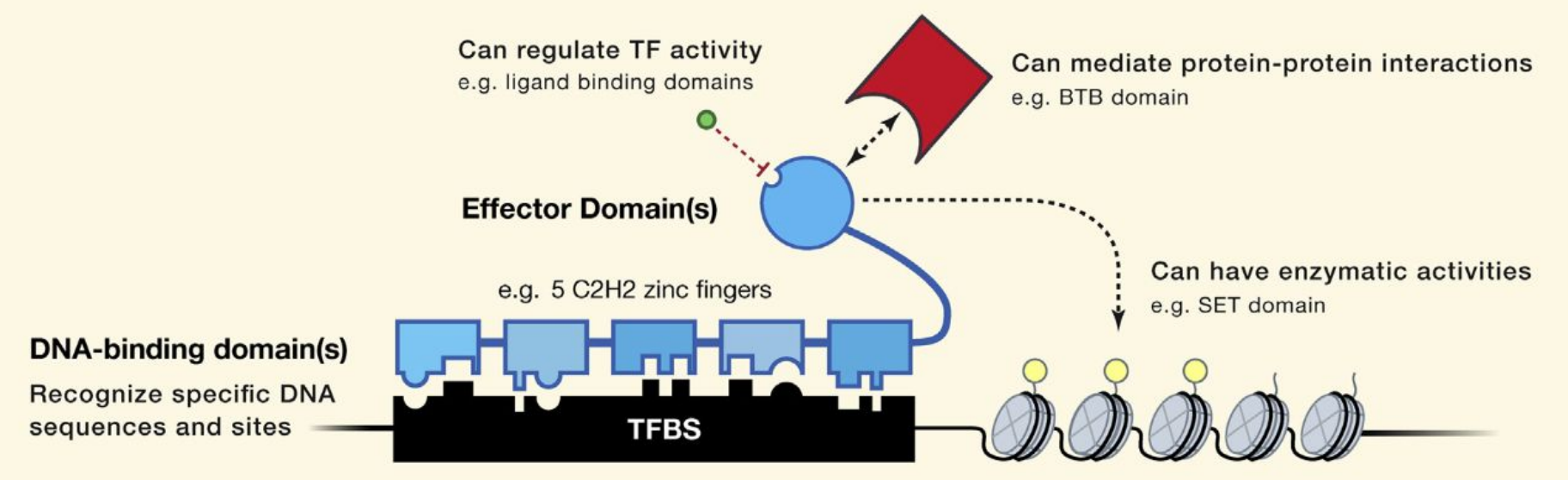
Why autoimmune diseases are more prevalent in females, though one X chromosome is randomly inactivated?

- Sex hormone signaling plays an important role in immune functions, especially estrogens. The hormone signalling apparently explains a lot, but not all, sex differences in autoimmune diseases.
- Mutations of genes on the X-chromosome, as expected, cause many primary immunodeficiencies only in males, because they have only one copy of the X chromosome.
- One of the two X chromosomes in females indeed get inactivated during the embryo stage. However, about 15-20% genes regularly escape the inactivation, among others important genes involved in innate and adaptive immune response, including TLR7 and CD40L.
- There are a few other hypotheses besides X-inactivation escaping, including loss of mosaicism, reactivation, and haploinsufficiency.

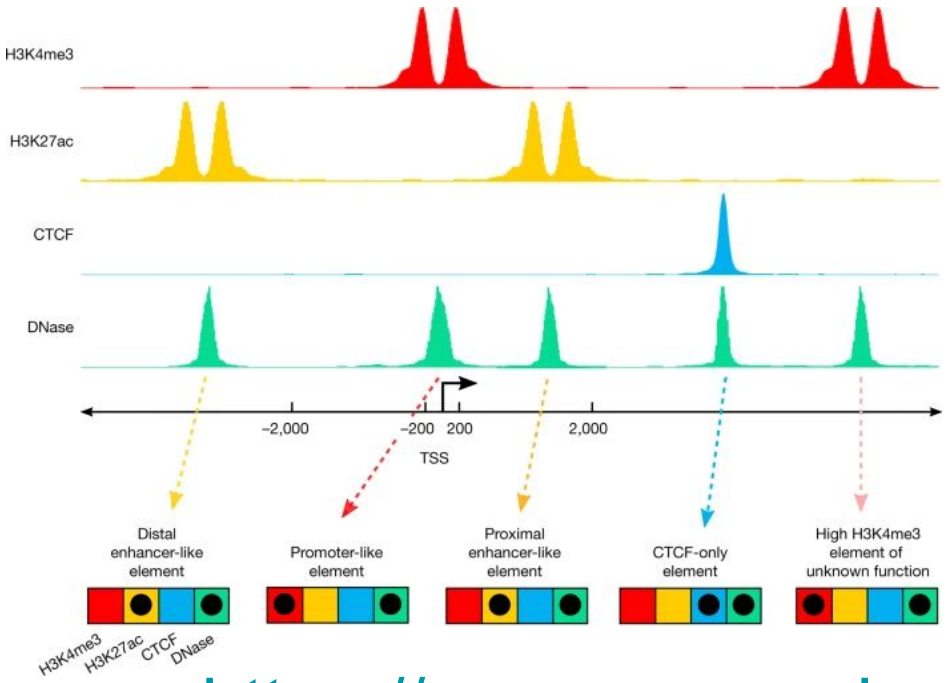
Correlation between DNase I hypersensitive (DHS) sites helps linking genetic variants with genes

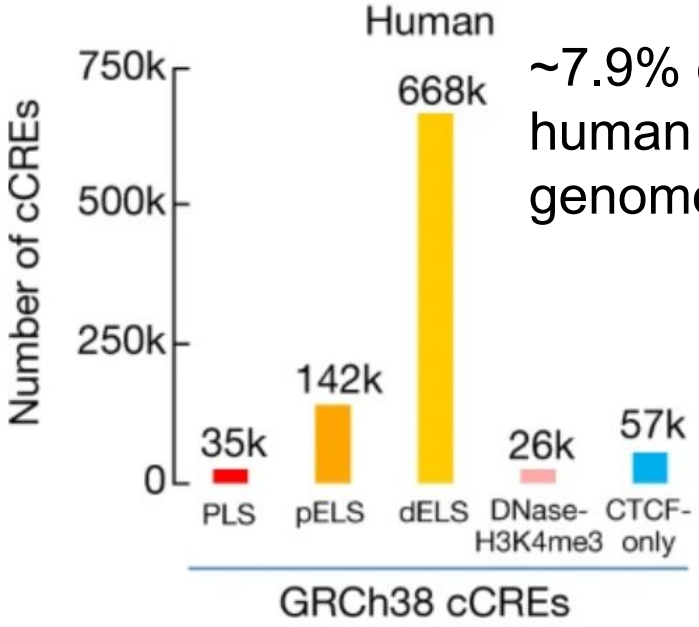


Transcription factors induce gene expression



TFs bind to candidate cis-regulatory elements (cCRE) to regulate gene expression

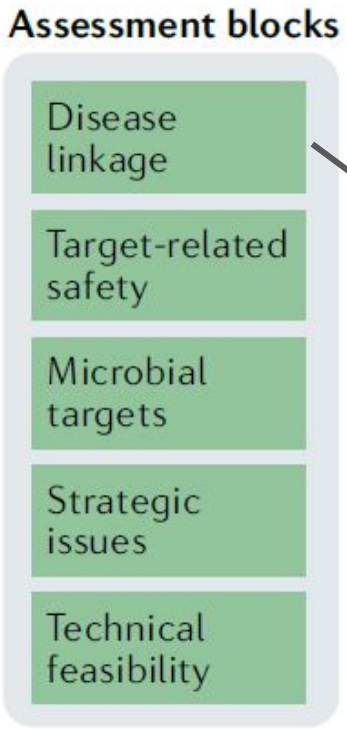




~7.9% of human genome

https://screen.encodeproject.org/

GOT-IT recommendations for target-disease linkage



AB1: target–disease linkage (human targets)

1. Is the target perturbation a cause or consequence of the human disease process?
2. Is the therapeutic relevance (such as human connection) of models used sufficiently high for decision-making?
3. Is the target expression pattern known (that is, within the anticipated patient population)?
4. Is the target manipulation process clinically relevant?
5. Is the read-out used to detect target-dependent processes disease-relevant?
6. Is the stimulus used to activate or influence target-dependent processes disease-relevant?
7. Are the biological consequences of an observed effect size known?

Public resources for target assessment

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7. Are the biological consequences of an observed effect size known?

- OpenTargets
- Online Mendelian Inheritance in Man (OMIM)

- Scattered in diverse information sources such as Wikipedia and literature

- Health: GTEx, The Human Protein Atlas
- Disease: Gene Expression Atlas, scattered

Public resources for target safety assessment

AB2: target-related safety (human targets)

8. Is the target selective and not genetically linked to other diseases (or phenotypes or organ systems)?
9. Is there prior knowledge on safety of the target or reported evidence for the role of the target in a known pathway and/or physiological process that may be harmful if disrupted?
10. Are in vitro or pharmacologically relevant animal models available for safety testing?
11. Do models used for safety testing translate well to humans?
12. Are safety biomarkers available and can adverse effects be monitored and/or predicted by safety biomarkers?
13. Is there sufficient confidence that a necessary safety window has been or can be established?
14. Is the disease life-threatening (at what stage of the disease is the target of relevance)?
15. Is the tissue distribution of the target known (in humans or in animals)?

- Comparative Toxicogenomics Database (CTD)

- DrugBank, DrugCentral
- FDA Adverse Event Reporting System (FAERS)

- NCBI HomoloGene
- ENSEMBL ComparaGenom
- Mouse Genome Informatics (MGI)

Other important information resources

- **Genomic variations**: gnomAD, dbSNP, and TCGA for oncology;
- **Protein domain and static structure**: InterPro, Pfam, and PDB;
- **Interaction network and pathway**: BioGRID, IntAct, Reactome, and KEGG;
- **Gene expression profiles associated with the target**: NCBI GEO (Gene Expression Omnibus), ARCHS4