Future of Individualized Medicine Conference

La Jolla, March 14, 2019

Human Genetics to validate drug targets in neurodegenerative disease

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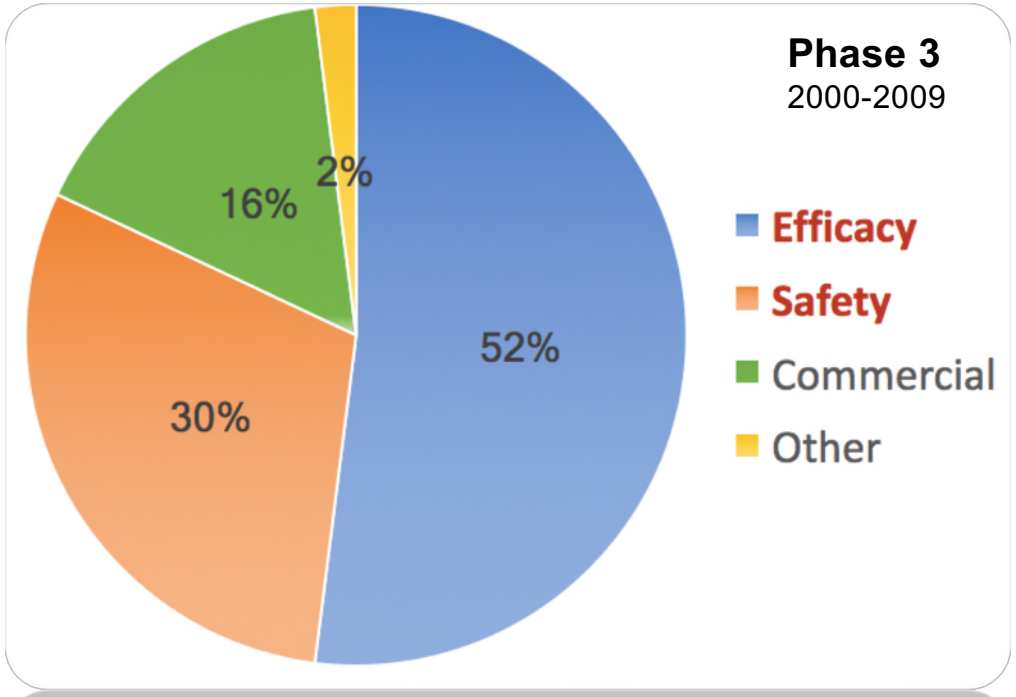
Disclosures:

- Employee at Biogen Inc.
- Stocks at Merck & Co.

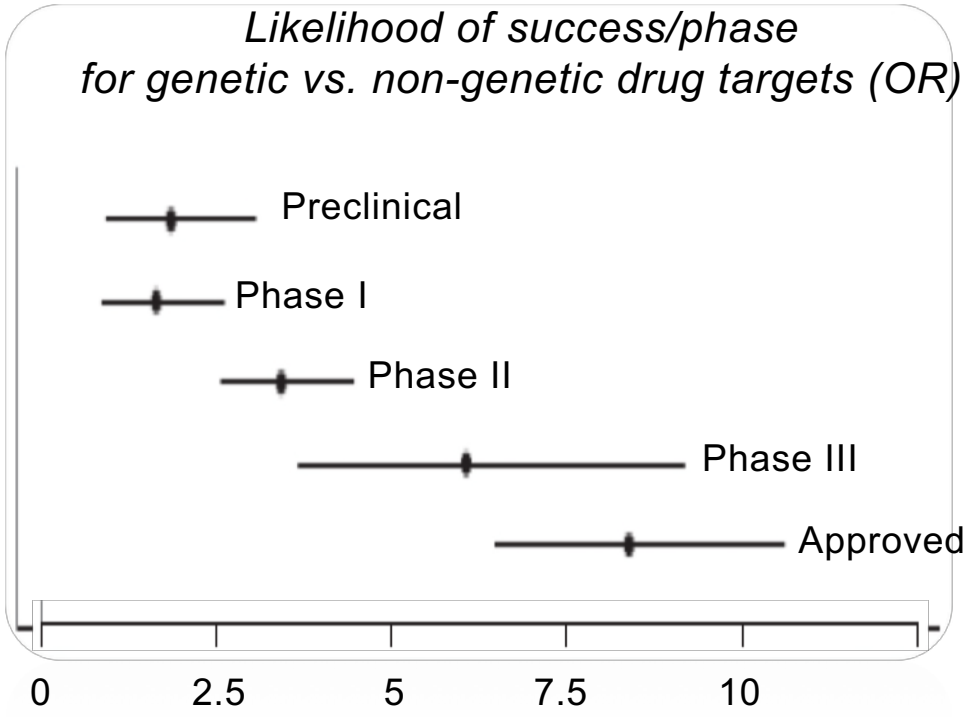
>90% of drug programs fail clinical trials because we pick the wrong targets

Causes of late-stage clinical failures



Tuft Center for the Study of Drug Development.. 2013

Genetic support tracks with success



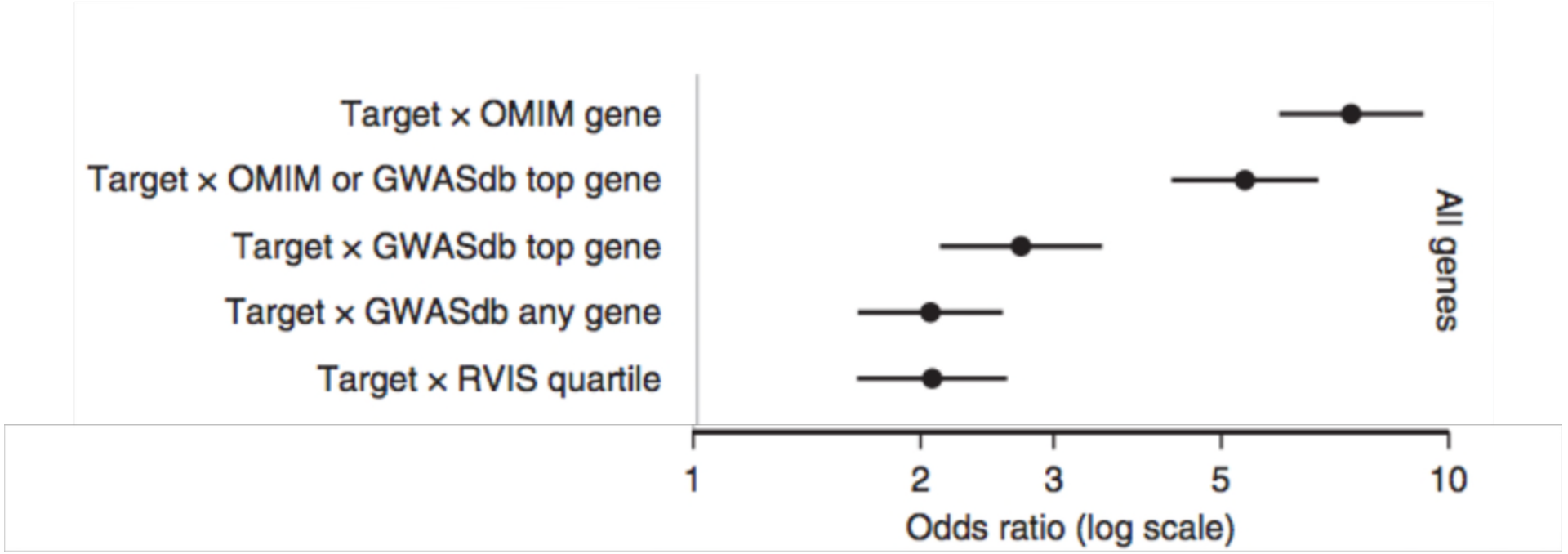
Nelson et al. Nat Genet. 2015

Drug targets with human genetic support have higher success rates

The support of human genetic evidence for approved drug indications

Matthew R Nelson[1], Hannah Tipney[2], Jeffery L Painter[1], Judong Shen[1], Paola Nicoletti[3], Yufeng Shen[3,4], Aris Floratos[3,4], Pak Chung Sham[5,6], Mulin Jun Li[6,7], Junwen Wang[6,7], Lon R Cardon[8], John C Whittaker[2] & Philippe Sanseau[2]

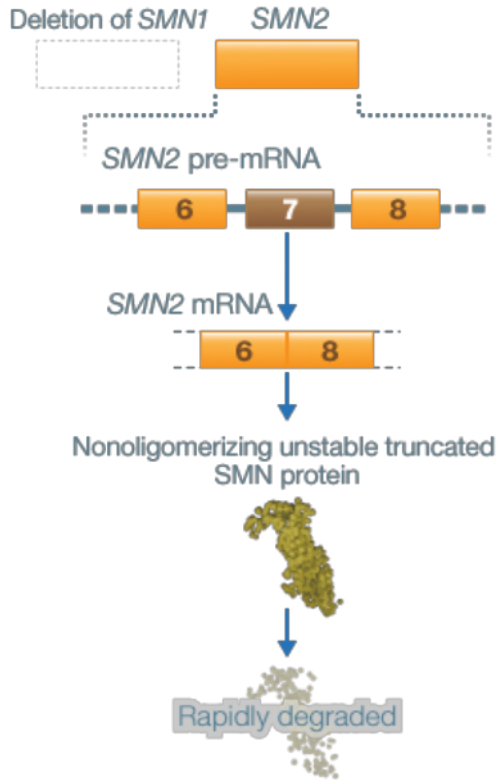
Nelson et al (2015) *Nature Genetics* 47, 856–860 (2015)



Mendelian Disease:

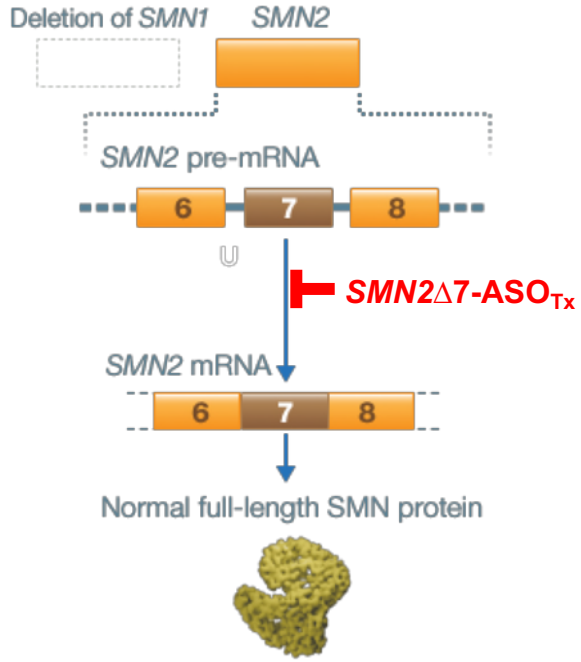
Nursinersen (Spinraza®) as a treatment for Spinal muscular atrophy

Spinal muscular atrophy



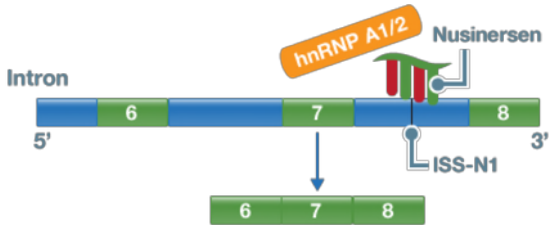
- cause: homozygous del*SMN1*
- *SMN2* nonfunctional due to alternative splicing

Therapeutic hypothesis: *SMN2*Δ7 splicing ⬇ -> SMN protein ⬆



- SMA severity correlates with SMN residual levels
- Can modulating *SMN2* splicing help in SMA?

Nusinersen antisense-oligonucleotide therapy

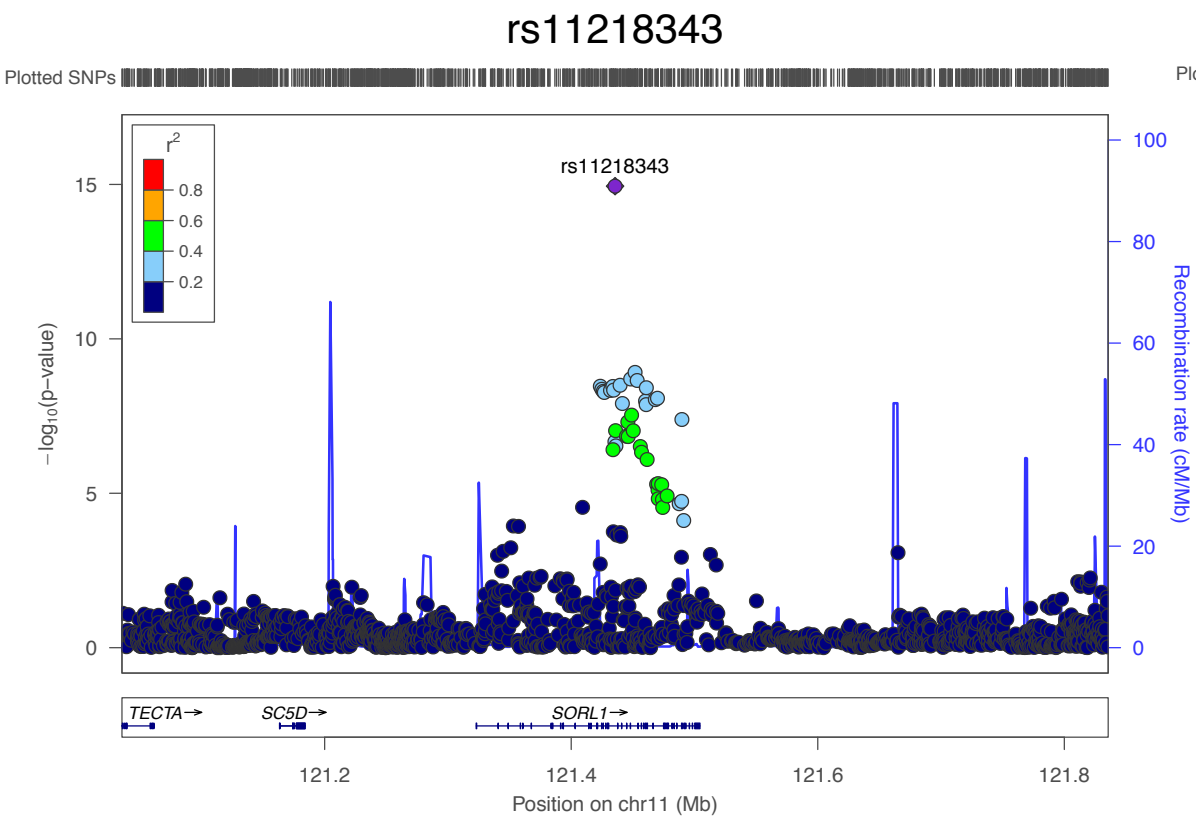


- **CS3A** Ph2 study in SMA infants: proof-of-biology
- **ENDEAR** Ph3 study in SMA infants: motor function ⬆, event-free survival ⬆
- **NURTURE** Ph2 pre-symptomatic study: all participants reach motor milestones
- 1000s SMA patients on treatment
- newborn screening implemented

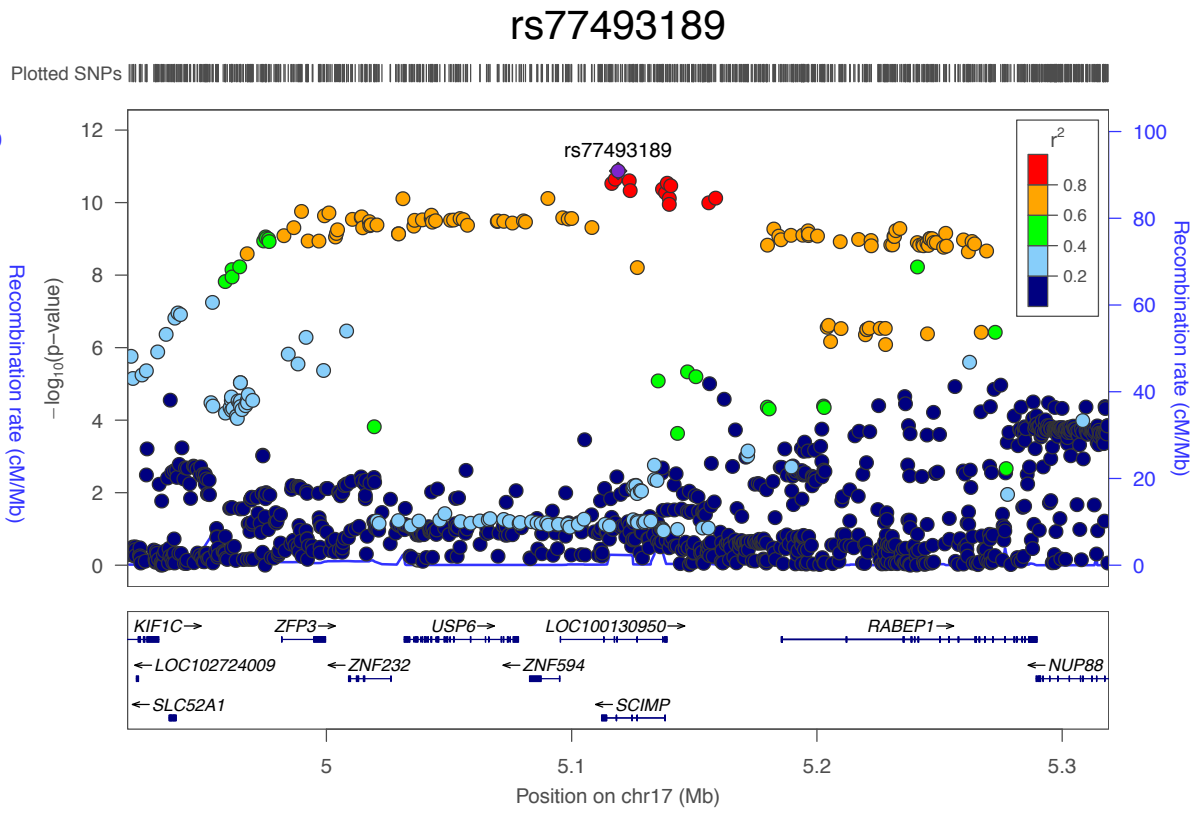
Complex Disease:

Identification of causal gene from GWAS loci is not trivial

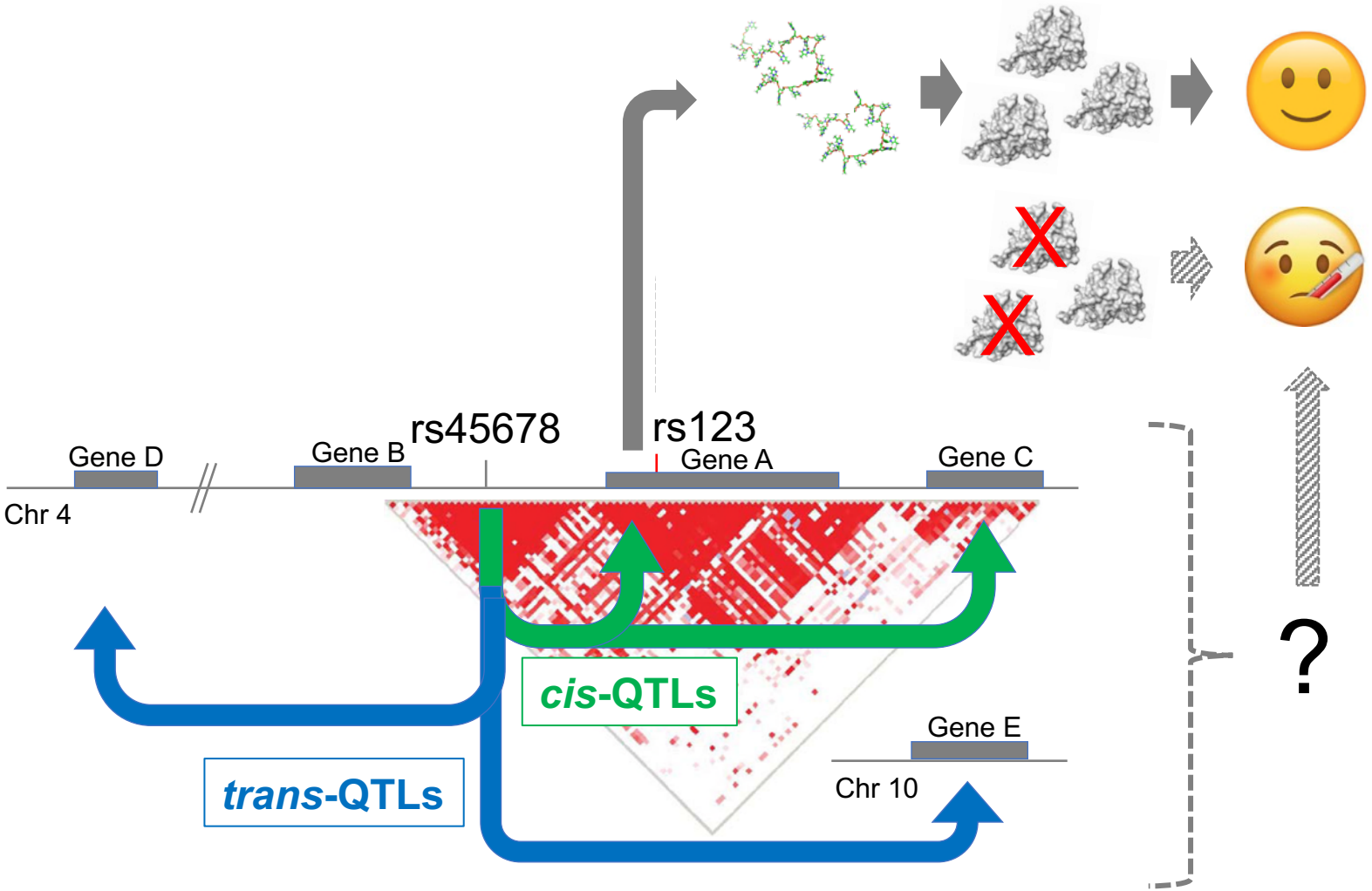
Some loci are discrete
with only one gene embedded



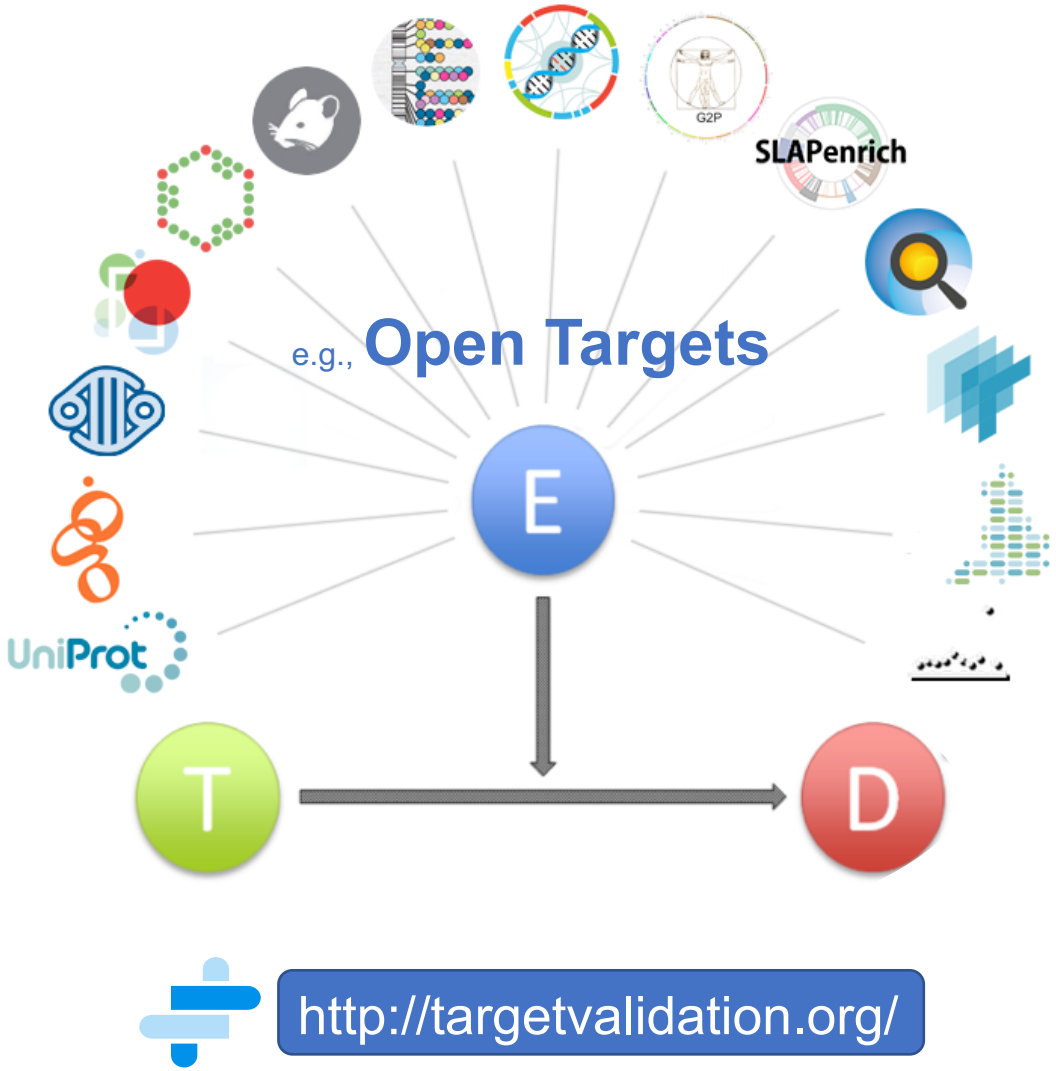
However, most loci have dozens of genes
making causal gene/variant identification difficult



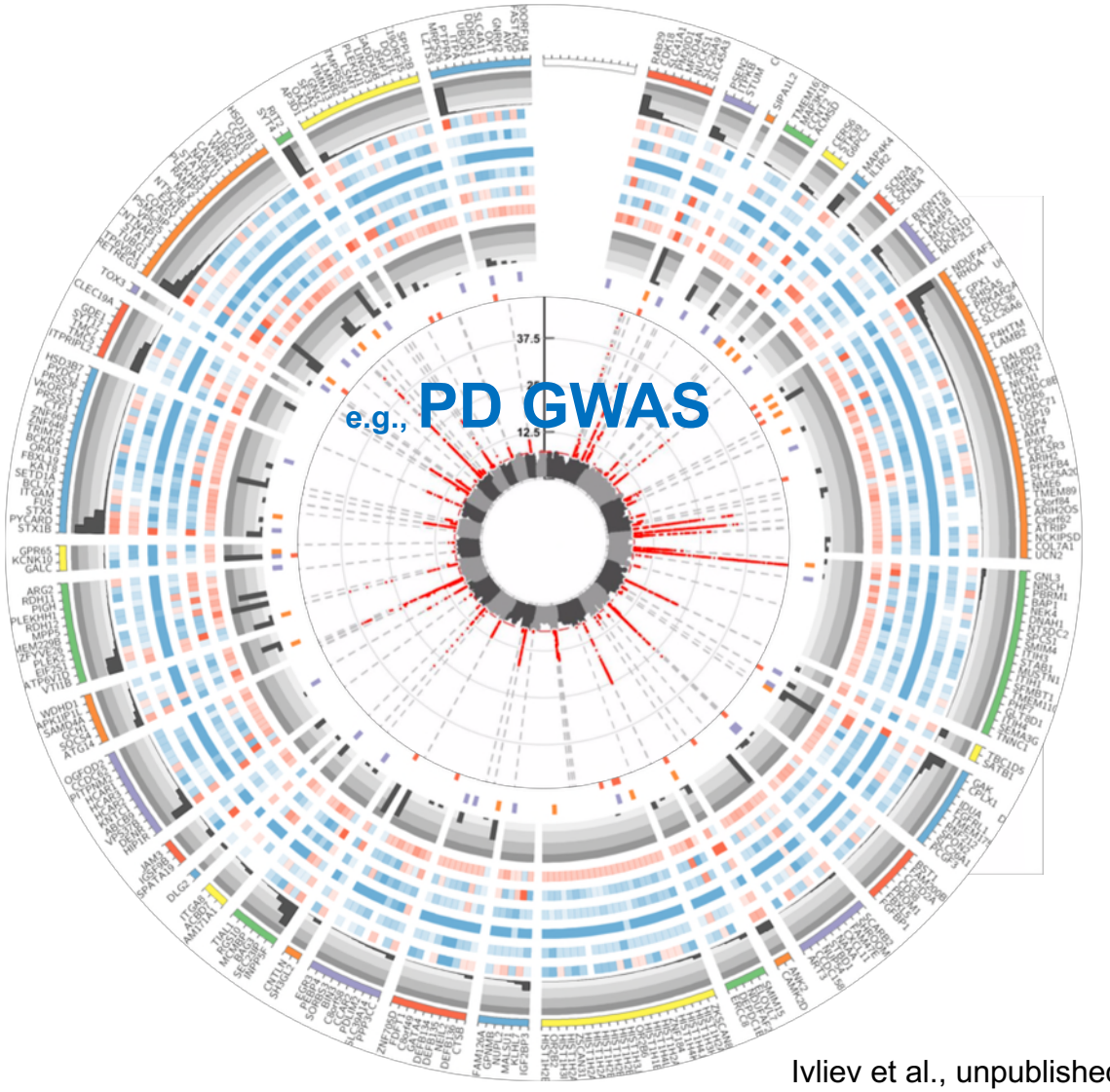
The challenge: 1. What's the causal gene in a GWAS locus?
2. Is it a suitable drug target?



Omics Evidence helps closing gaps between genes (= Targets) and Disease



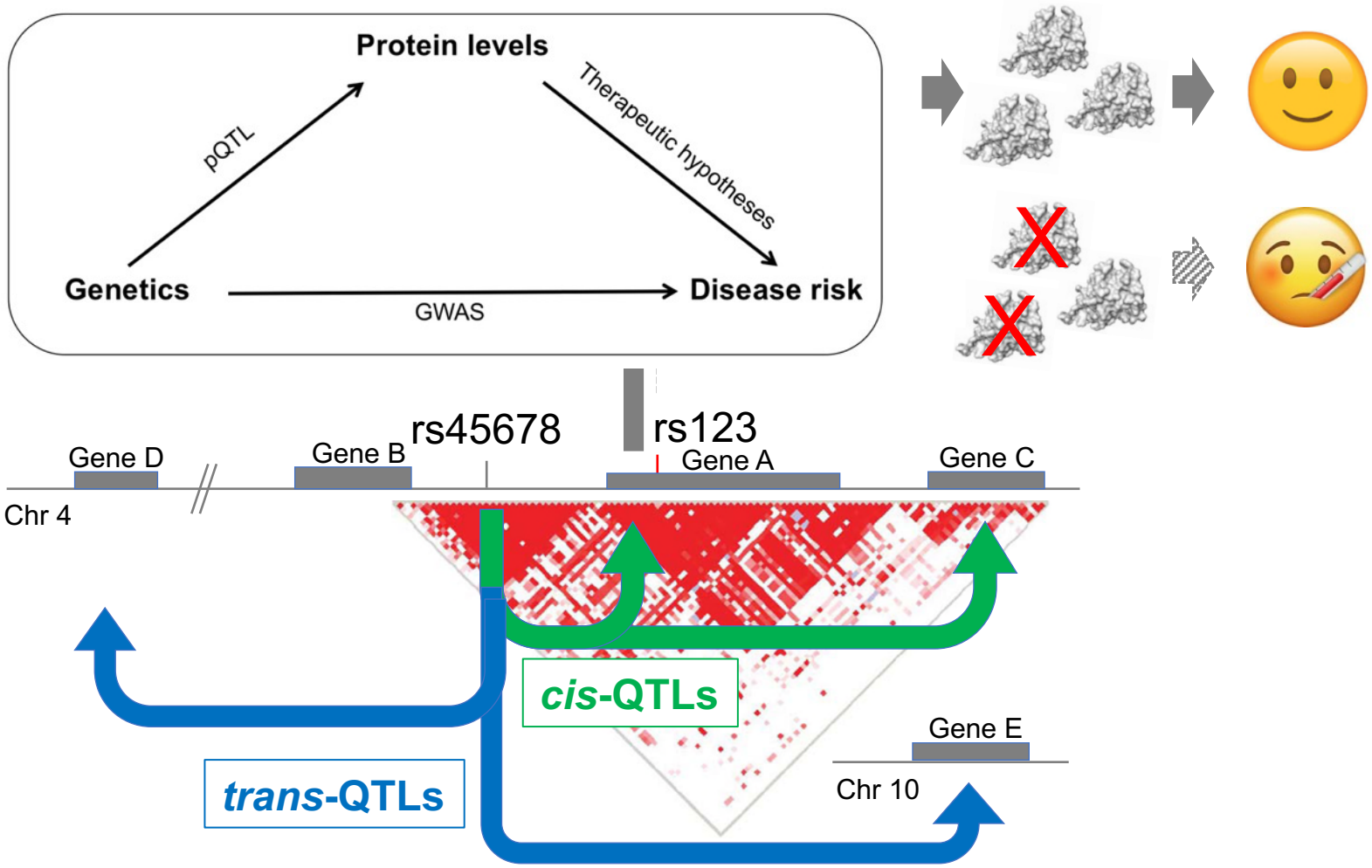
http://targetvalidation.org/



Ivliev et al., unpublished

Yet: Data have yet been missing to directly the genome and the proteome

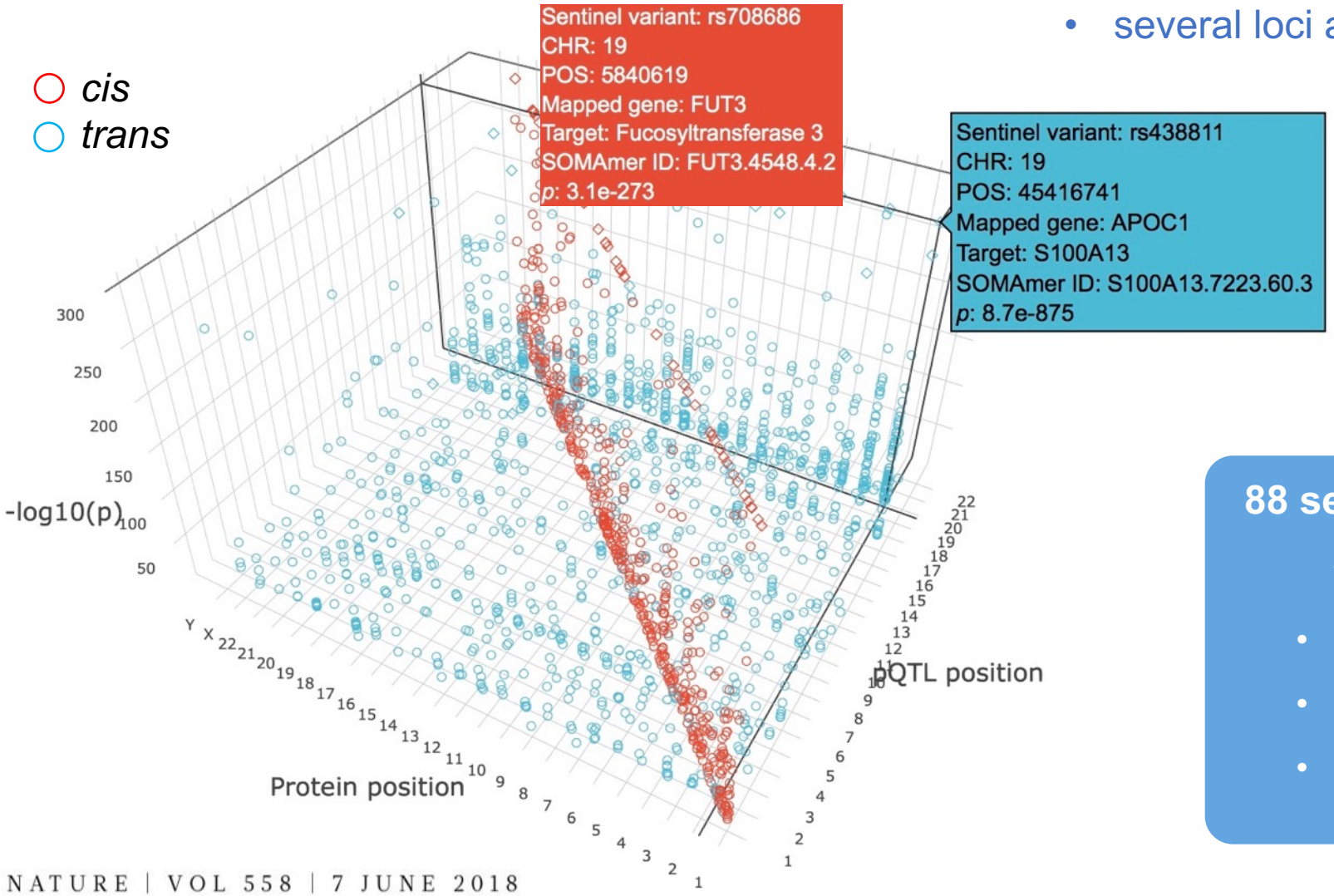
Proteins are the targets of most drugs, culprits of disease, and relied on as intermediate biomarkers, but we know little about how their levels are influenced by variation in the genome



Genomic atlas of the human plasma proteome

Benjamin B. Sun[1,22], Joseph C. Maranville[2,20,22], James E. Peters[1,3,22], David Stacey[1], James R. Staley[1], James Blackshaw[1], Stephen Burgess[1,4], Tao Jiang[1], Ellie Paige[1,5], Praveen Surendran[1], Clare Oliver-Williams[1,6], Mihir A. Kamat[1], Bram P. Prins[1], Sheri K. Wilcox[7], Erik S. Zimmerman[7], An Chi[2], Narinder Bansal[1,8], Sarah L. Spain[9], Angela M. Wood[1], Nicholas W. Morrell[3,10], John R. Bradley[11], Nebojsa Janjic[7], David J. Roberts[12,13], Willem H. Ouwehand[3,14,15,16,17], John A. Todd[18], Nicole Soranzo[3,14,16,17], Karsten Suhre[19], Dirk S. Paul[1], Caroline S. Fox[2], Robert M. Plenge[2,20], John Danesh[1,3,16,17]*, Heiko Runz[2,21,23] & Adam S. Butterworth[1,17,23]*

- 1,927 pQTLs ($p<1.5 \times 10^{-11}$)
- link 1,478 proteins and 764 genomic regions
- 89% novel, 529 (28%) *cis*-acting
- 12% of proteins controlled both, in *cis* and in *trans*
- several loci are highly pleiotropic



88 sentinel pQTLs in high LD ($r^2 \geq 0.8$) with sentinel GWAS variants

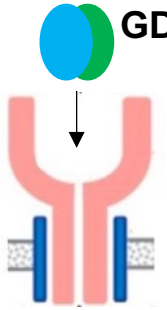
- 30 with *cis*, 54 with *trans*, and 4 with both
- 253 distinct genotype–disease associations
- 96 PP>0.8 for shared causal variants

NATURE | VOL 558 | 7 JUNE 2018

Myostatin (*GDF8*), a plasma protein and drug target for neuromuscular disease

Plasma myostatin (*GDF8*) is a target for muscle wasting disease

Δ*GDF8* causes muscle hypertrophy

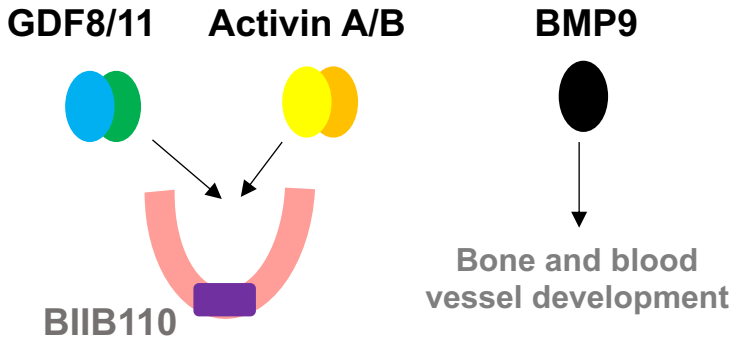


GWAS associate GDF8/11-receptor *ACVR2B* with hand-grip strength

Therapeutic hypothesis:

GDF8 in plasma ⬇️ -> muscle growth ⬆️

The impact of modulating myostatin pathway is being tested in clinical trials



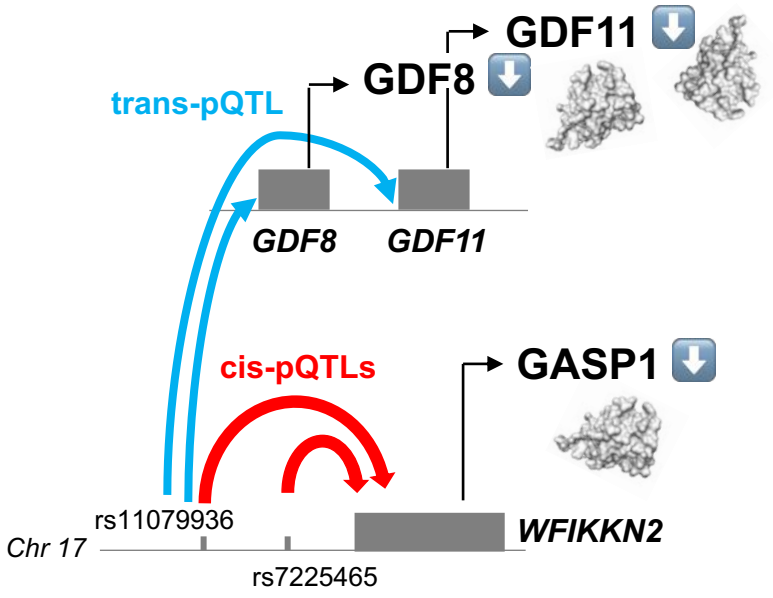
BIIB110: extracellular ActRII domain with BMP9-sparing hinge for improved efficacy & safety

BIIB110 is currently in a **Phase1a** study

Potential for complementary benefit when used combined with SPIRAZA

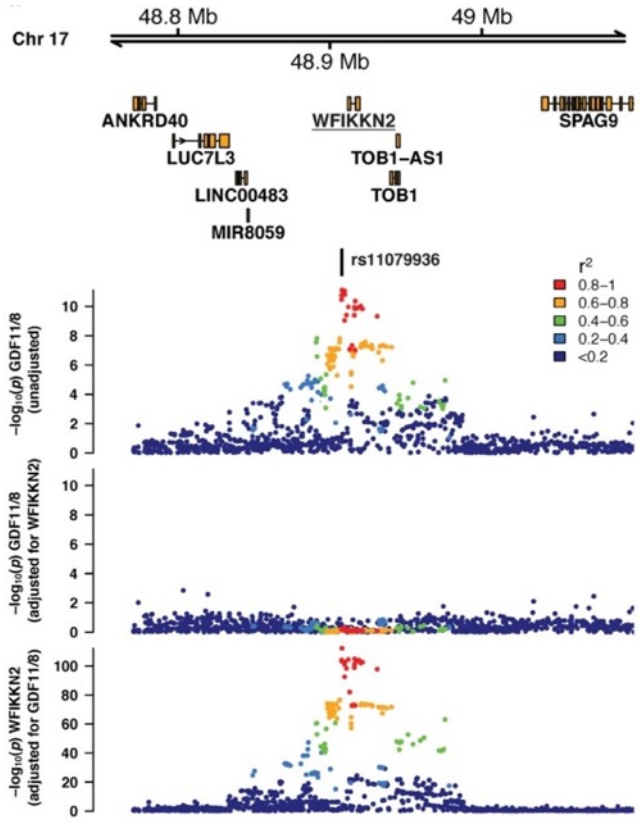
Myostatin levels and function underlie genetic control by GASP1 (*WFIKKN2*)

Plasma levels of GDF8, GDF11 and GASP1 (*WFIKKN2*) are genetically controlled



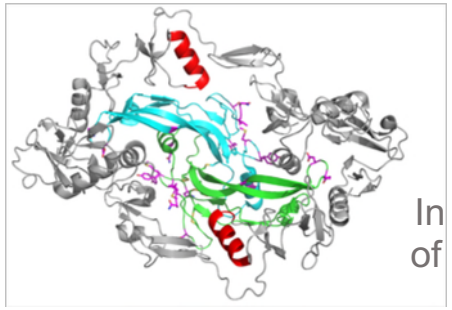
rs11079936-C → GASP1 ↓, myostatin ↓

GASP1 regulates GDF8/11 at the protein level

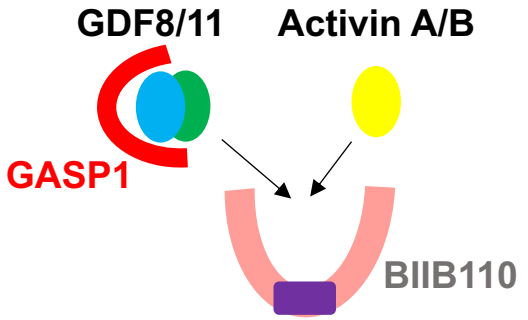


rs11079936-C → GASP1 ↓ → myostatin ↓

Mass spec proposes a GASP1/GDF8/GDF11 complex regulating GDF8 activity

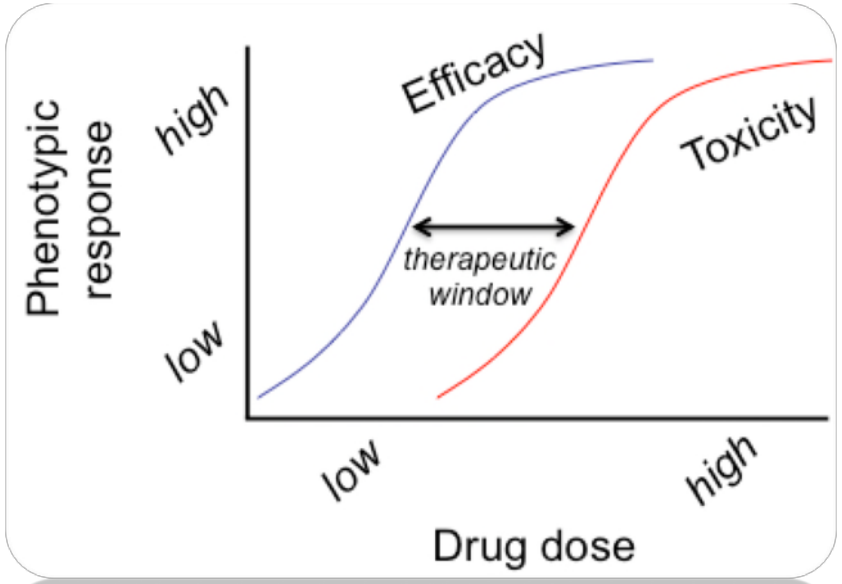


In silico prediction of protein complex



GASP1: a new target modulating GDF8/11 function and/or BIIB110 efficacy

We use genetics to predict targets that will be safe and efficacious in humans



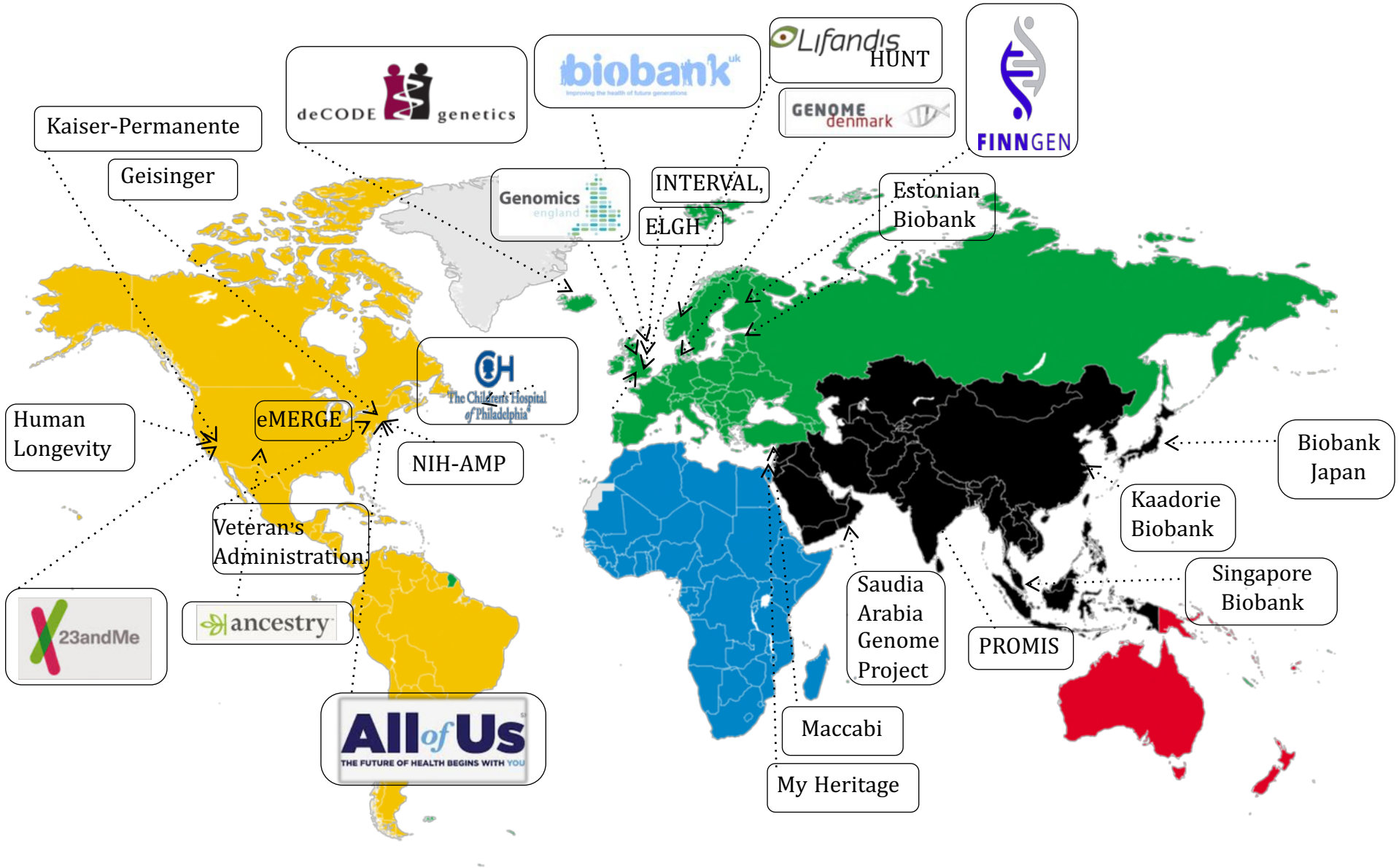
Genetic dose

Target ID and Validation → **Lead Optimization** → **Early Development** → **Phase II-III Clinical Trials**

We aspire to determine dose-response at the time of target ID and validation

We determine dose-response in clinical trials, after many years and millions of dollars

Biobanks that link genetic with health outcomes provide the source data



Deep phenotypes in biobanks enable more comprehensive target assessments

disease-agnostic population

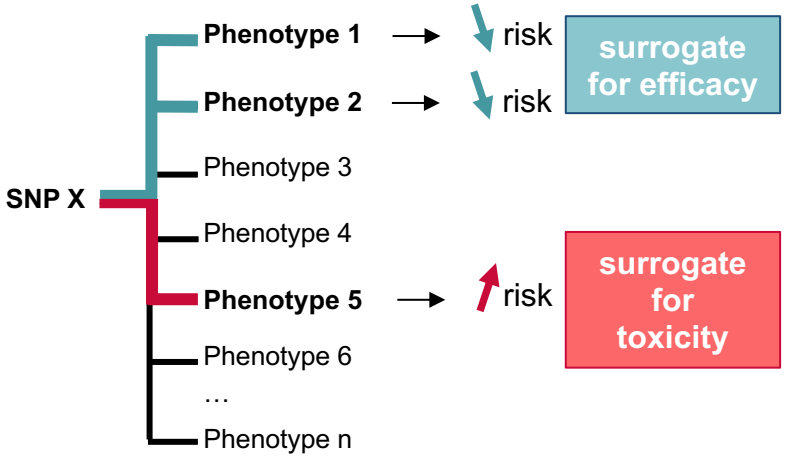
Genetics

„Real-World phenotypic Data“

GWAS traits | EHRs | EMRs | self reports

Phenome-wide association studies (PheWAS)

Testing the association of selected SNPs with a large list of phenotypic endpoints



Is all this data of any concrete use for drug discovery and development?

nature COMMUNICATIONS

ARTICLE

DOI: 10.1038/s41467-018-06540-3 OPEN

Phenome-wide association studies across large population cohorts support drug target validation

Dorothee Diogo

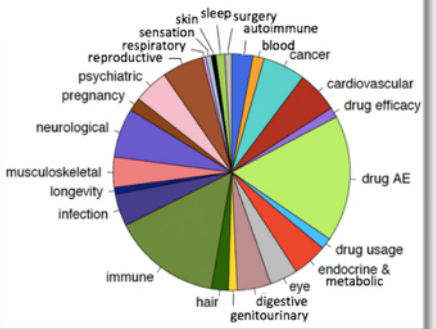
Can we inform on drug target safety / efficacy through meta-PheWAS across multiple large real-world biobank cohorts?

23andMe

654
disease endpoints

self reports

N=671,151



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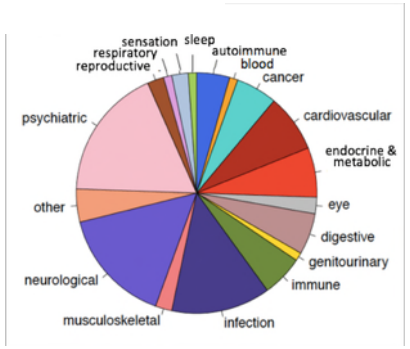
GENOMICS plc

UK Biobank v1

90
disease endpoints

self reports,
medical interviews

N=112,337



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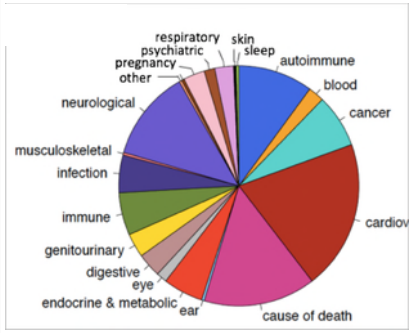
IPHG
FINRISK

278
disease endpoints

EHRs
(ICD)

N=21,371



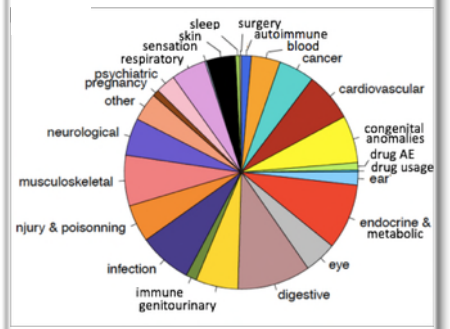
+

The Children's Hospital of Philadelphia

870
disease endpoints

pediatric EHRs
(ICD)

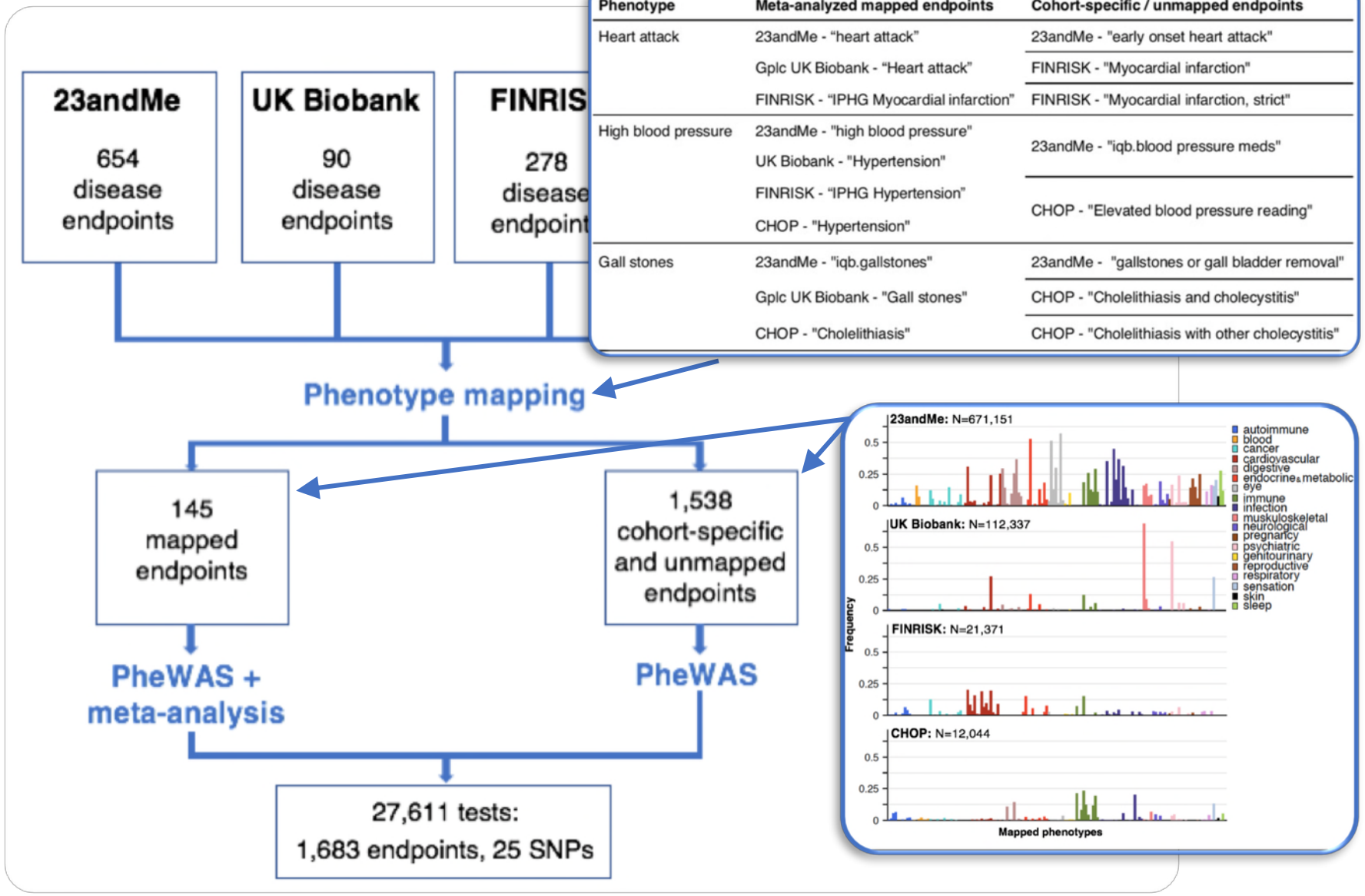
N=12,044



<u>Study outline:</u> 25 SNPs in 19 drug targets across indication -> 4 RWD cohorts + 44 GWAS

Diogo,…, Runz; *NatureCOMMS* 2018

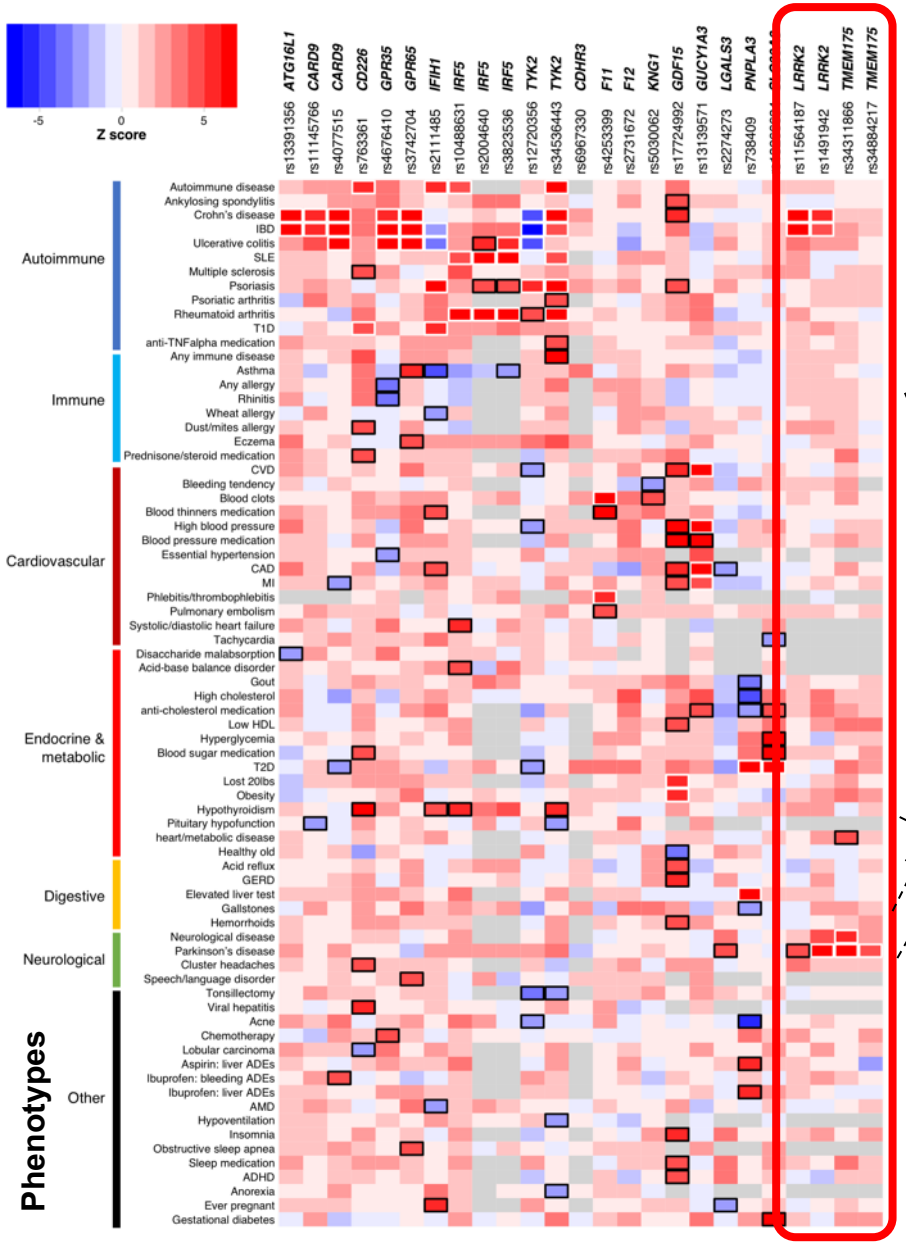
Phenotype mapping for „meta-PheWAS“ in 700k individuals



Phenotype	Meta-analyzed mapped endpoints	Cohort-specific / unmapped endpoints
Heart attack	23andMe - “heart attack”	23andMe - "early onset heart attack"
	GpIc UK Biobank - “Heart attack”	FINRISK - "Myocardial infarction"
	FINRISK - “IPHG Myocardial infarction”	FINRISK - "Myocardial infarction, strict"
High blood pressure	23andMe - "high blood pressure"	23andMe - "iqb.blood pressure meds"
	UK Biobank - "Hypertension"	
	FINRISK - “IPHG Hypertension”	CHOP - "Elevated blood pressure reading"
	CHOP - "Hypertension"	
Gall stones	23andMe - "iqb.gallstones"	23andMe - "gallstones or gall bladder removal"
	GpIc UK Biobank - "Gall stones"	CHOP - "Cholelithiasis and cholecystitis"
	CHOP - "Cholelithiasis"	CHOP - "Cholelithiasis with other cholecystitis"

Diogo,…, Runz; *NatureCOMMS* 2018

PheWAS help validate hypotheses, propose novel indications and hint at AEs

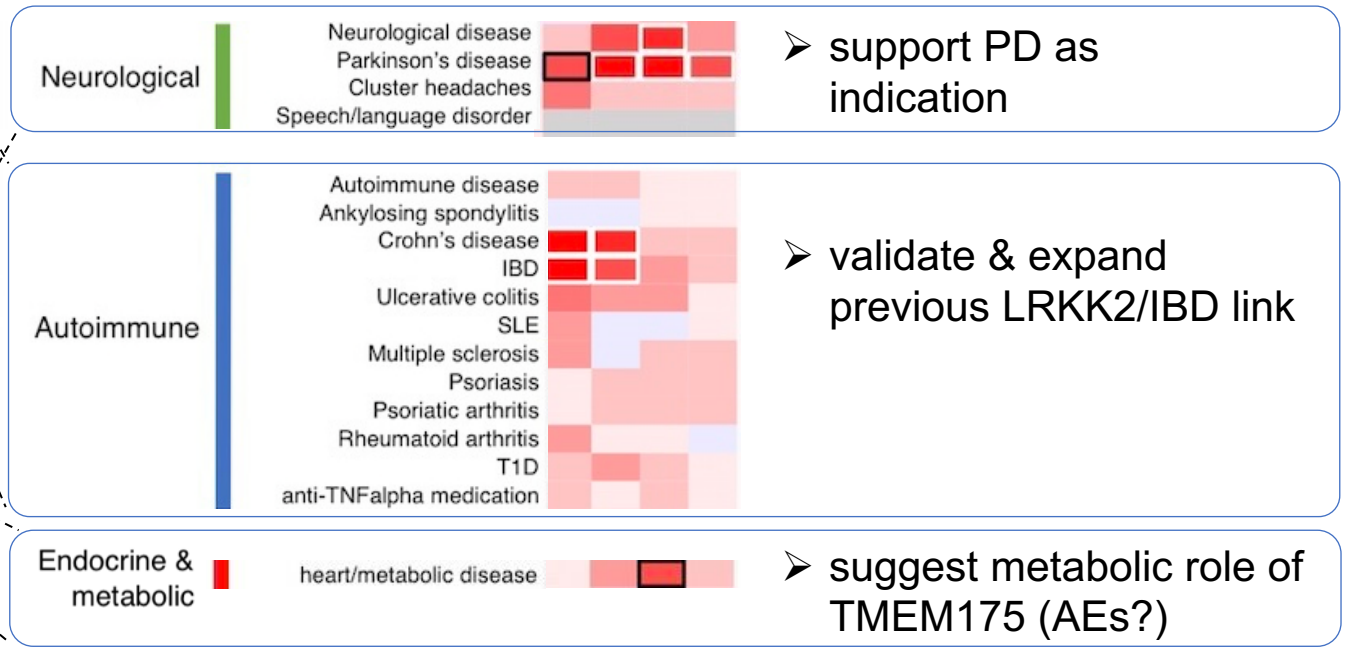


Example:

Parkinsons Disease

2 loci: a) LRRK2
b) TMEM175

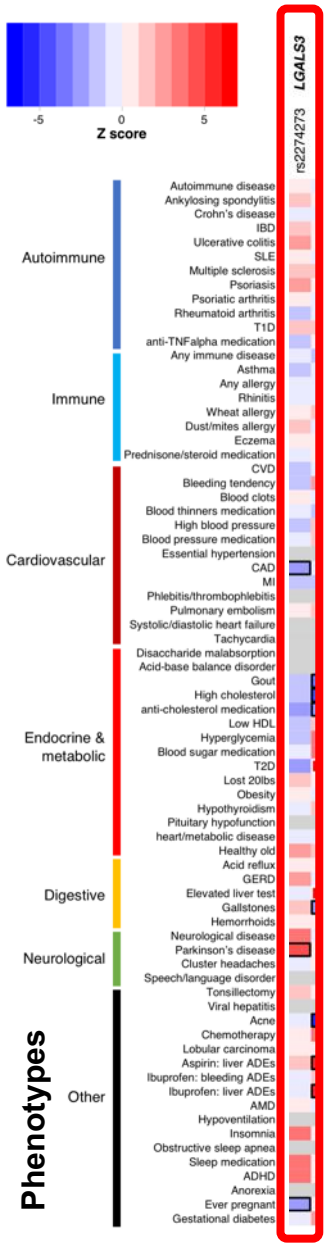
PheWAS results:



- support PD as indication
- validate & expand previous LRKK2/IBD link
- suggest metabolic role of TMEM175 (AEs?)

Diogo,…, Runz; *NatureCOMMS* 2018

Genetic follow-up to PheWAS can help validate or rule out hypotheses



LGALS3
(rs2274273)

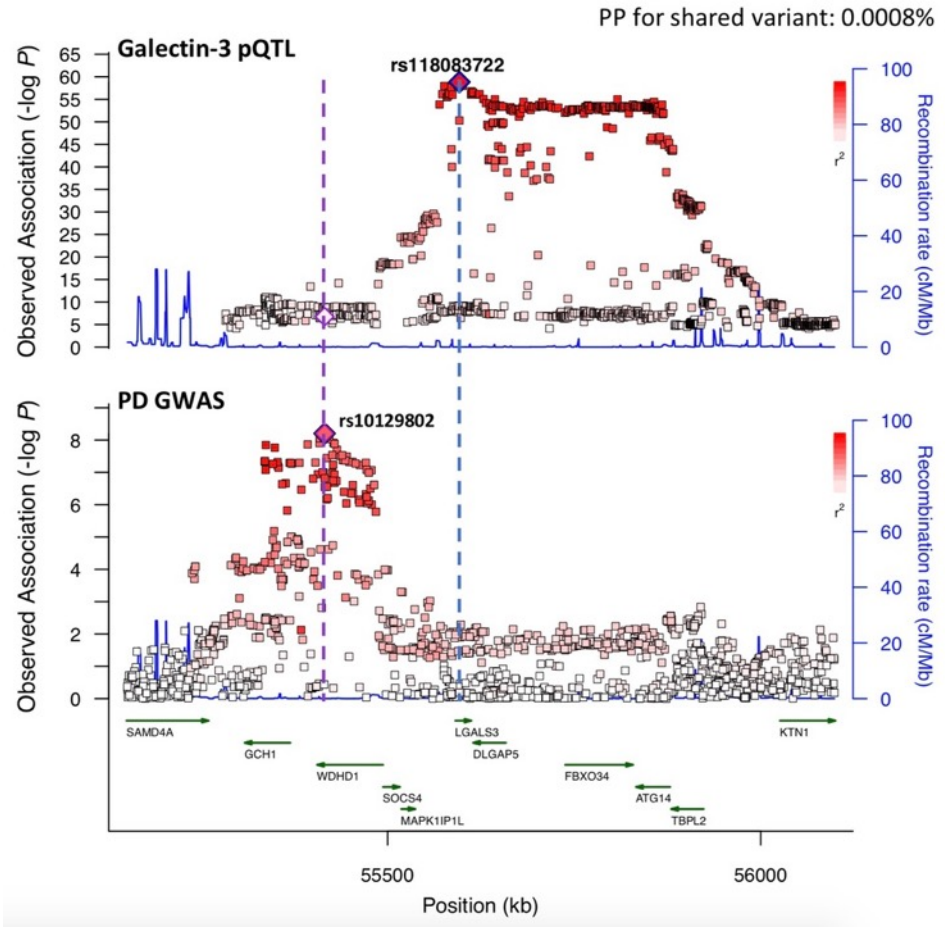
Cardiovascular

Blood pressure medication
Essential hypertension
CAD
MI

Neurological

Neurological disease
Parkinson's disease
Cluster headaches
Speech/language disorder

Question:
Is there truly an association between Galactin-3 levels and PD?



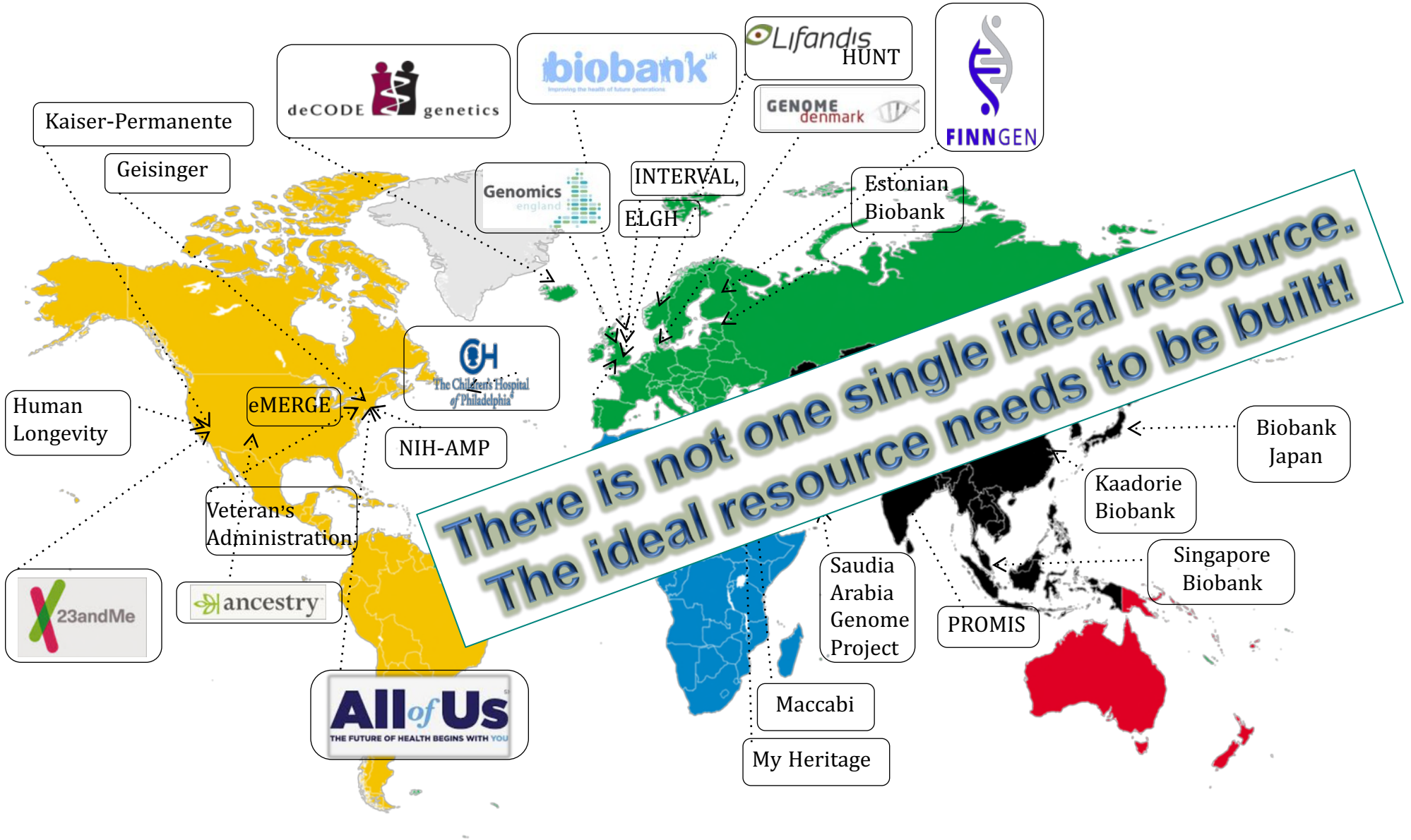
Genetic conditional analyses with pQTL data

PD signal not explained through Galectin-3 plasma levels

No use as PD target

Diogo,…, Runz; *NatureCOMMS* 2018

Conclusions: meta-PheWAS across "real-world data" cohorts *can* inform drug discovery on efficacy, alternative indications and safety risks



We contribute to establish the framework for optimally utilizing human data and improved discovery of novel medicines

biobank uk

Improving the health of future generations

Life Science Genetics Consortium

FINNGEN

REGENERON

Takeda

Biogen

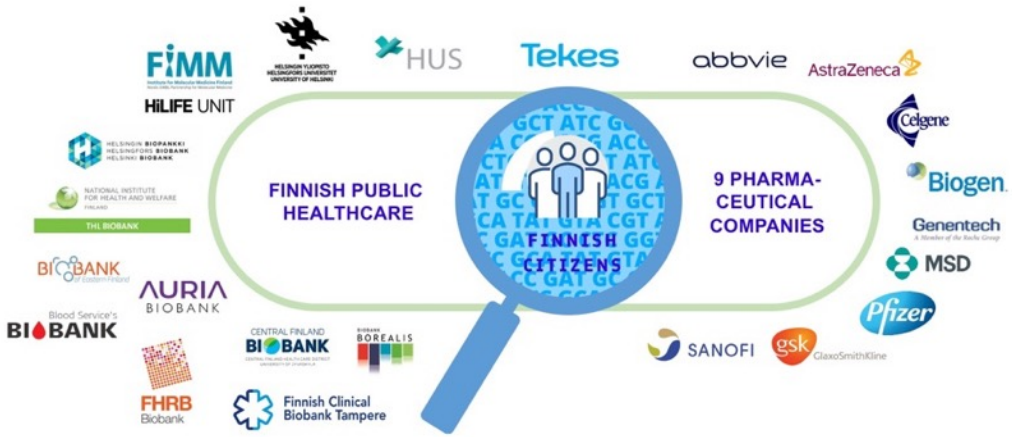
Alnylam PHARMACEUTICALS

Pfizer

abbvie

Bristol-Myers Squibb

AstraZeneca



Aim: To sequence the exomes of 500k UKBB participants

Aim: To link genetics to health data in 500k Finns

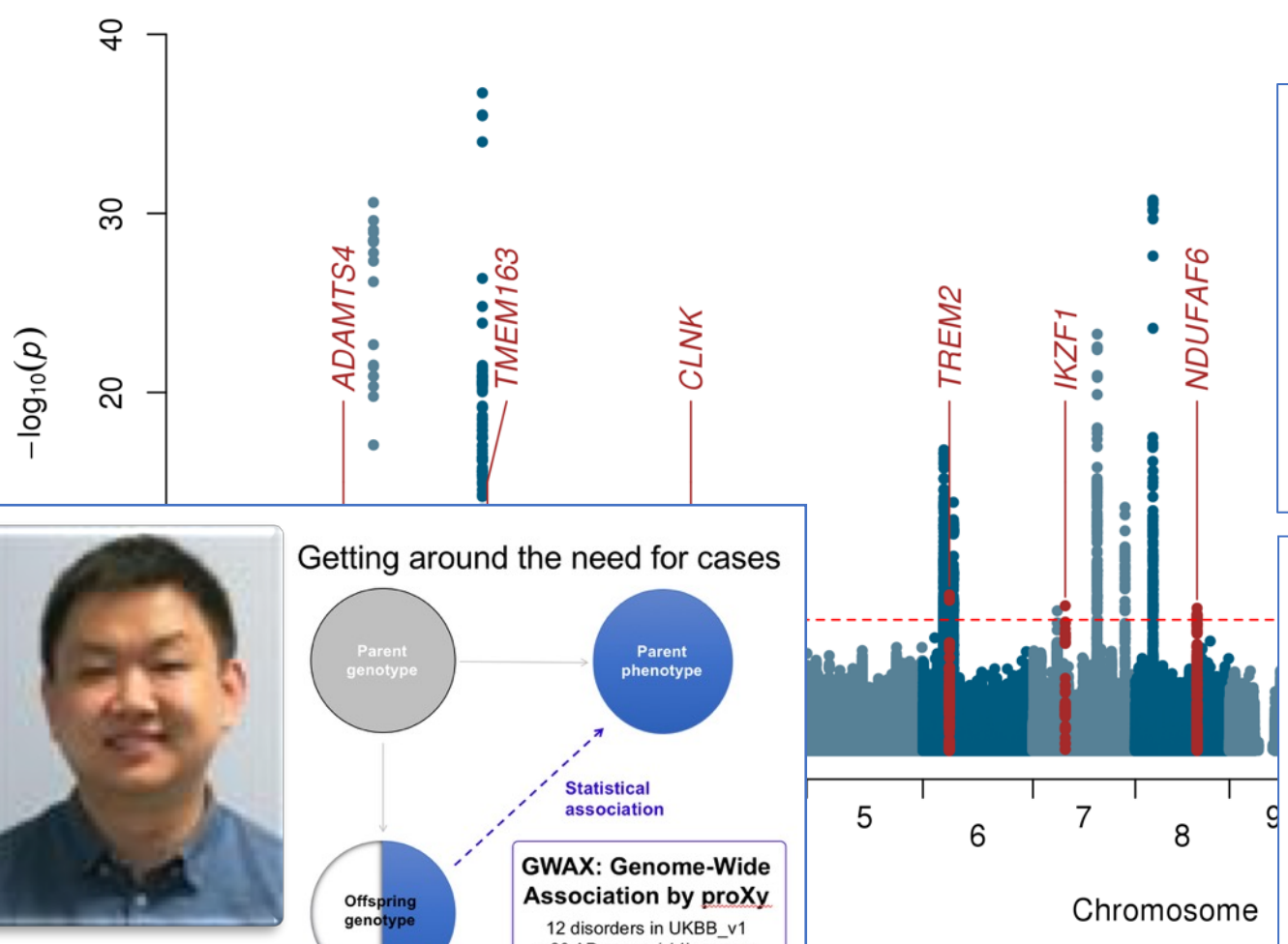
Are such investments delivering any value?

"YES – clearly for nominating new targets"

GWAS on family history of Alzheimer's disease:

- only ~400 AD cases in 500k UKBB
- family history available

⇒ 52,715 proxy cases /354,628 controls (power equivalent to largest AD GWAS)



Jimmy Liu

Getting around the need for cases

GWAX: Genome-Wide Association by proXy

12 disorders in UKBB_v1
<20 AD cases / 14k proxys

Liu et al, Nature Genetics 2017

Article | OPEN | Published: 18 May 2018

GWAS on family history of Alzheimer's disease

Riccardo E. Marioni, Sarah E. Harris, Qian Zhang, Allan F. McRae, Saskia P. Hagenaars, W. David Hill, Gail Davies, Craig W. Ritchie, Catharine R. Gale, John M. Starr, Alison M. Goate, David J. Porteous, Jian Yang, Kathryn L. Evans, Ian J. Deary, Naomi R. Wray & Peter M. Visscher

Translational Psychiatry **8**, Article number: 99 (2018) | Download Citation

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Genetic meta-analysis identifies 9 novel loci and functional pathways for Alzheimers disease risk

Iris Jansen, Jeanne Savage, Kyoko Watanabe, Julien Bryois, Dylan Williams, Stacy Steinberg, Julia Sealock, Ida Karlsson, Sara Hagg, Lavinia Athanasiu, Nicola Voyle, Petroula Proitsi, Aree Witoelar, Sven Stringer, Dag Aarsland, Ina Almdahl, Fred Andersen, Sverre Bergh, Francesco Bettella, Sigurbjorn Bjornsson, Anne Braekhus, Geir Brathen, Christiaan de Leeuw, Rahul Desikan, Srdjan Djurovic, Logan Dumitrescu, Tormod Fladby, Timothy Homan, Palmi Jonsson, Steven Kiddle, Arvid Rongve, Ingvild Saltvedt, Sigrid Sando, Geir Selbak, Nathan Skene, Jon Snaedal, Eystein Stordal, Ingun Ulstein, Yunpeng Wang, Linda White, Jens Hjerling-Leffler, Patrick Sullivan, Wiesje van der Flier, Richard Dobson, Lea Davis, Hreinn Stefansson, Kari Stefansson, Nancy Pedersen, Stephan Ripke, Ole Andreassen, Danielle Posthuma

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Liu et al., unpublished

Are such investments delivering any value?

"WE HOPE SO – to change how drugs will be developed in the future"

We aspire to test therapeutic hypotheses in "Virtual Clinical Trials"

Imagine we'd never have to run trials to test if ActRII2 or GASP1 improve SMA?

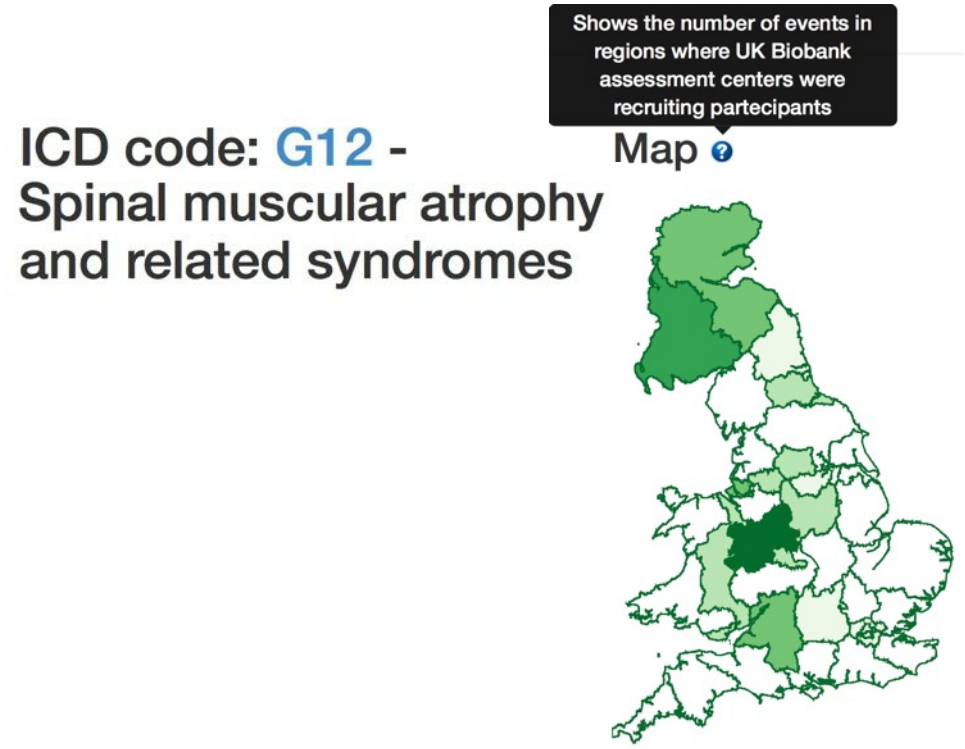
$MSTN_{wt}$

$MSTN_{\Delta}$

$SMN1_{\Delta}$/ $MSTN_{wt}$

$SMN1_{\Delta}$/ $MSTN_{\Delta}$

Imagine we'd know early which patients benefit the most from a drug, where and why?



RiSTEYES (Andrea Ganna, FIMM)

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Positions open!!