Unifying lessons from genetically guided drug discovery for neurodegenerative diseases

Eric Vallabh Minikel

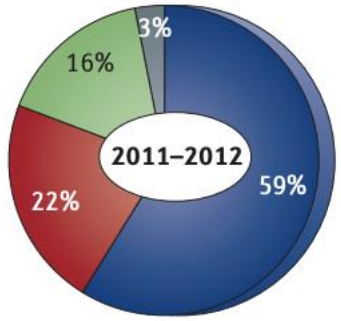
Broad Institute

November 12, 2024

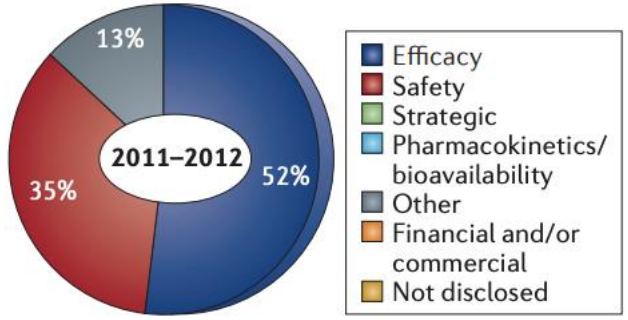
The problem: most drugs fail

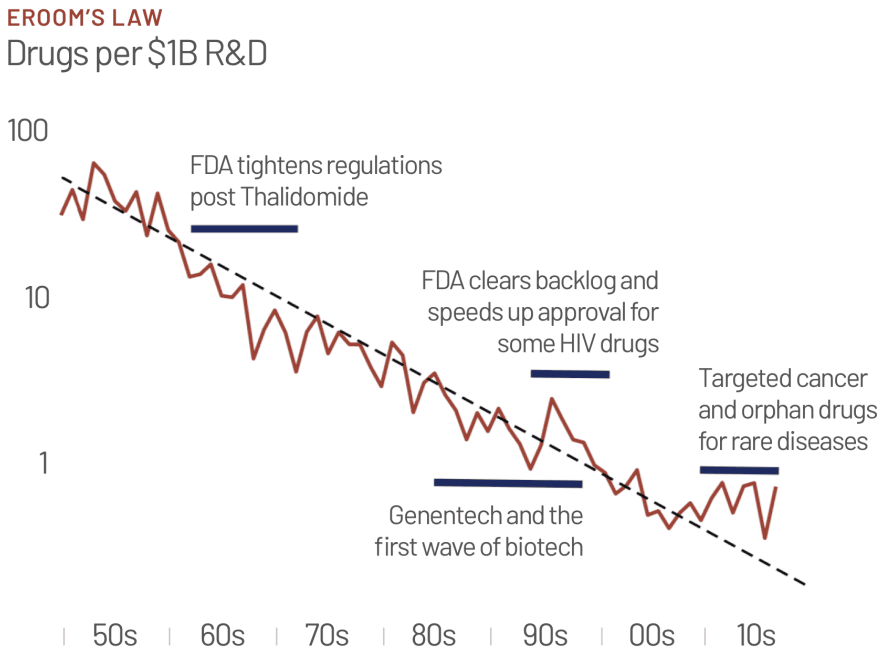
- Overall 8-14% success rate for Phase I to Launch
- Productivity has declined for decades
- Lack of efficacy accounts for much/most failure

Phase II



Phase III

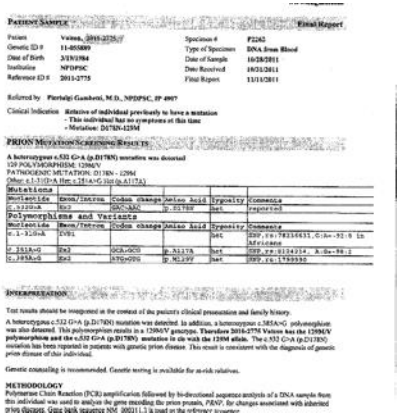


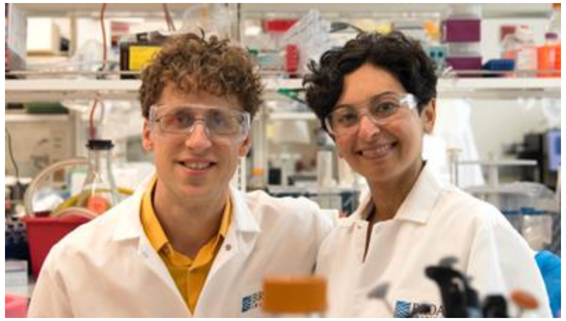


Arrowsmith & Miller 2013. Phase II and Phase III attrition rates 2011–2012. PMID: 23903212
https://refoundable.com/research/life-after-erooms-law-interview-with-jack-scannell
Thomas 2021.BIO Report: Clinical Development Success Rates and Contributing Factors 2011–2020.
Wong 2019. Estimation of clinical trial success rates and related parameters.
Hay 2014. Clinical development success rates for investigational drugs.

Our personal journey

My wife Sonia Vallabh and I learned in 2011 that she had inherited a lethal genetic mutation in *PRNP* from her mother who died of prion disease. We changed careers to become scientists and now run a lab dedicated to developing drugs for prion disease.





The NEW ENGLAND JOURNAL of MEDICINE

The Patient-Scientist's Mandate

Sonia M. Vallabh, Ph.D.

Eight years ago, at the age of 27, I learned that I had inherited a fatal genetic mutation in the prion protein gene (*PRNP*). Pathogenic mutations in this gene questions we fielded from day one: whether it was wise to pursue genetic testing for a currently incurable disease; how we would weather the setbacks inherent in drome, testing drugs in healthy carriers will require a primary prevention strategy based on genetic risk. This realization has defined our priorities for the past

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vallabhminikel.org

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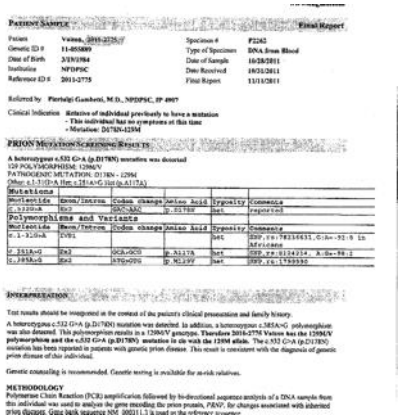

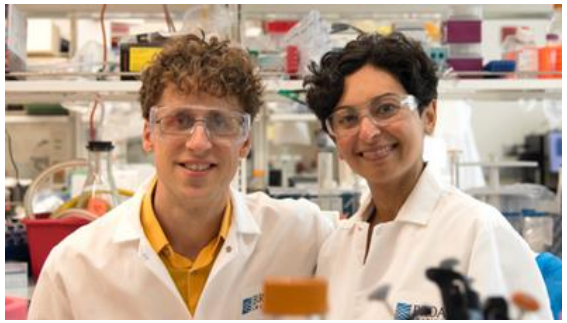

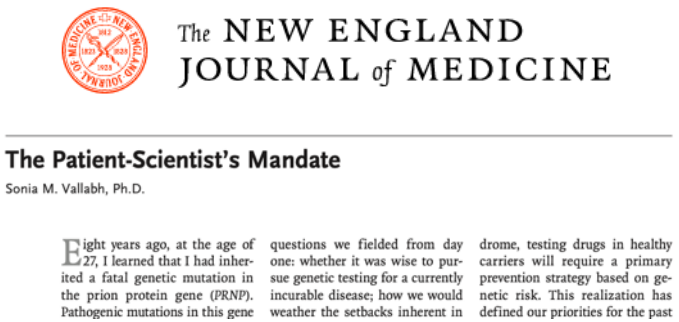

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Sonia Vallabh
11:30a – 12:40p
Thursday 11/14
Rational drug design for prion disease and how this informs other ADRDs

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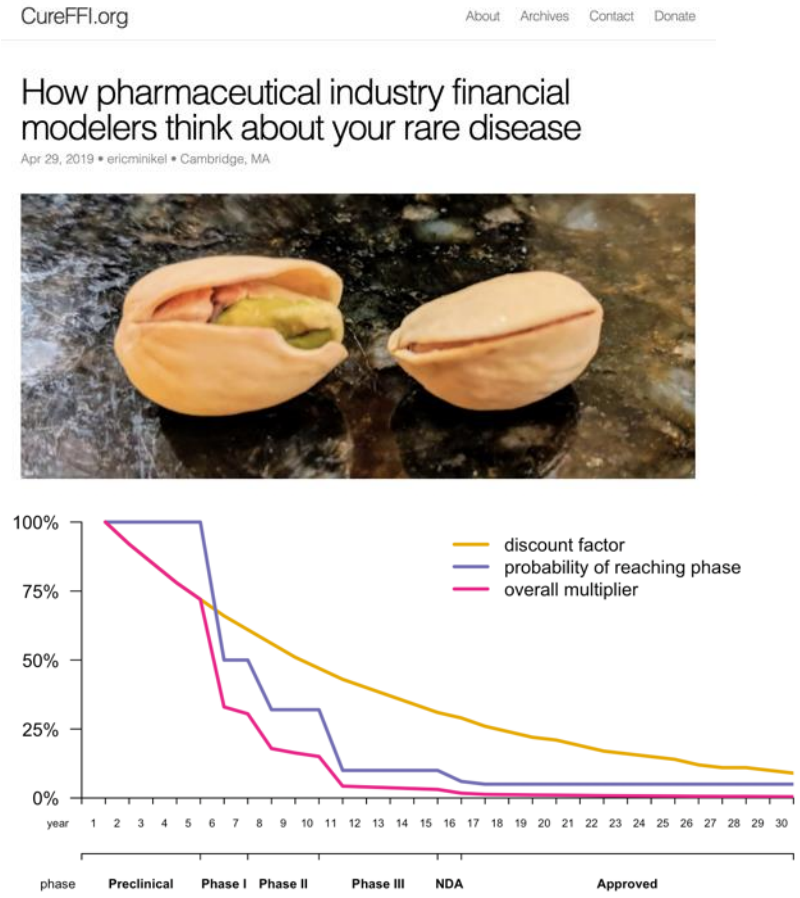
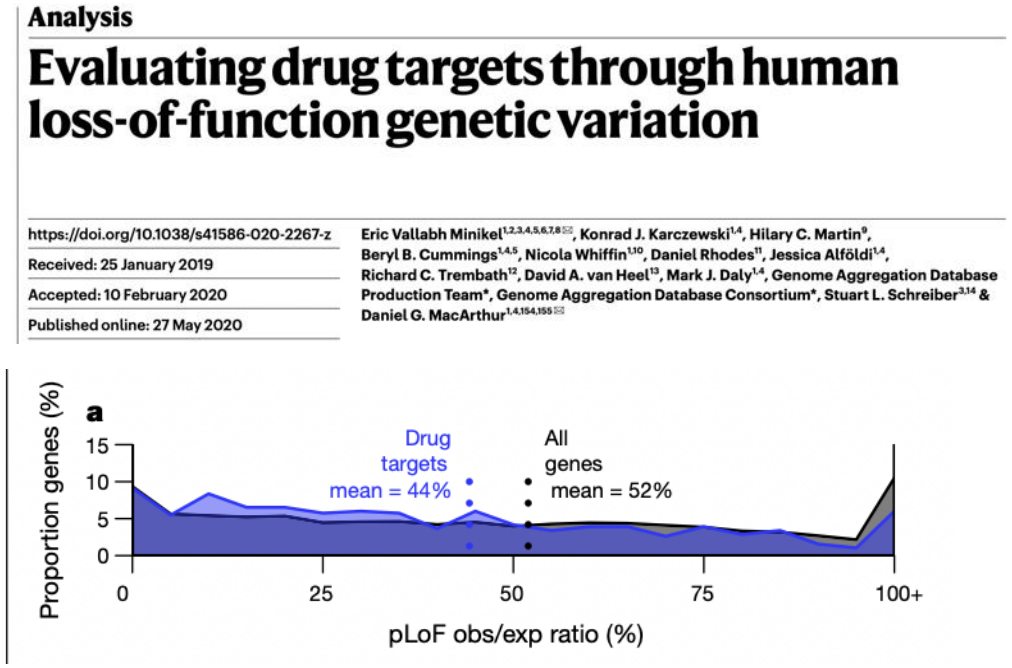
Our quest has motivated me to better understand many aspects of pharma & drug discovery





https://www.cureffi.org/2019/04/29/financial-modeling-in-rare-disease/

Minikel 2020, Evaluating drug targets through human loss-of-function genetic variation. PMID: 32461653

Analysis

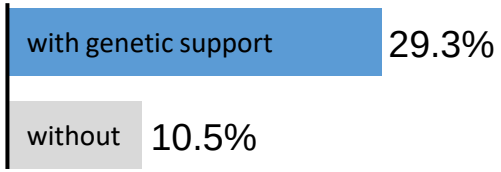
Refining the impact of genetic evidence on clinical success

https://doi.org/10.1038/s41586-024-07316-0

Eric Vallabh Minikel[1], Jeffery L. Painter[2,5], Coco Chengliang Dong[3] & Matthew R. Nelson[3,4]✉

Which associations matter?

success rate



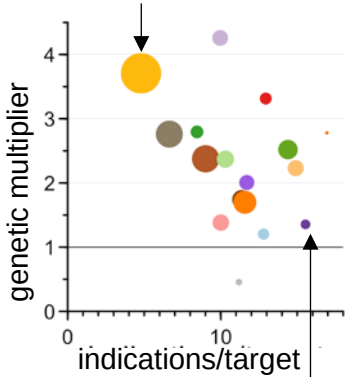
no obvious effect:

- ✓ year of discovery
- ✓ effect size
- ✓ # of associated genes
- ✓ minor allele frequency

Which indications benefit?

metabolic

- ✓ genetics has high value
- ✓ targets narrowly utilized
- ✓ *more disease-modifying?*



opthalmology

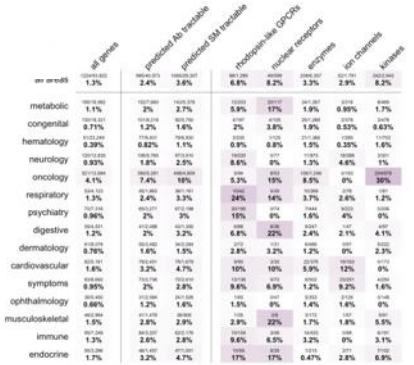
- ✓ genetics has low value
- ✓ targets broadly utilized
- ✓ *more symptom-managing?*

What is the opportunity?

Only

2.1%

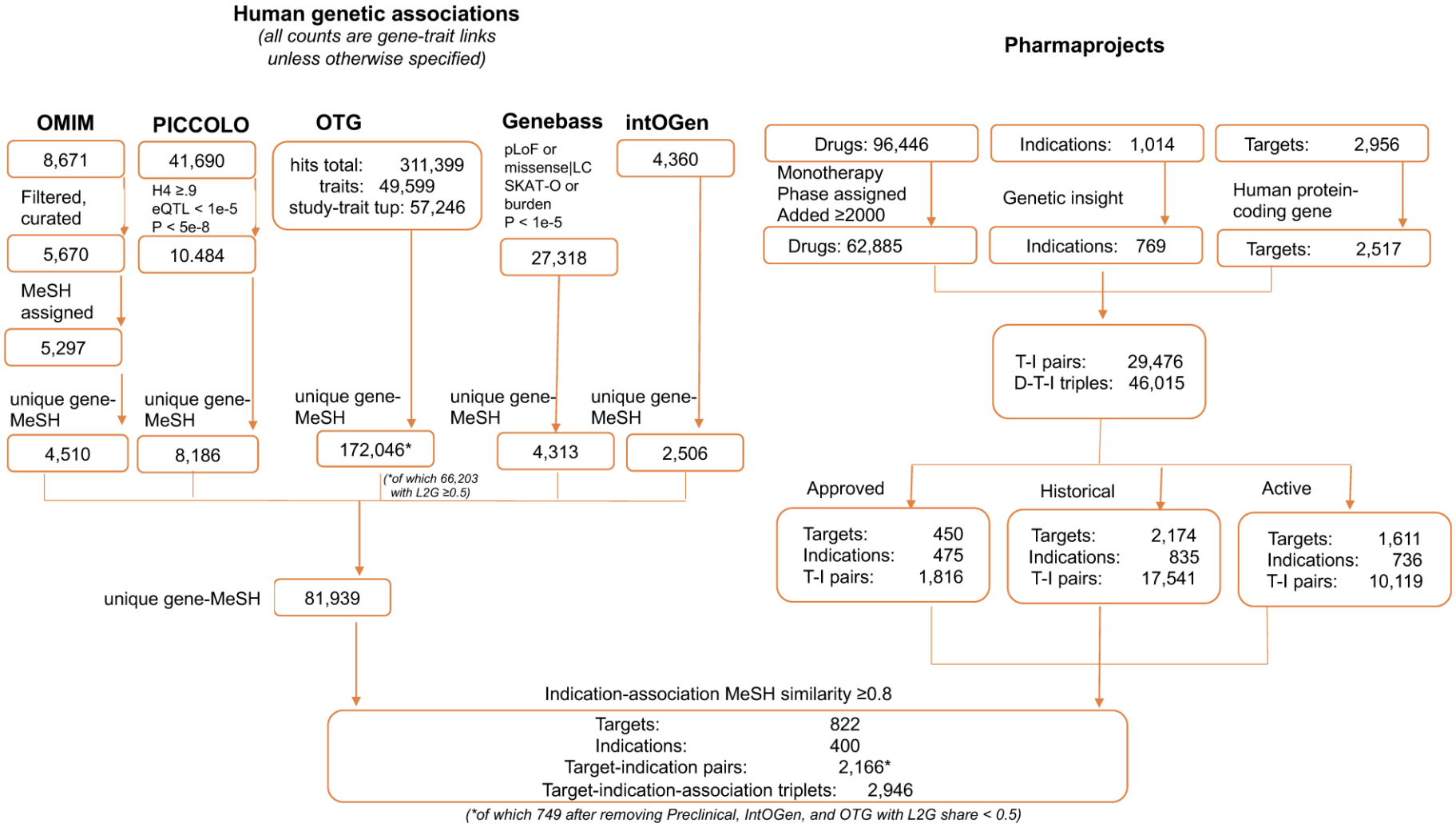
of all genetically supported target-indication pairs have been pursued clinically



No more than half in any therapy area / protein class substratum

Minikel 2024, Refining the impact of genetic evidence on clinical success. PMID: 38632401

Datasets, processing, joining, filtering

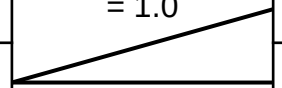


Minikel 2024, Refining the impact of genetic evidence on clinical success. PMID: 38632401

What we mean by "genetic support"

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



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

Unit of analysis: target-indication pair
Targets – human genes (refers to the gene or gene product)
Indications with "genetic insight" i.e. that have been studied genetically

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Calculating probability of success P(S)

Phase I

with genetic support

$$\frac{322}{438}$$

succeeded
- entered Phase II

target-indication pairs that entered Phase I, outcome known:
- entered Phase II+
- terminated
- timed out (presumed abandoned)

Calculating probability of success P(S)

Phase I
with genetic support

$$\frac{322}{438} = 73.5\%$$

Calculating probability of success P(S)

Phase I
with genetic support

Phase II
with genetic support

Phase III
with genetic support

$$\frac{322}{438} \times \frac{191}{390} \times \frac{183}{225} = 29.3\%$$

Calculating relative success (RS)

Phase I with genetic support / **Phase II with genetic support** / **Phase III with genetic support**

$$\frac{322}{438} \times \frac{191}{390} \times \frac{183}{225} = 29.3\%$$

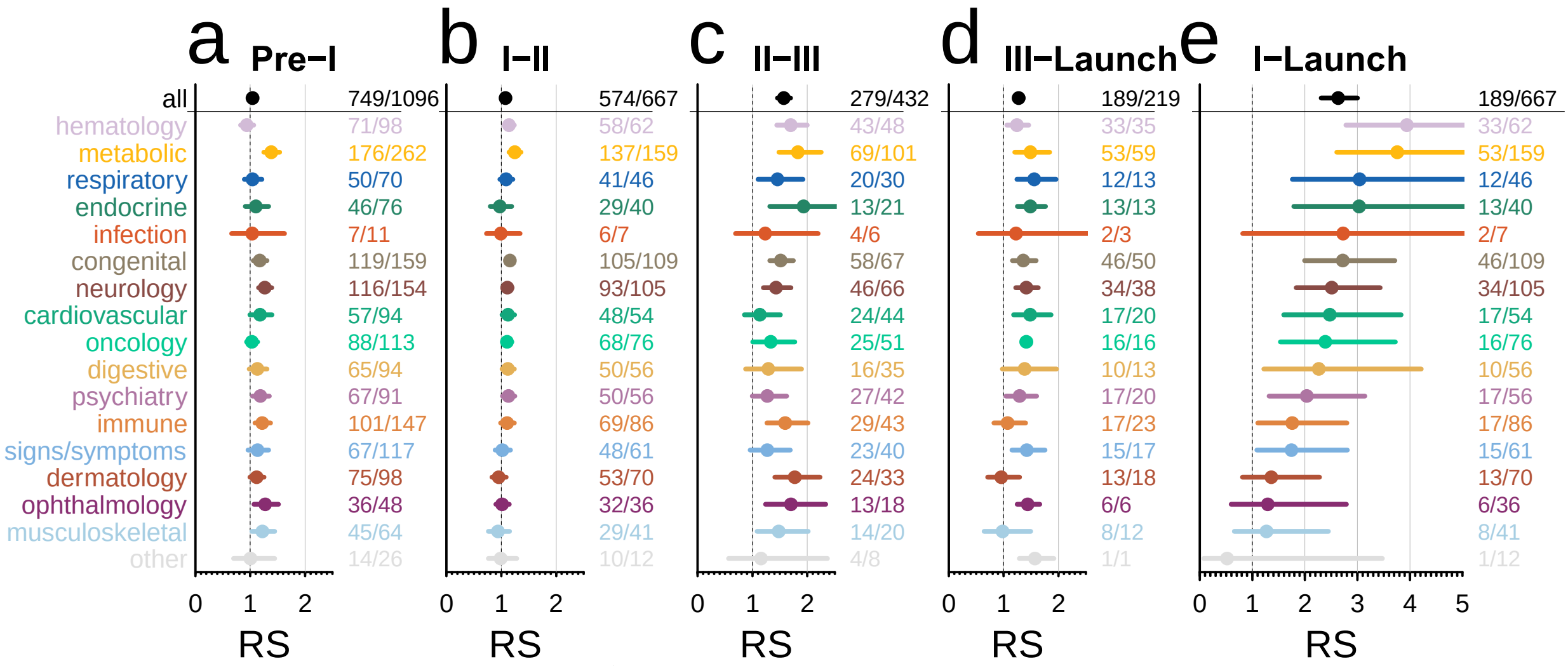
Phase I no genetic support / **Phase II no genetic support** / **Phase III no genetic support**

$$\frac{5{,}490}{8{,}200} \times \frac{2{,}071}{7{,}044} \times \frac{1{,}378}{2{,}578} = 10.5\%$$

Calculating relative success (RS)

$$\frac{\frac{322}{438} \times \frac{191}{390} \times \frac{183}{225}}{\frac{5{,}490}{8{,}200} \times \frac{2{,}071}{7{,}044} \times \frac{1{,}378}{2{,}578}} = \mathbf{2.78}$$

How does relative success vary by therapy area?



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Why does genetic evidence affect different therapy areas differently?

- Matt Nelson's hypothesis:
  1. genetic evidence matters more for **disease-modifying** than **symptom-managing** drugs
  2. different proportions of these types of drugs across therapy areas

- This distinction is not captured in any known database

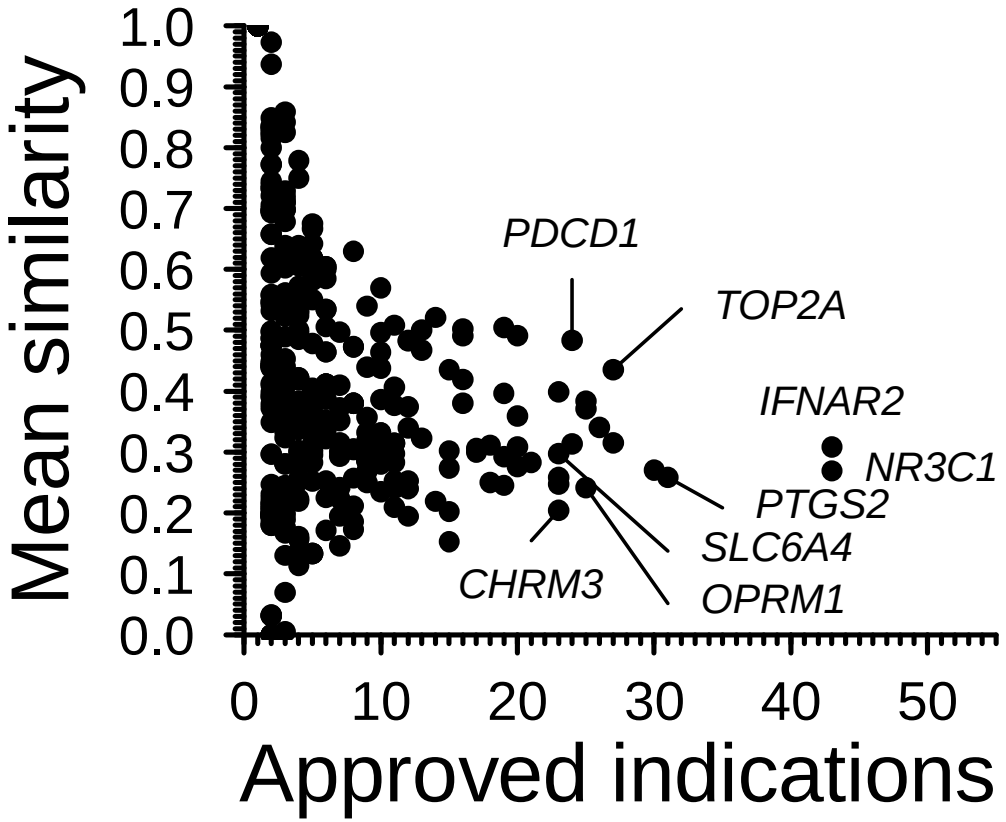
Why does genetic evidence affect different therapy areas differently?

- In search for proxy variables, I browsed all the approved T-I pairs in neurology...

target	N	approved indications
DRD2	12	alzheimer disease, migraine disorders, parkinson disease, tourette syndrome, hyperprolactinemia, acromegaly, restless legs syndrome, dementia, dementia, vascular, nervous system diseases, dyskinesias, psychomotor agitation
SCN1A	11	epilepsy, neuralgia, trigeminal neuralgia, epilepsy, tonic-clonic, status epilepticus, epilepsies, partial, epilepsy, absence, lennox gastaut syndrome, epilepsies, myoclonic, migraine disorders, epilepsy, generalized
GABRA1	9	sleep initiation and maintenance disorders, epilepsy, generalized, epilepsy, sleep wake disorders, nervous system diseases, spasm, epilepsies, partial, lennox gastaut syndrome, status epilepticus
SLC6A2	9	brain ischemia, stroke, diabetic neuropathies, fibromyalgia, neuralgia, alzheimer disease, cataplexy, narcolepsy, sleep initiation and maintenance disorders
NR3C1	8	pituitary acth hypersecretion, dermatomyositis, multiple sclerosis, optic neuritis, spasms, infantile, polymyositis, muscular dystrophy, duchenne, brain edema
SMN2	1	muscular atrophy, spinal
TLR3	1	fatigue syndrome, chronic
TLR4	1	cerebral infarction
TPP1	1	neuronal ceroid-lipofuscinoses
TTR	1	amyloid neuropathies, familial

- Hypothesis: symptom-managing drugs tend to be re-used for many diverse indications, while disease-modifying drugs have narrower use in one or a few indications

Targets for *more* indications are also approved for *less similar* indications



- Of 450 targets of approved drugs, 42 with ≥10 indications are 39% of approved T-I pairs
  - Examples: corticosteroids, painkillers, anti-inflammatories, anti-muscarinics, anti-dopaminergics, and chemotherapy
- Inverse correlation between number of indications and similarity thereof (r = -0.72) — but similarity also provides orthogonal information

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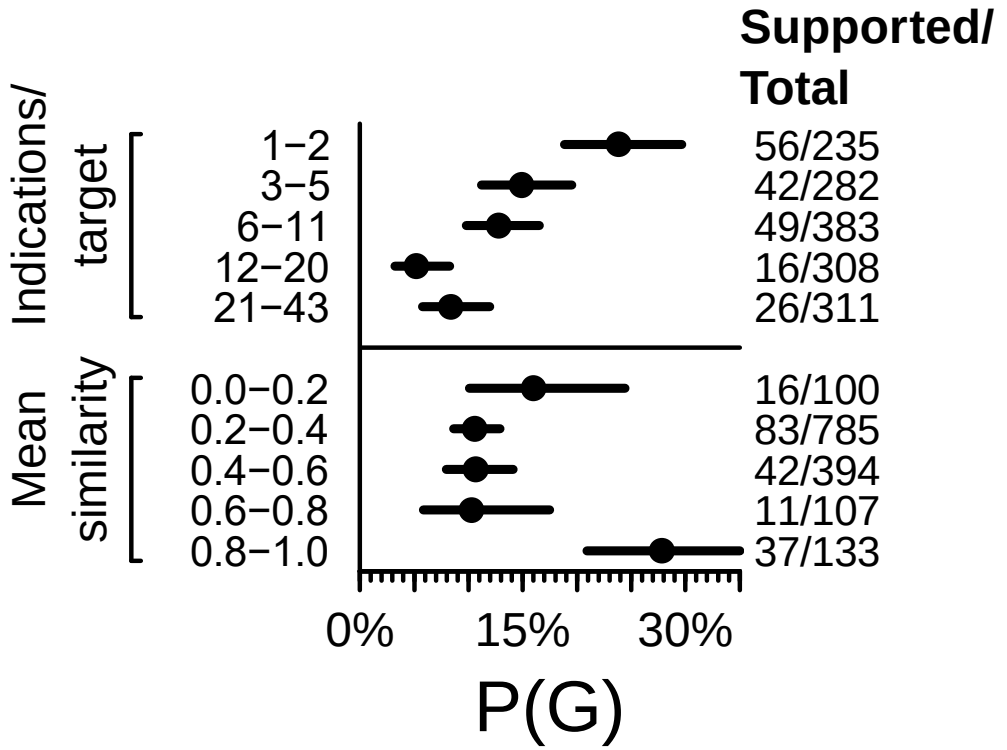
Genetic support for approved drugs is enriched for targets with few or highly similar indications



- Group all targets by the count or similarity of approved indications — what proportion of their indications have genetic support?
- Genetic support more common for T-I pairs where the target has fewer or more similar indications

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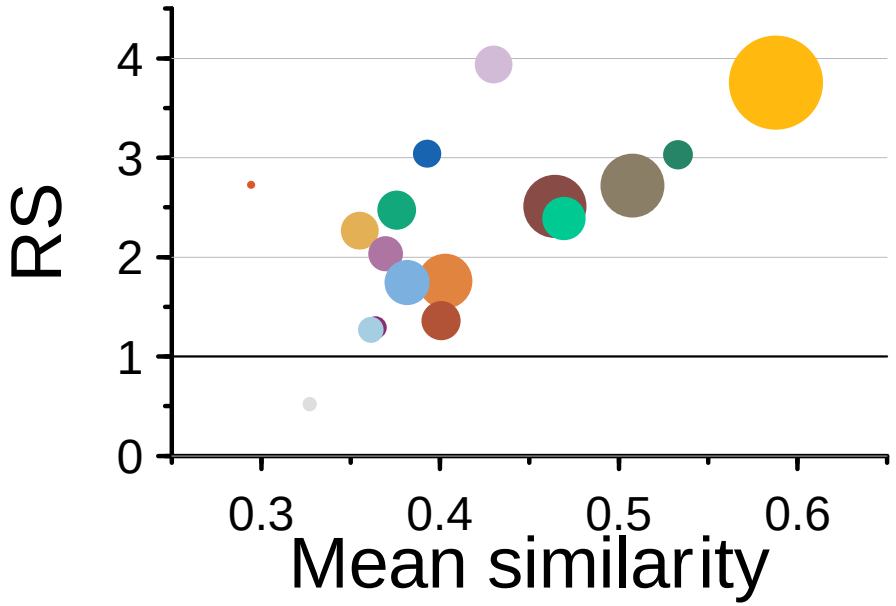
Across therapy areas, number and diversity of indications per target correlates with value of genetic evidence



- Similarity vs. RS: r = 0.74, P = 0.001

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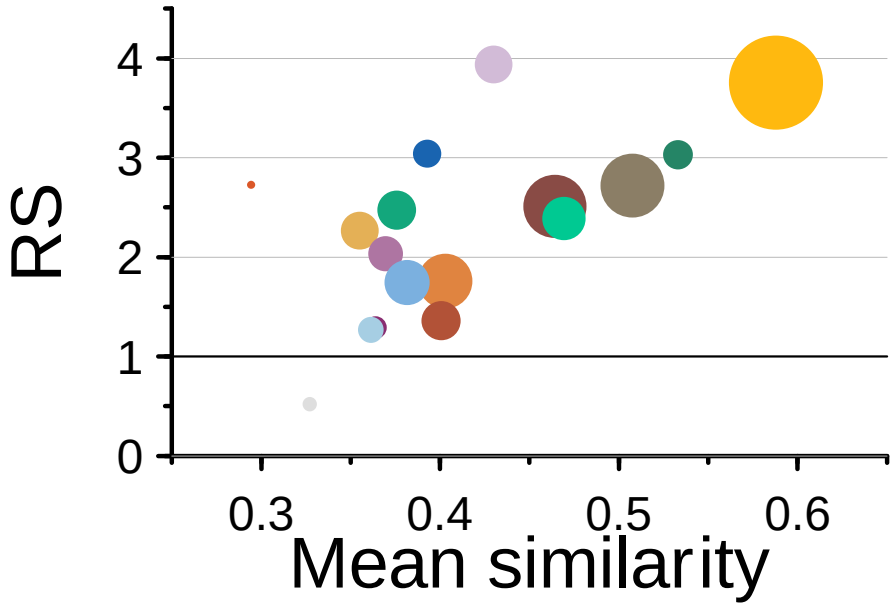

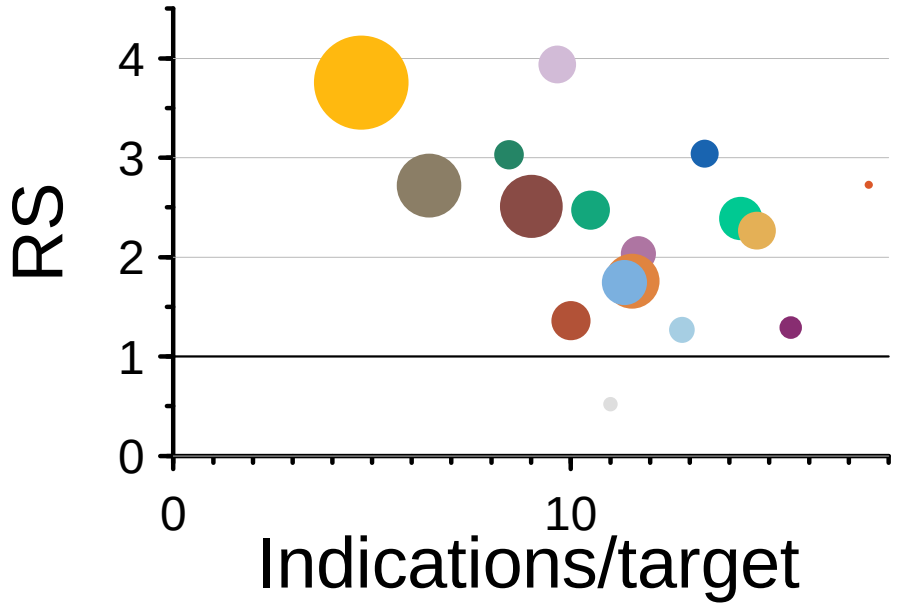

- Similarity vs. RS: r = 0.74, P = 0.001
- Indications per target vs. RS: r = -0.62, P = 0.008

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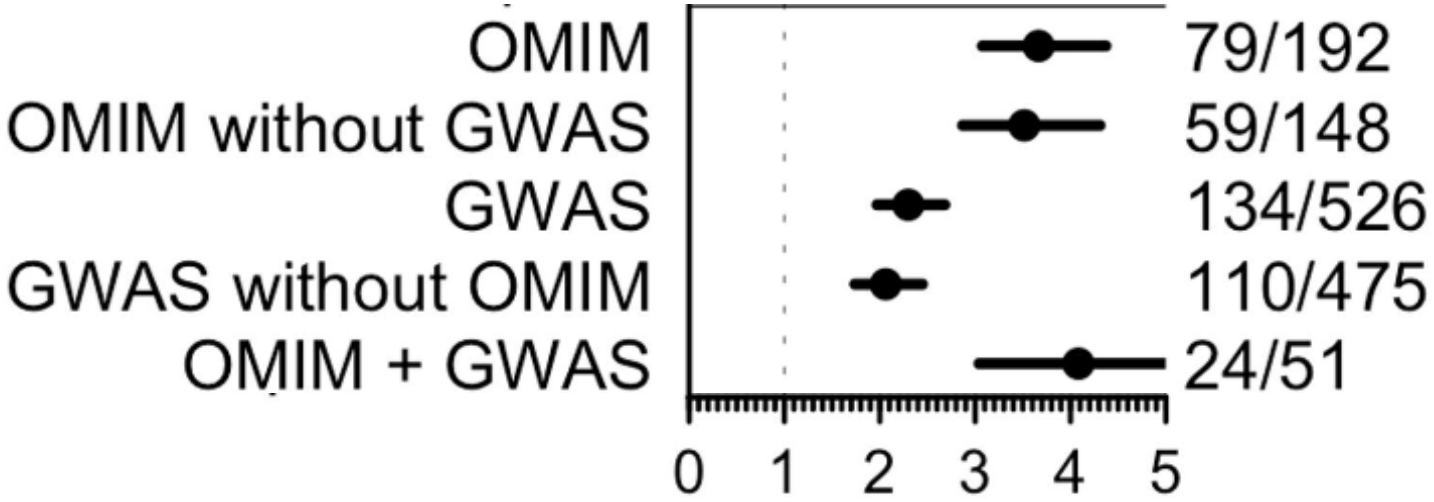
Conclusion/hypothesis: genetic evidence really matters for *disease modification*

- If true:
  - differences between therapy areas simply reflect how much of the portfolio is disease modifying vs. symptom-managing
  - the true value of genetic evidence is even higher than we estimate

- Limitations: all indirect evidence, still no direct “gold standard” to test this

Are GWAS hits just as good as Mendelian targets a priori?



- Remember, this is relative success from Phase I onward
- What about preclinical target selection?
  - 65% of disclosed preclinical programs progress to Phase I — but many failures are never disclosed

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Developing a GWAS hit as a drug requires believing that phenotypic impact scales with target engagement

	GWAS hit	Drug
Functional impact (on gene expression or function)	small	large
Phenotypic impact	small	large

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Defining relative success versus yield

Type 2 diabetes (T2D) example

	Supported potential targets	Supported successful targets	Supported unsuccessful targets	"Yield"
Mendelian	19	4	0	21%
GWAS	862	7*	7	0.8%

GWAS discoveries are:

- More recent
- Mechanism often not initially clear

But, GWAS hits can also be invalidated in early functional studies…

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GPR151 is an example where larger functional effect did *not* yield larger phenotypic impact

2019

ARTICLE

https://doi.org/10.1038/s41467-019-11953-9 OPEN

Components of genetic associations across 2,138 phenotypes in the UK Biobank highlight adipocyte biology

metric phenotypes. PheWAS analysis of these variants confirmed strong associations with obesity-related phenotypes including waist circumference (*GPR151*, marginal association beta = -0.065, $p = 2.5 \times 10^{-8}$), whole-body fat mass (*GPR151*, beta = -0.069, $p = 1.4 \times 10^{-7}$), trunk fat mass (*GPR151*, beta = -0.071,

2022

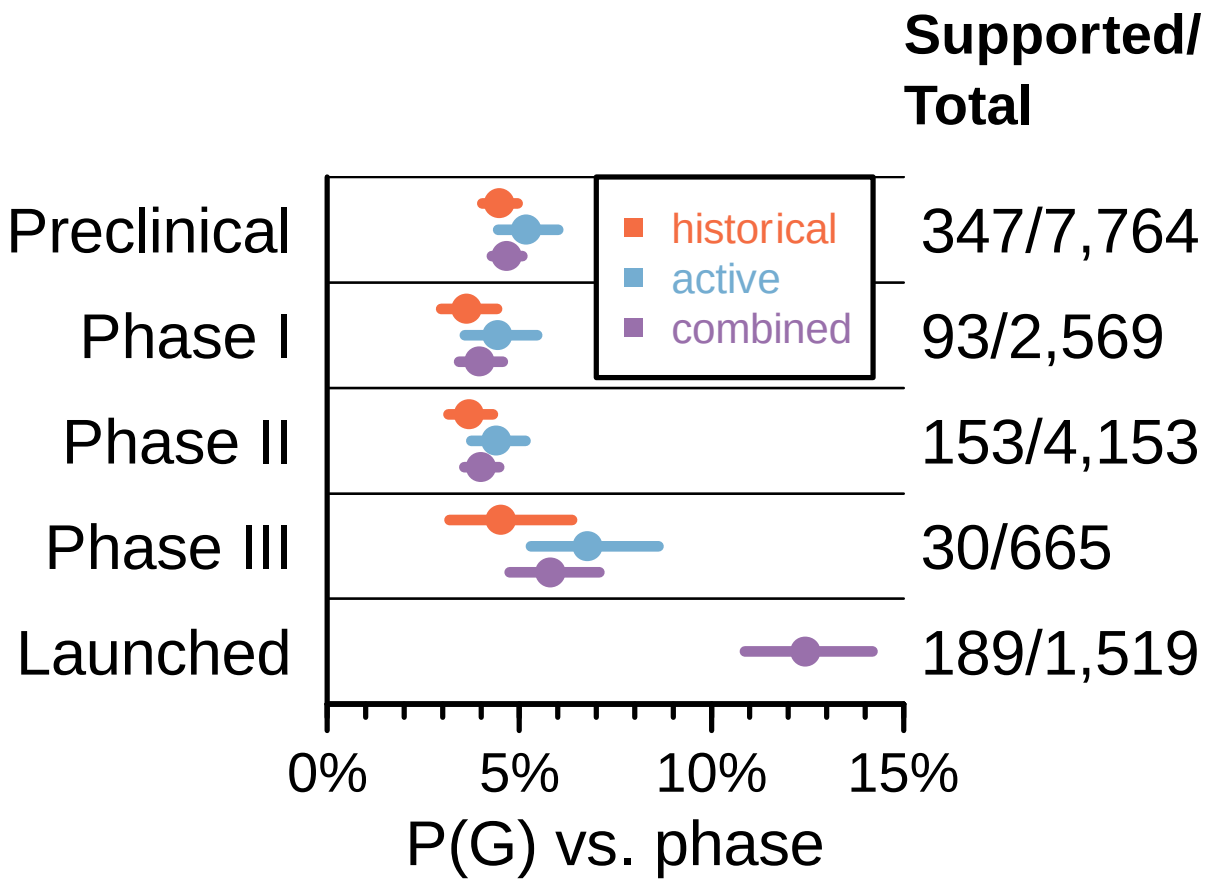
RESEARCH ARTICLE

Analyzing human knockouts to validate *GPR151* as a therapeutic target for reduction of body mass index

Table 1. ***GPR151*** **associations with BMI.**

GRCh38 chr: pos	Reference allele	Alternate allele	HGVSp	Genotype counts (RR|RA|AA)	P-value	Beta [95% CI] kg/m^2 (additive)	P-value (knockouts only)	Beta [95% CI] kg/m^2 (knockouts only)
5:146515831	G	A	Arg95Ter	27273|55|1	0.82	-0.126 [-1.23–0.98]		
5:146515817	G	T	Tyr99Ter	26350|945|34	0.92	0.0131 [-0.24–0.27]	0.55	0.431 [-0.99–1.85]
5:146515587	CTA	C	Phe175LeufsTer7	27206|120|3	0.28	0.406 [-0.32–1.14]		
Gene Burden				26150|1141|38	0.73	0.0405 [-0.20–0.28]	0.98	-0.021 [-1.37–1.33]

Portfolios are not much more enriched for genetic support today than historically



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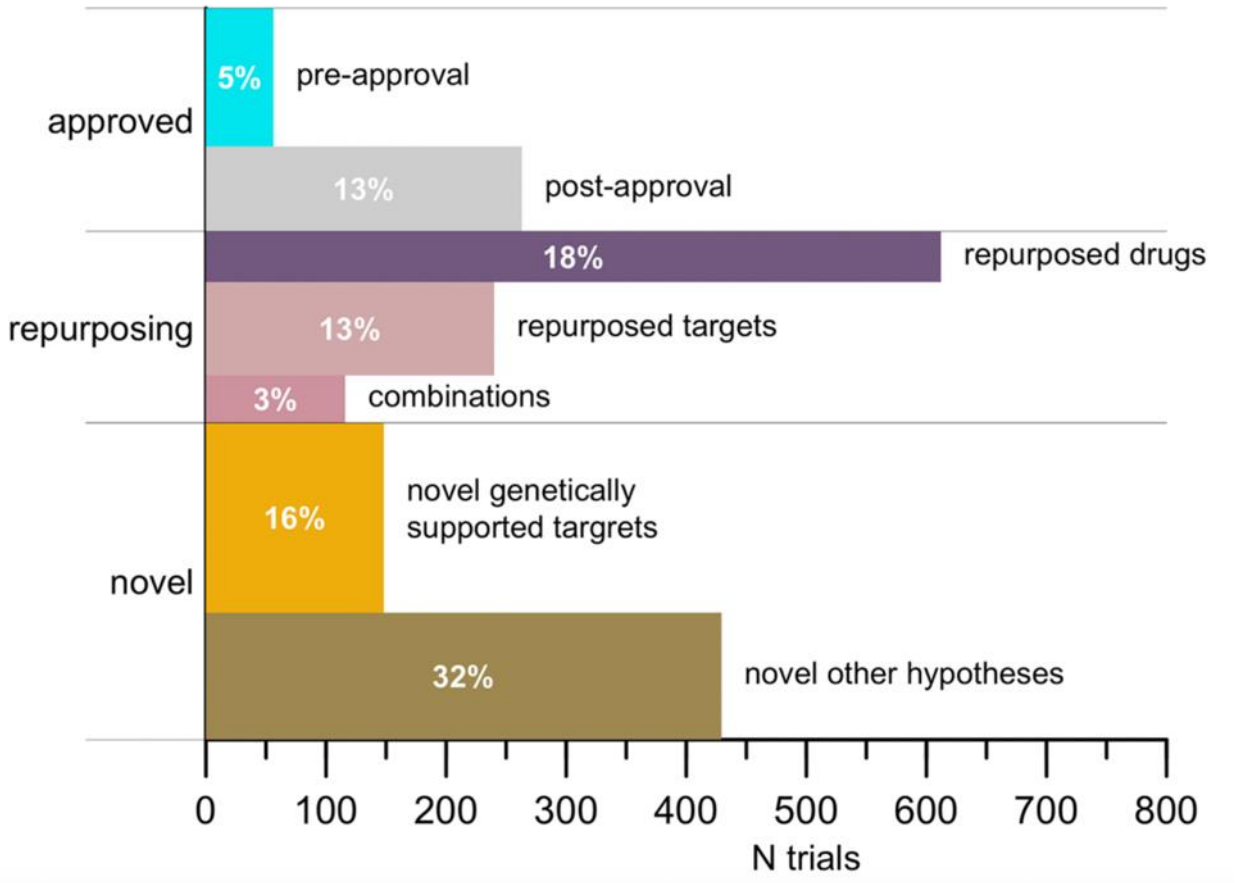
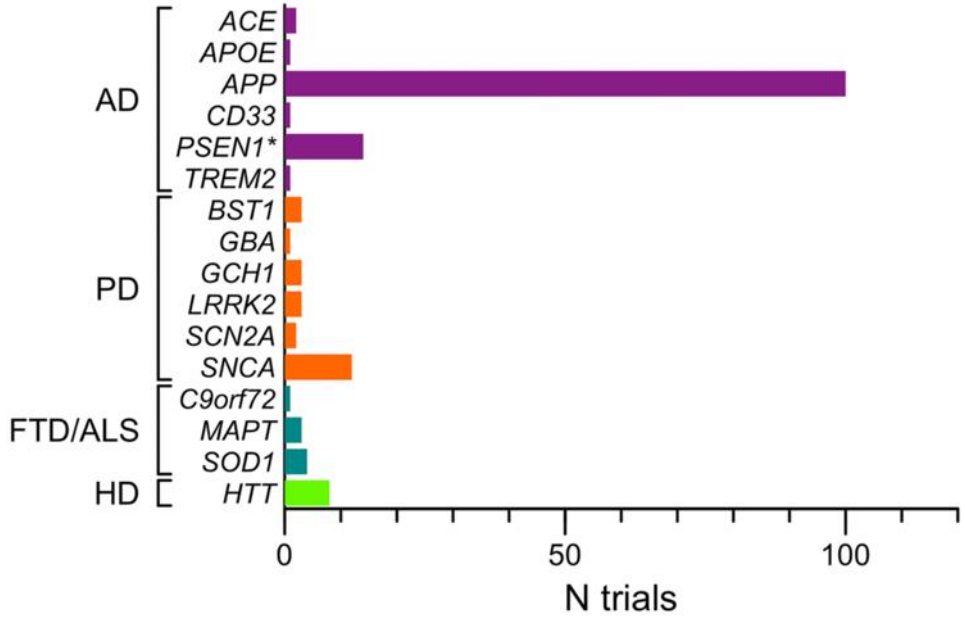
A minority of trials in neurodegenerative diseases are genetically supported…



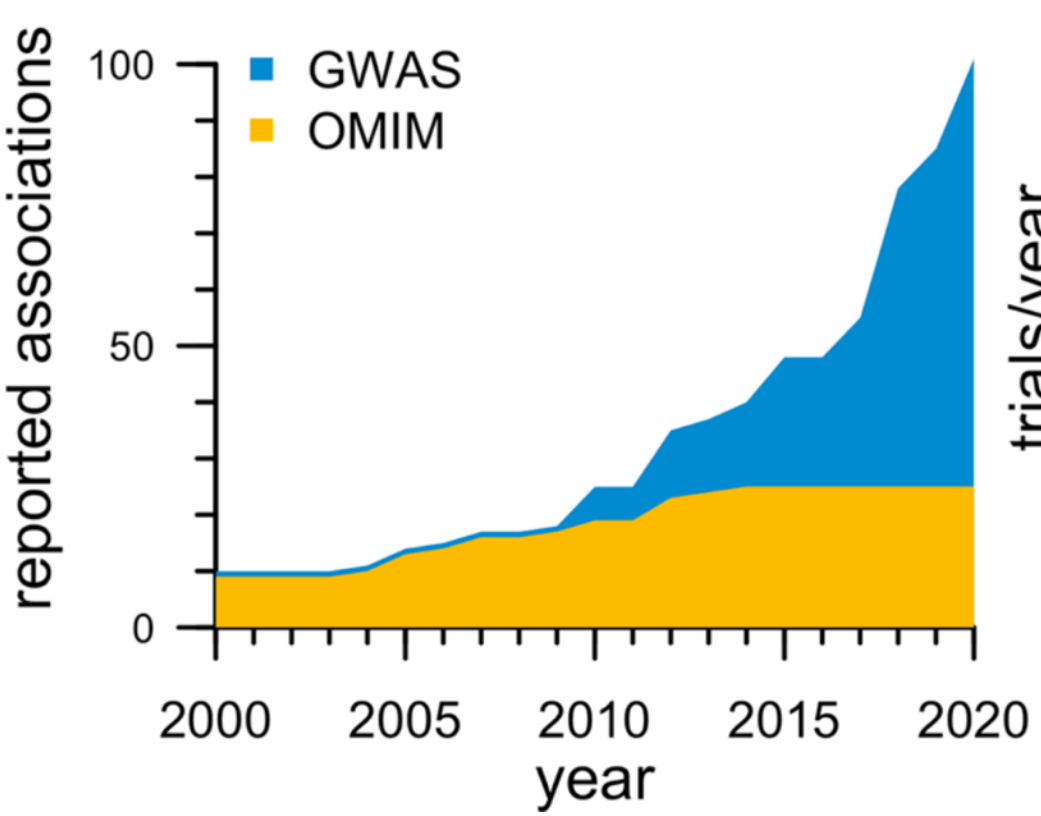
Genetically supported targets account for a small (and non-increasing) minority of all trials in neurodegeneration

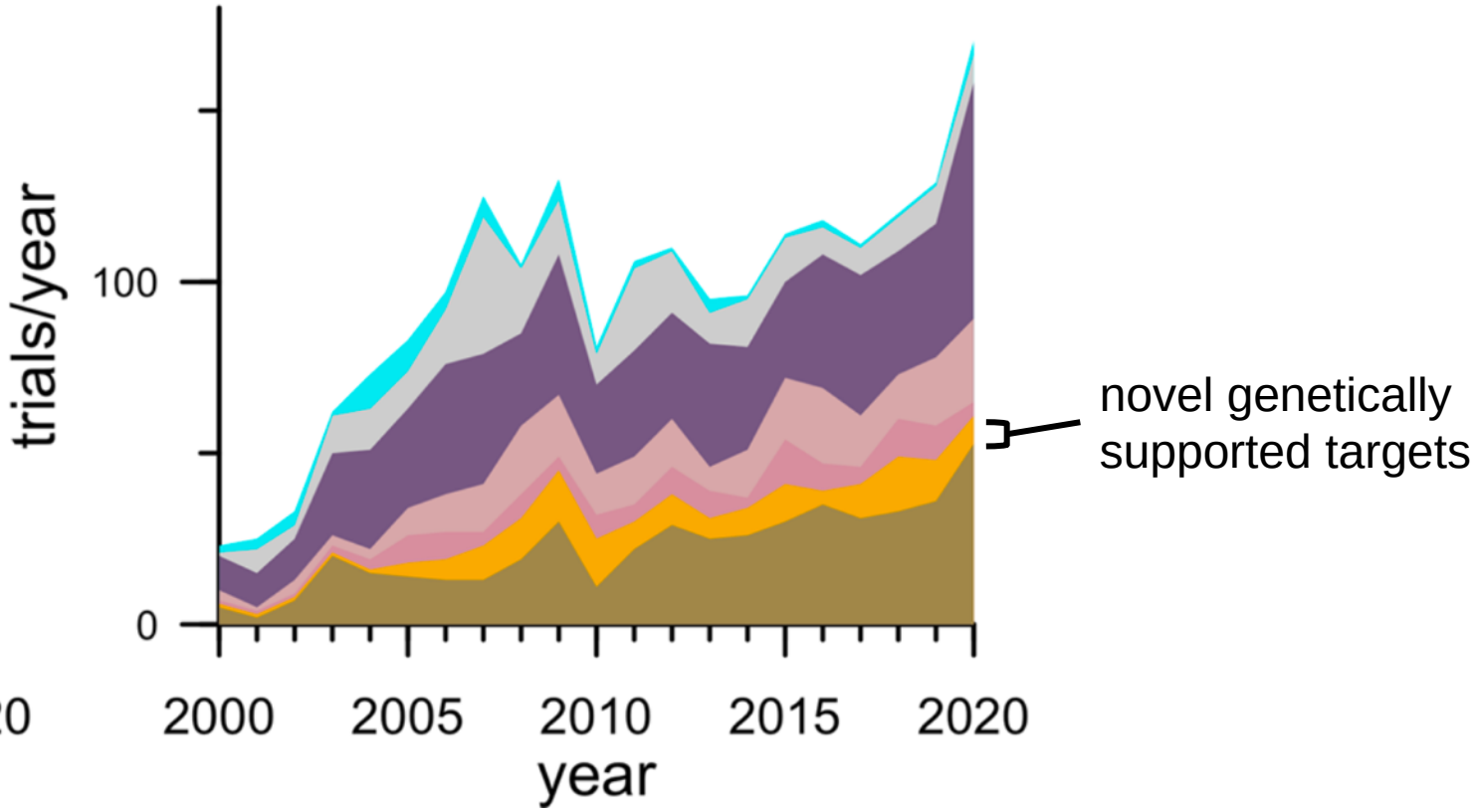
And almost all focus is on amyloid beta



Mortberg 2022, Disease stages and therapeutic hypotheses in two decades of neurodegenerative disease clinical trials. PMID: 36271285

… and that proportion has not risen over time

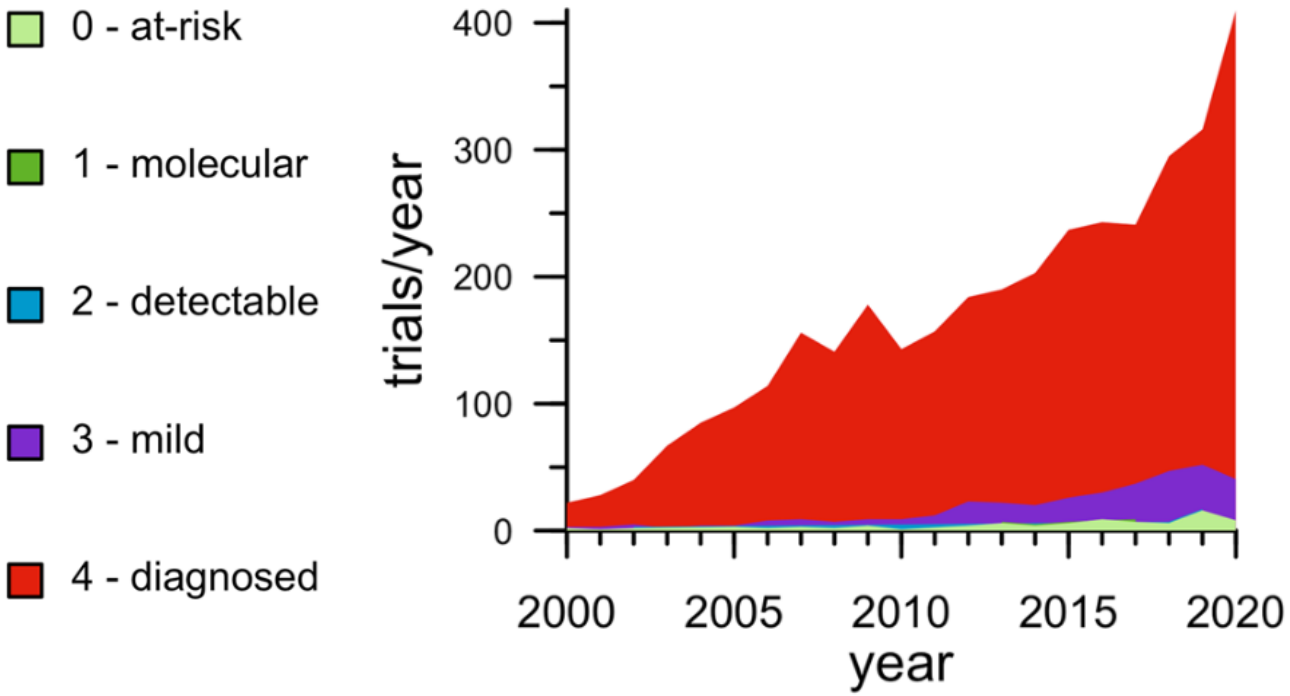




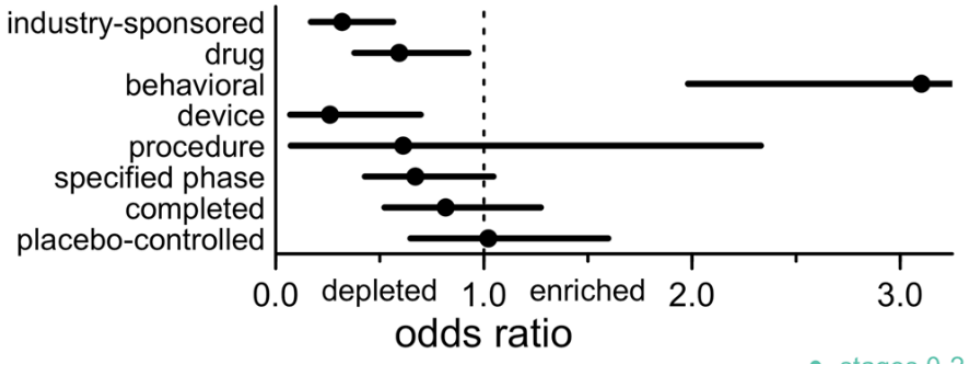
Mortberg 2022, Disease stages and therapeutic hypotheses in two decades of neurodegenerative disease clinical trials. PMID: 36271285

Potential for misalignment between disease stages in genetic studies and in clinical trials

Disease stage recruited in AD/PD/FTD/ALS/HD trials, 2000-2020



Characteristics of the 3% of trials that recruited presymptomatic people



Mortberg 2022, Disease stages and therapeutic hypotheses in two decades of neurodegenerative disease clinical trials. PMID: 36271285

Are the same mechanisms operative in *initiation* and *progression* of disease?

Sometimes **no**:

Genetic Risk for Alzheimer Disease Is Distinct from Genetic Risk for Amyloid Deposition

Our study suggests that *APOE* mostly contributes to amyloid accumulation and the PRS affects risk of further conversion to AD.

Genome-wide association study of rate of cognitive decline in Alzheimer's disease patients identifies novel genes and pathways

Discussion: Pathways related to AD, intelligence, and neurological function determine AD progression, while previously identified AD risk variants, including the apolipoprotein (*APOE*) $\varepsilon 4$ and $\varepsilon 2$ variants, do not have a major impact.

We also examined the top SNPs in 32 known AD risk genes,[77-79] and also the SNPs tagging the *APOE* $\varepsilon 2$ and $\varepsilon 4$ alleles, for association with ROD. After correcting for the number of SNPs tested, only rs1476679 in zinc finger CW-type and PWWP domain containing 1 (*ZCWPW1*, $p_{LME} = 3.07 \times 10^{-6}$, $p_{GEE} = 3.9 \times 10^{-4}$), was significantly associated with ROD. Notably, the minor allele (C) is protective for AD and associated with slower ROD.[77] Although the associations were observed with different variants, *CNTNAP2*[79] and phospholipase C gamma 2 (*PLCG2*)[80] have also recently been implicated as AD risk genes.

Are the same mechanisms operative in *initiation* and *progression* of disease?

Sometimes **yes**:

- PrP lowering
- HTT somatic instability mitigation
- Amyloid beta clearance

Are the same mechanisms operative in different neurodegenerative diseases?

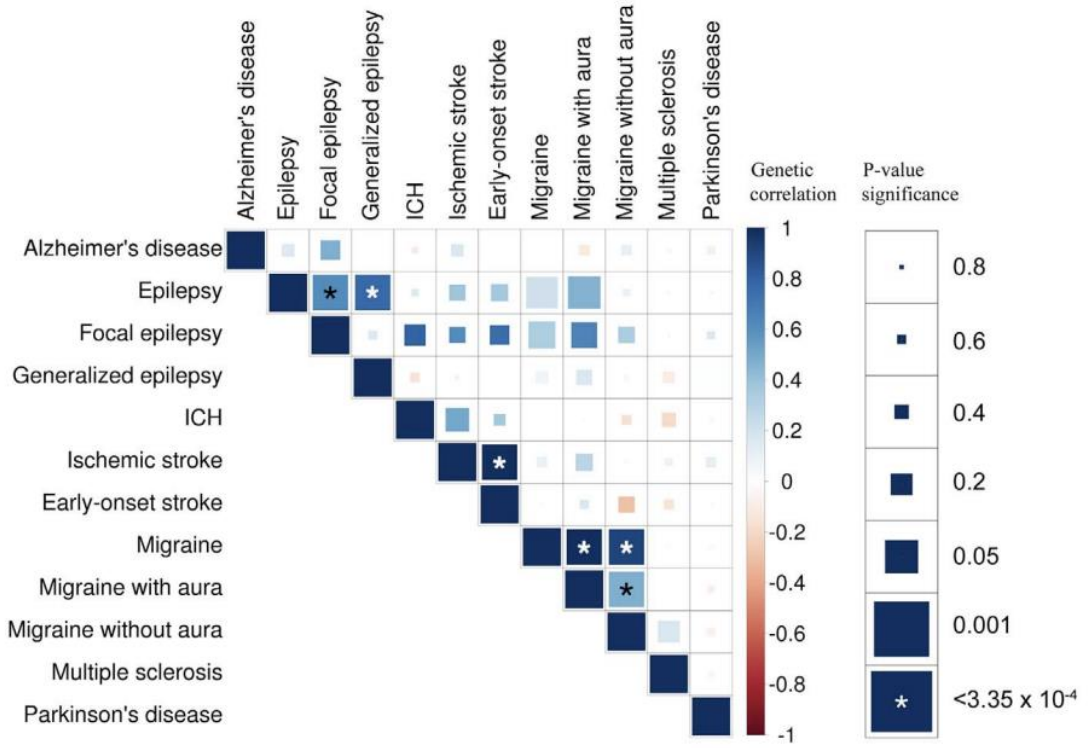


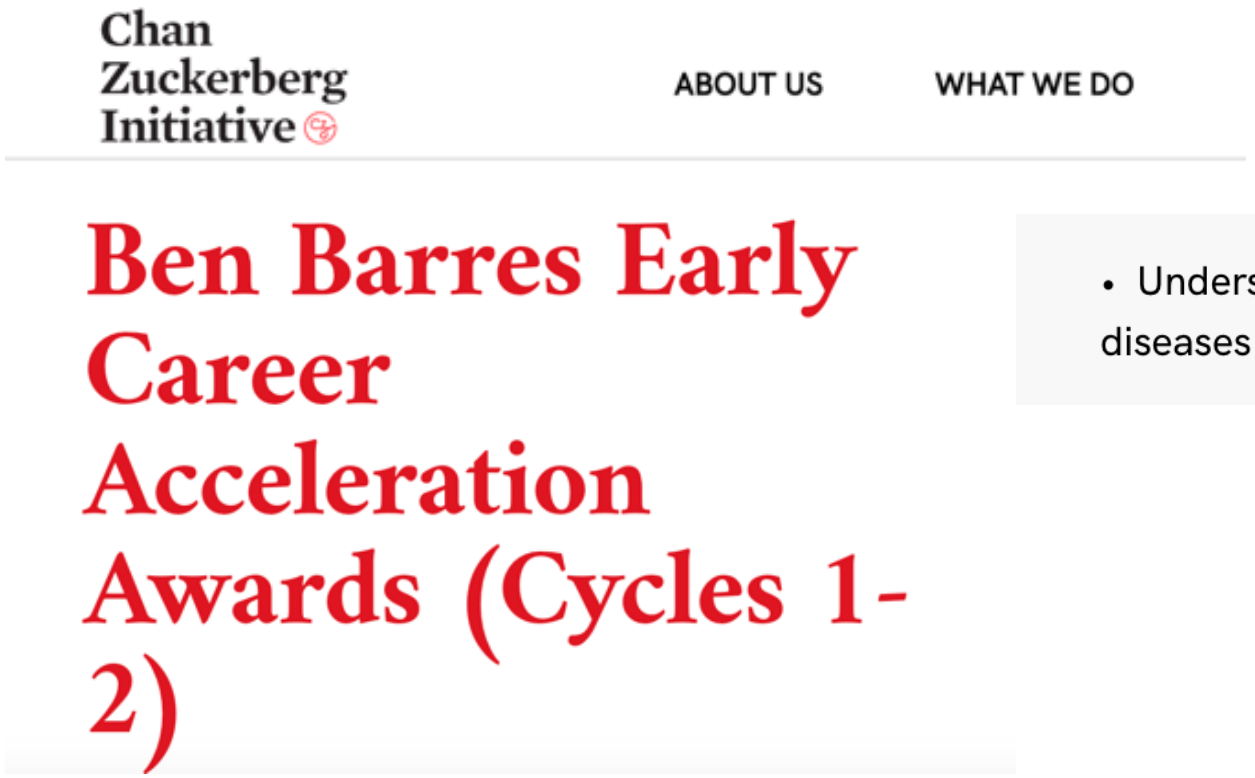
Fig. 2. Genetic correlations across neurological phenotypes. The color of each box indicates the magnitude of the correlation, and the size of the box indicates its significance (LDSC), with significant correlations filling each square completely. Asterisks indicate genetic correlations that are significantly different from zero after Bonferroni correction. Some phenotypes have substantial overlaps (Table 1)—for instance, all cases of generalized epilepsy are also cases of epilepsy. Asterisks indicate significant genetic correlation after multiple testing correction.

No correlation between AD and PD genetic risk coefficients, genome-wide

Of curated genetic hits (Mendelian & GWAS) for AD, PD, FTD/ALS, and HD as of 2022, *MAPT* was the **only** overlap for >1 disease

Anttila 2018. Analysis of shared heritability in common disorders of the brain. PMID: 29930110
Mortberg 2022, Disease stages and therapeutic hypotheses in two decades of neurodegenerative disease clinical trials. PMID: 36271285

“Cross-cutting mechanisms” sounds good, but is it really?



https://chanzuckerberg.com/rfa/ben-barres-early-career-acceleration-awards/
https://cziscience.medium.com/a-new-approach-to-solving-neurodegeneration-2aa50654ed04

If the drug targets are not the same, then what do Alzheimer’s disease, prion disease, etc. have in common?

If the drug targets are not the same, then what do Alzheimer's disease, prion disease, etc. have in common?

- Prion mechanism
  - Seeding assays for diagnosis
  - Strain typing to predict clinical phenotypes
  - Challenge-based animal models
  - Decontamination & transmission concerns
- Neurodegeneration & neuroinflammation
  - NfL, T-tau, GFAP, etc. biomarkers for prognostication & monitoring
- At-risk, prodromal, and manifest disease stages
  - Need for longitudinal observational studies
  - Need for new clinical paths & regulatory flexibility

Common needs for drug discovery

- Platform technologies to target specific genes
- Delivery systems for the human CNS

Holly Kordasiewicz

Ken Chan

11:30a – 12:40p
Thursday 11/14
Rational drug design for prion disease and how this informs other ADRDs

Platform technologies for targeting specific disease proteins

- DNA-targeted
  - Base editing
  - Epi-editing
  - Transcriptional repressors
- RNA-targeted
  - ASO
  - siRNA
  - ADAR
- Protein-targeted
  - mAbs
  - Secretory inhibitors

Platform technologies for delivery

- Engineered AAVs
- Engineered Fc mAbs
- mAb-RNA conjugates
- Conjugated / chemically stabilized oligonucleotides

Conclusions

- Success is rare in drug discovery, especially neurodegeneration
- Human genetic evidence improves success rate
  - But not all hits are good drug targets
- Consideration regarding disease stage is merited
- Specific targets are rarely shared between diseases
  - And when they are, they still may not be the best targets
- The real opportunity: develop **platforms** and **delivery systems** that cross-cut diseases

Thank you

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