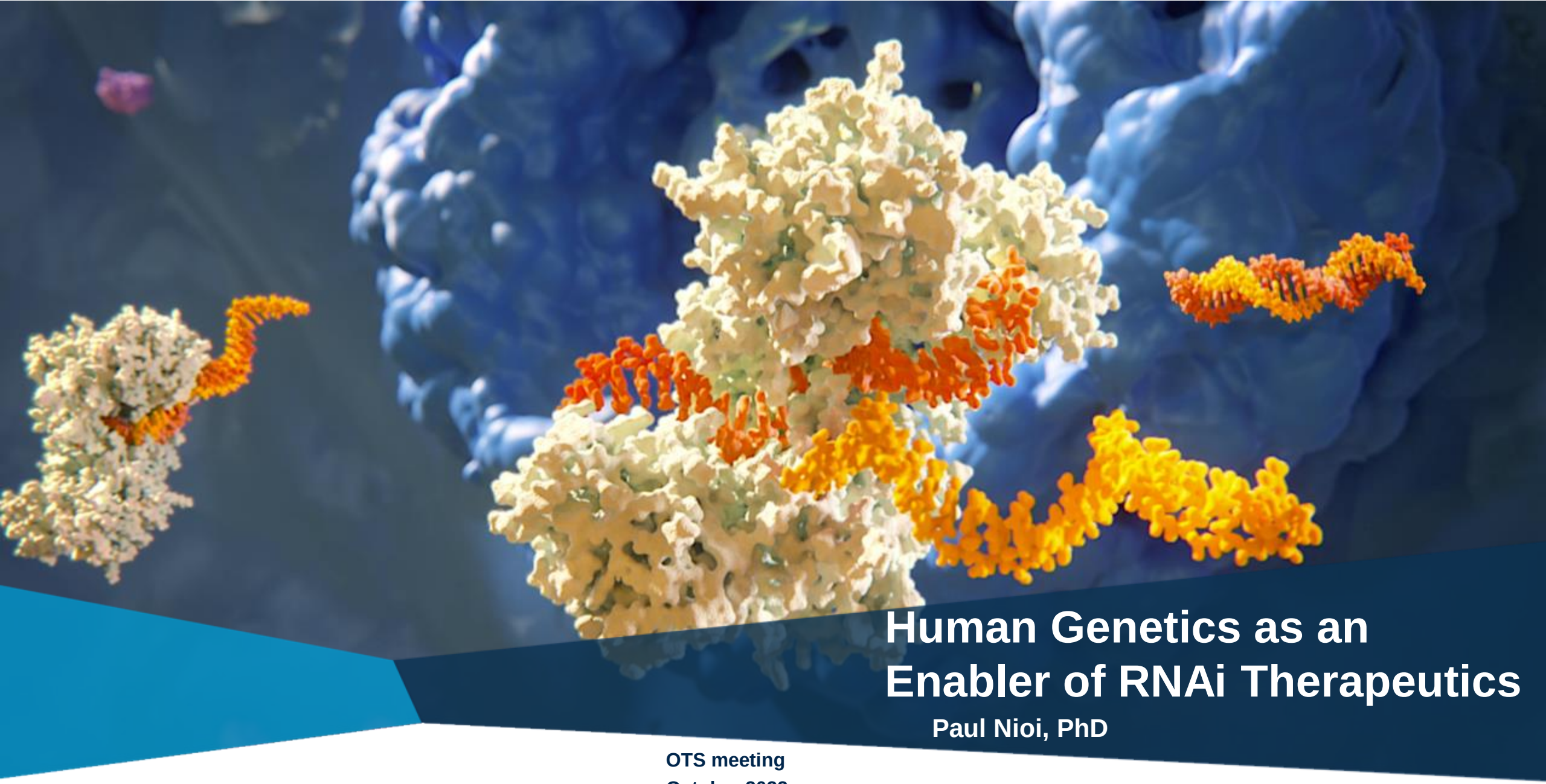


Human Genetics as an Enabler of RNAi Therapeutics

Paul Nioi, PhD

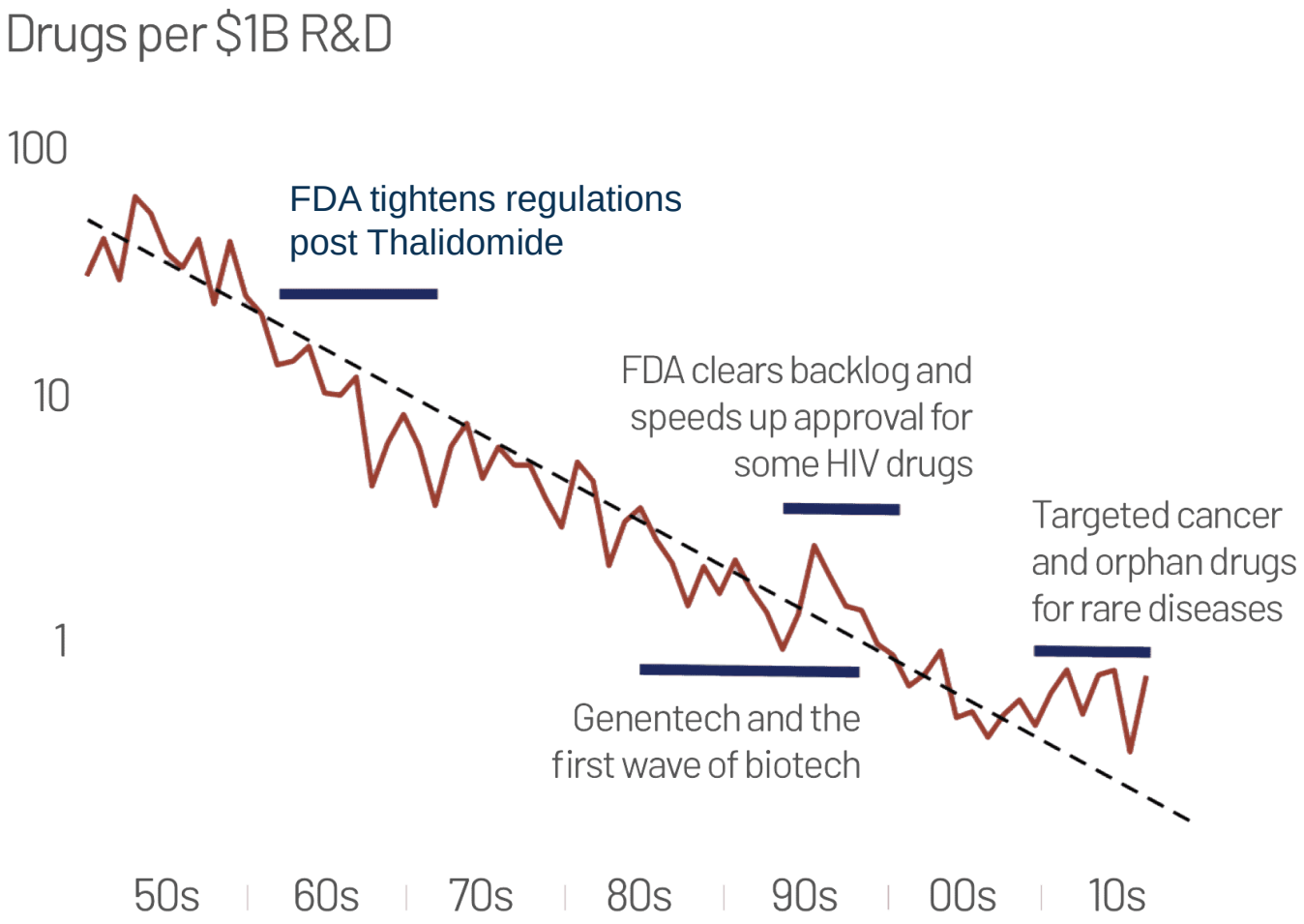
OTS meeting
October 2022

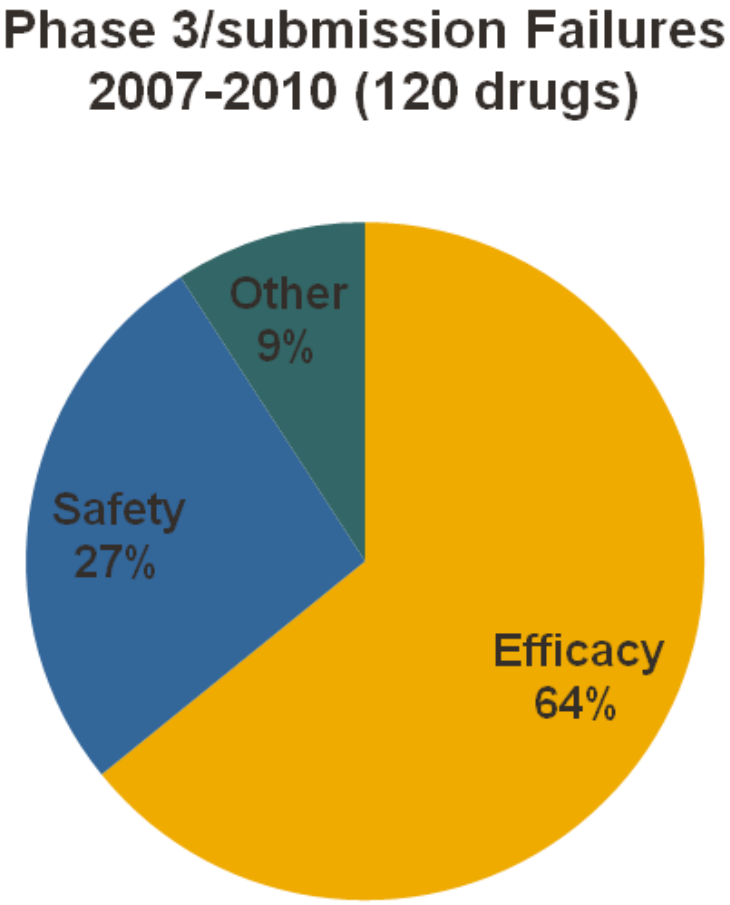
Alnylam@20

Disclosures

- I am an employee of- and shareholder in- Alnylam

RNAi is a powerful therapeutic modality but what are the right targets?





https://refoundable.com/research/life-after-erooms-law-interview-with-jack-scannell

Hay et al. (2014) Nat. Biotech. 32:40-51

Arrowsmith & Miller (2013) Nat. Rev. Drug. Disc. 12:569

Why?

Traditional Target Discovery has Failed

A Lack of Understanding of Disease Mechanisms in Humans

≠

Human genetically validated targets are more likely to lead to an approved drug

Mutation in gene encoding drug target

Phenotype that matches drugs' indication

Medicines are 2x more likely to be approved if target is genetically validated

Progression	*p*(progress|genetics) / *p*(progress|no genetics)
Phase I to Phase II	1.2 (1.1-1.3)
Phase II to Phase III	1.5 (1.3-1.7)
Phase III to Approval	1.1 (1.0-1.2)
Phase I to Phase III	1.8 (1.5-2.1)
Phase I to Approval	2.0 (1.6-2.4)

Nelson et al., Nat Gen. 2015,47:856-60.

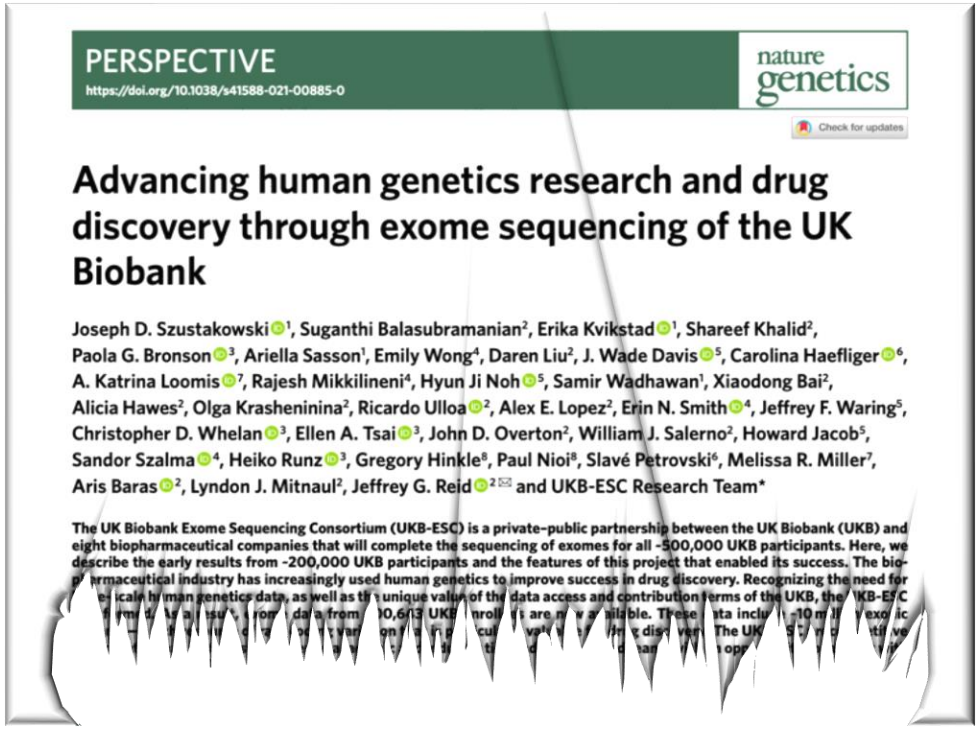
UK Biobank Exome Sequencing Consortium (UKB-ESC)

Alnylam is a founding member of the UKB-ESC

biobank uk

Enabling scientific discoveries that improve human health

500,000 participants
Age 40-69 at recruitment
Access to EHRs, biomarker data, imaging…


PERSPECTIVE
https://doi.org/10.1038/s41588-021-00885-0
nature genetics
Check for updates

Advancing human genetics research and drug discovery through exome sequencing of the UK Biobank

Joseph D. Szustakowski[1], Suganthi Balasubramanian[2], Erika Kvikstad[1], Shareef Khalid[2], Paola G. Bronson[3], Ariella Sasson[1], Emily Wong[4], Daren Liu[2], J. Wade Davis[5], Carolina Haefliger[6], A. Katrina Loomis[7], Rajesh Mikkilineni[4], Hyun Ji Noh[5], Samir Wadhawan[1], Xiaodong Bai[2], Alicia Hawes[2], Olga Krasheninina[2], Ricardo Ulloa[2], Alex E. Lopez[2], Erin N. Smith[4], Jeffrey F. Waring[5], Christopher D. Whelan[3], Ellen A. Tsai[3], John D. Overton[2], William J. Salerno[2], Howard Jacob[5], Sandor Szalma[4], Heiko Runz[3], Gregory Hinkle[8], Paul Nioi[8], Slavé Petrovski[6], Melissa R. Miller[7], Aris Baras[2], Lyndon J. Mitnaul[2], Jeffrey G. Reid[2]✉ and UKB-ESC Research Team*

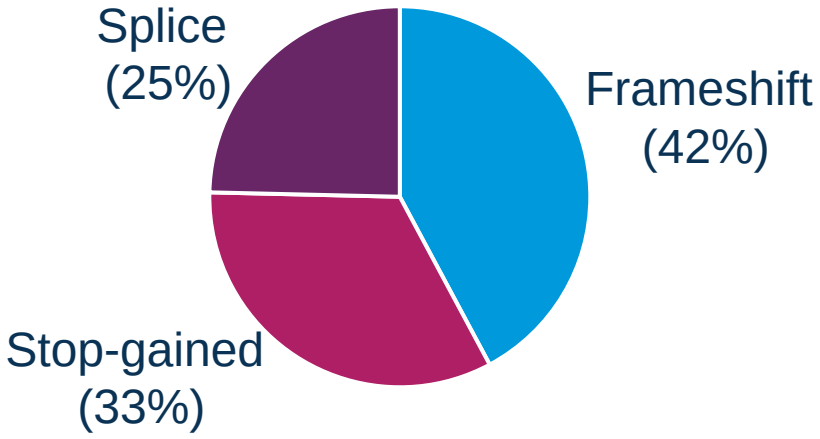
The UK Biobank Exome Sequencing Consortium (UKB-ESC) is a private–public partnership between the UK Biobank (UKB) and eight biopharmaceutical companies that will complete the sequencing of exomes for all ~500,000 UKB participants. Here, we describe the early results from ~200,000 UKB participants and the features of this project that enabled its success. The bio-pharmaceutical industry has increasingly used human genetics to improve success in drug discovery. Recognizing the need for

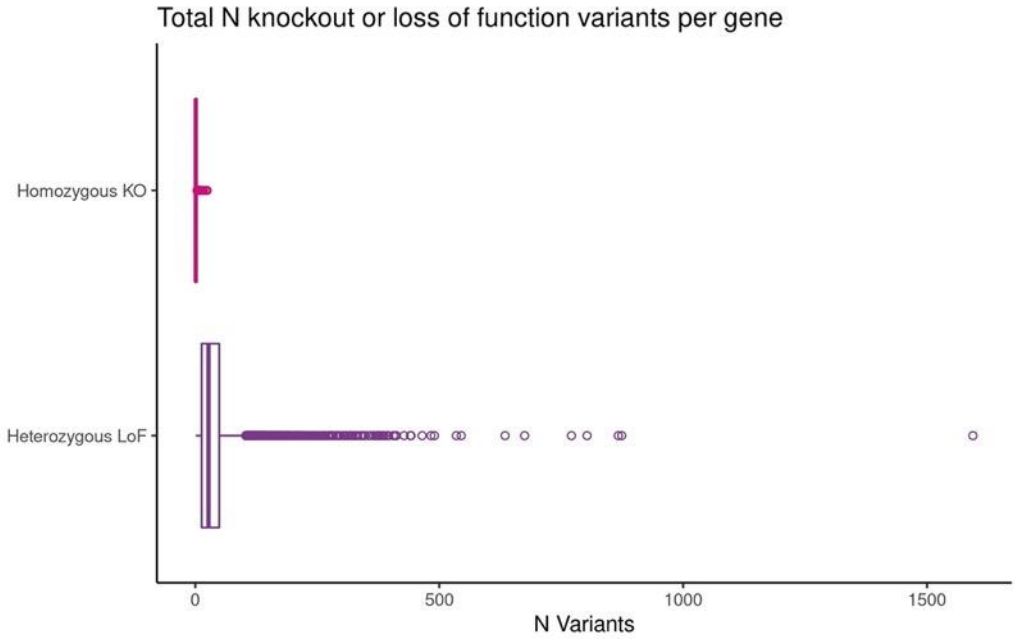
UKB-ESC goal – exome sequence all 500,000 participants

Alnylam goal – use genotype-phenotype data to discover genetically validated drug targets

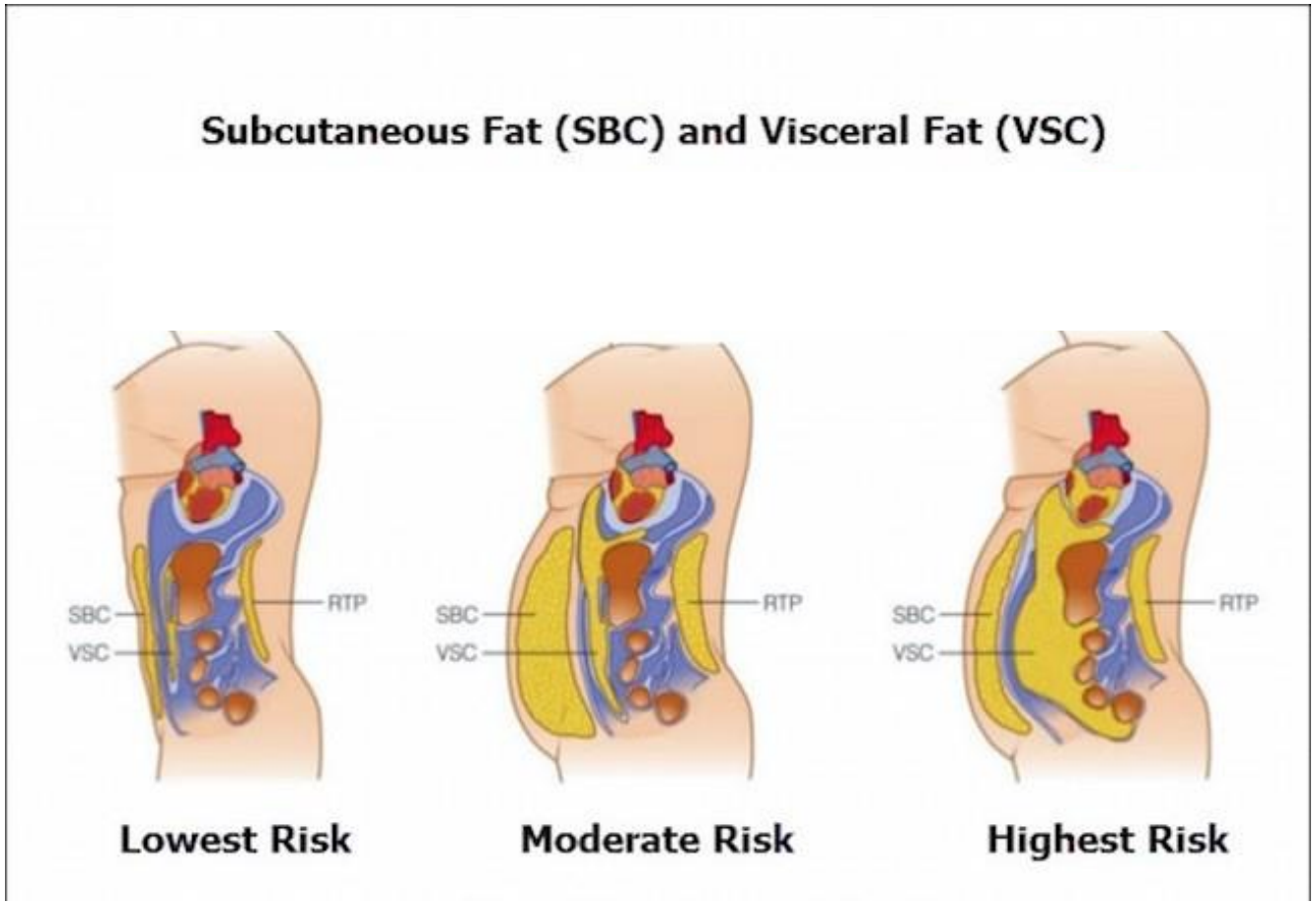
Human “knockout” and LOF variants in UKBB exomes

	N Genes	% Singleton	% N <= 10 carriers
Homozygous LOF ("knockouts") Genes	2261 (12%)	43%	75%
Heterozygous LOF Genes	16406 (86%)	1%	9%





Discovering New Targets for Metabolic Syndrome (MetS)



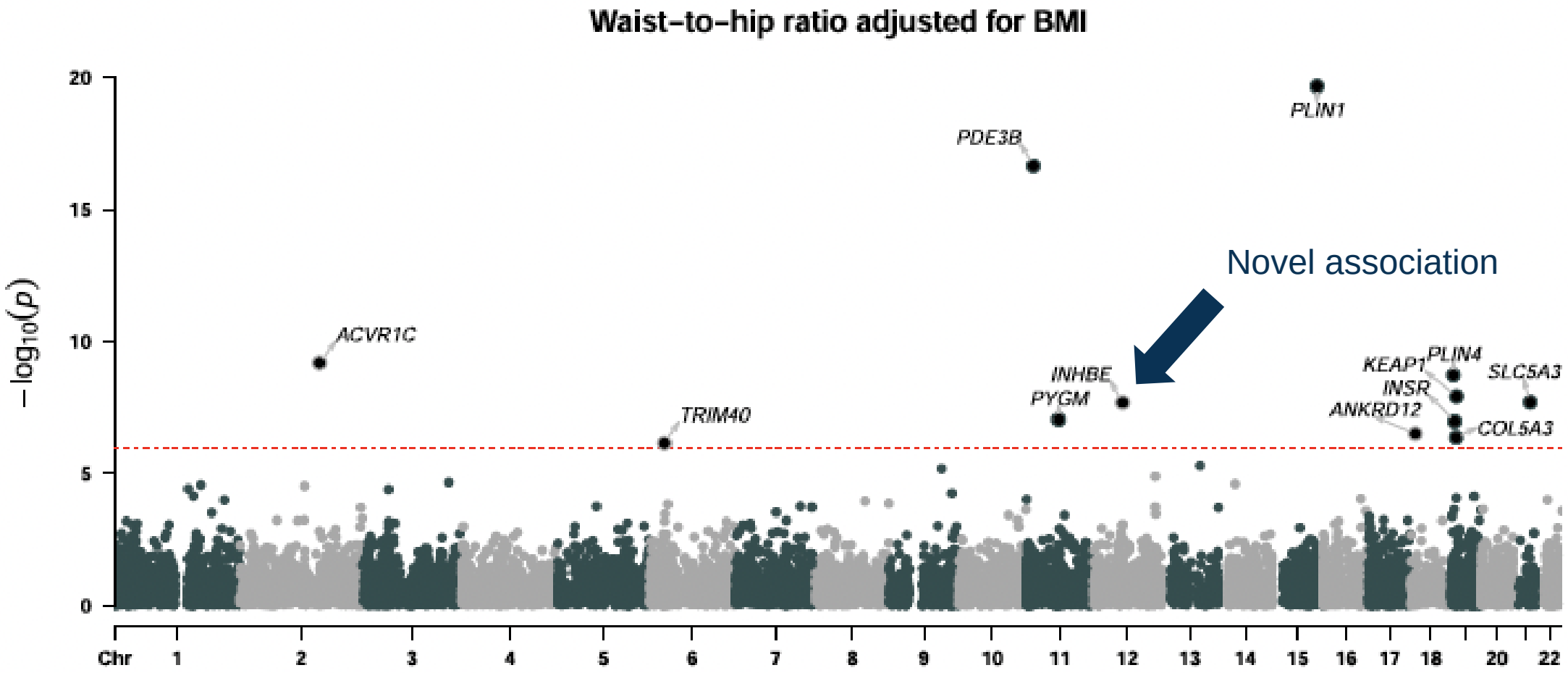
A major cause of Cardiovascular disease

Characterized by visceral obesity, high triglycerides, low HDL, insulin resistance and hypertension

Waist:Hip is a good surrogate for visceral adiposity

Affects > 20% of adults, globally

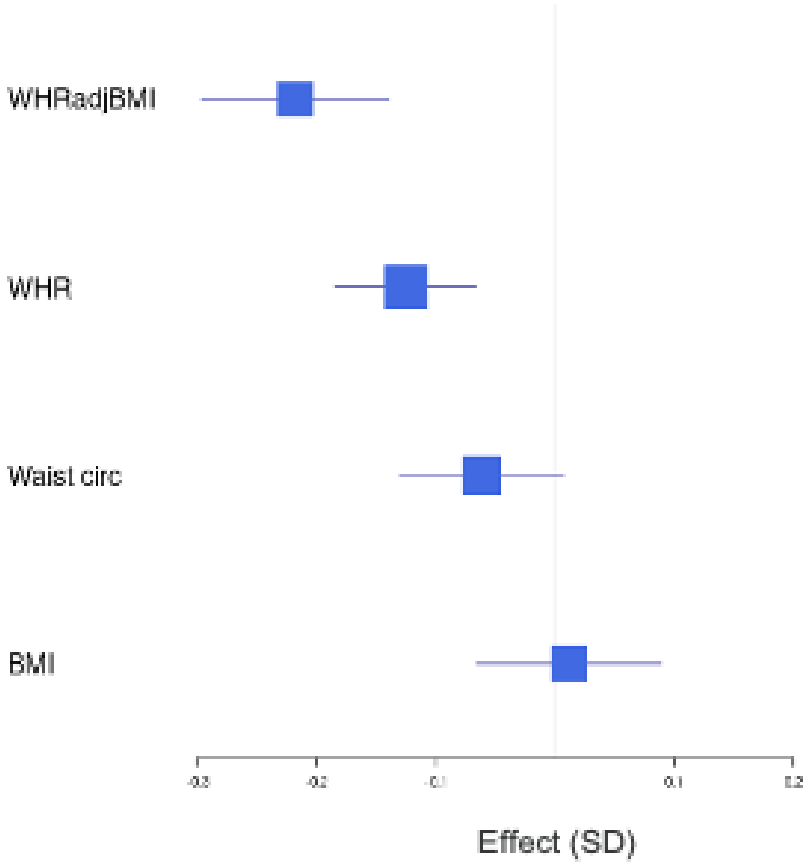
Genome wide association study of waist to hip ratio



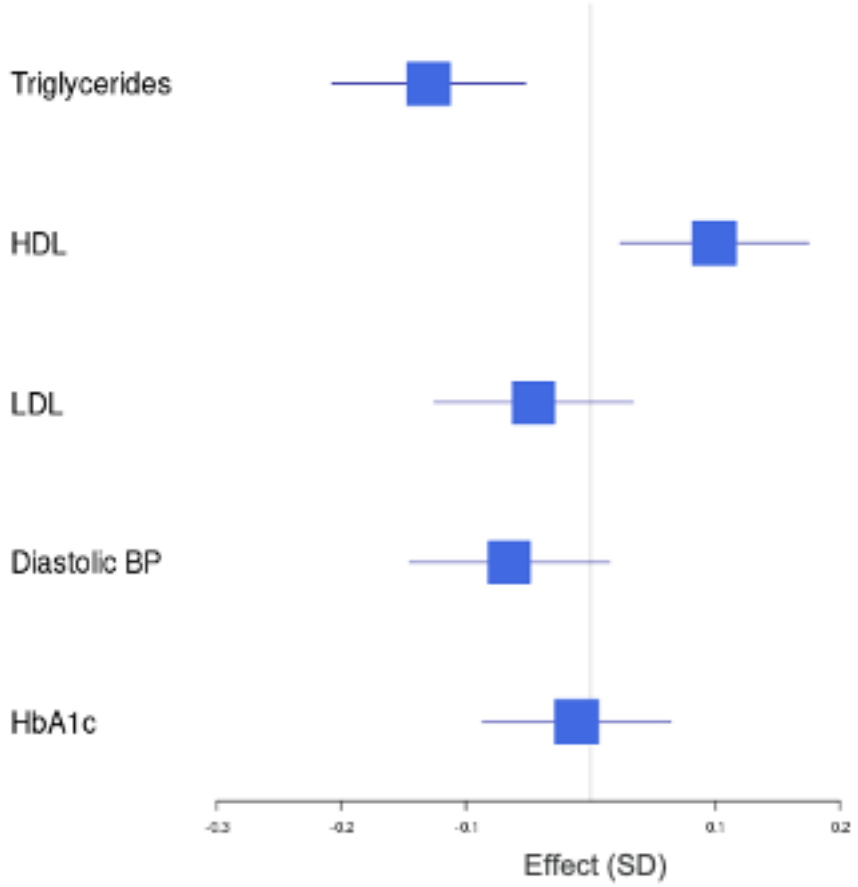
Deaton et al Nat Comm (2022) 4319

INHBE LOF carriers show traits consistent with protection from metabolic syndrome

Anthropometric traits

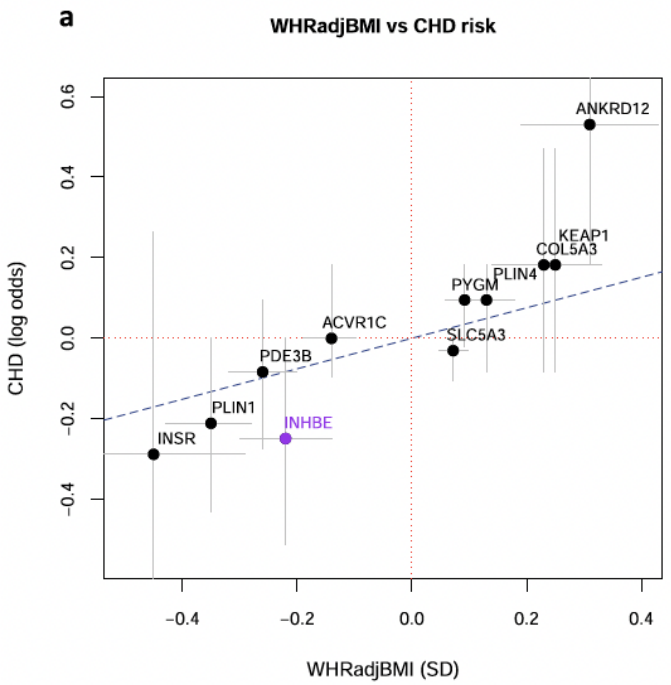


Quantitative metabolic traits



Deaton et al Nat Comm (2022) 4319

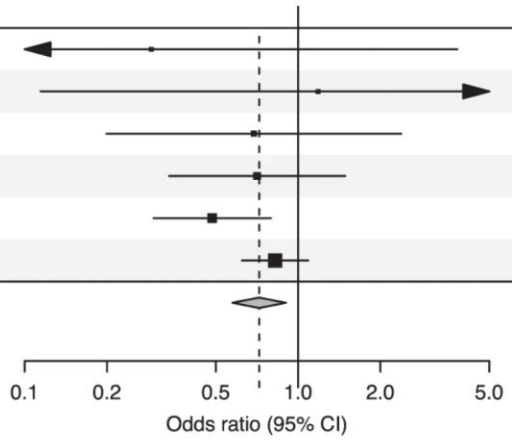
INHBE LOF carriers have lower risk of cardiometabolic disease



Type 2 diabetes (INHBE – pLoF, AAF < 1%)

Cohort	Ancestry	Cases RR|RA|AA	Controls RR|RA|AA	Odds ratio (95% CI)	P
UKB	SAS	1,936|0|0	8,195|5|0	0.29 (0.02, 3.82)	3.5×10^{-1}
SINAI	EUR	978|1|0	7,492|6|0	1.18 (0.11, 12.24)	8.9×10^{-1}
MDCS	EUR	3,802|2|0	21,117|22|0	0.69 (0.20, 2.38)	5.6×10^{-1}
MCPS	AMR	26,482|6|1	81,936|43|0	0.71 (0.34, 1.48)	3.6×10^{-1}
GHS	EUR	26,740|18|0	64,737|111|0	0.49 (0.30, 0.80)	4.1×10^{-3}
UKB	EUR	23,862|45|0	401,975|953|0	0.82 (0.62, 1.09)	1.7×10^{-1}
Meta–analysis	**ALL**	**83,800|72|1**	**585,452|1,140|0**	**0.72 (0.58, 0.90)**	4.3×10^{-3}

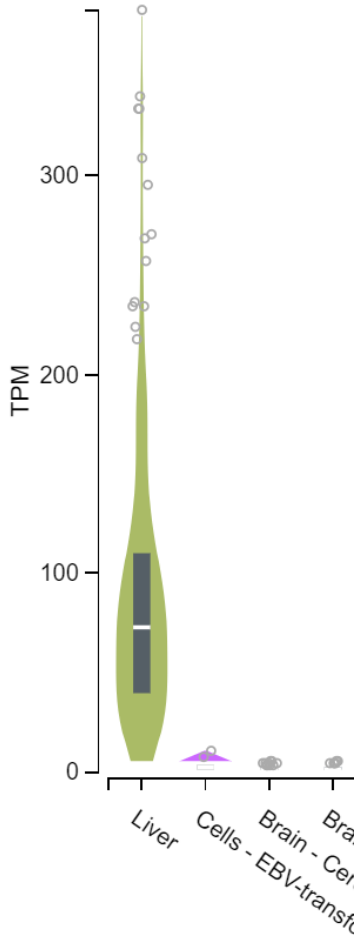
Heterogeneity I2=0%; P=0.55



Sources: Deaton et al Nat Comm (2022) 4319; Akbari et al Nat Comm (2022) 4844

INHBE is a hepatokine with liver restricted expression

INHBE mRNA expression



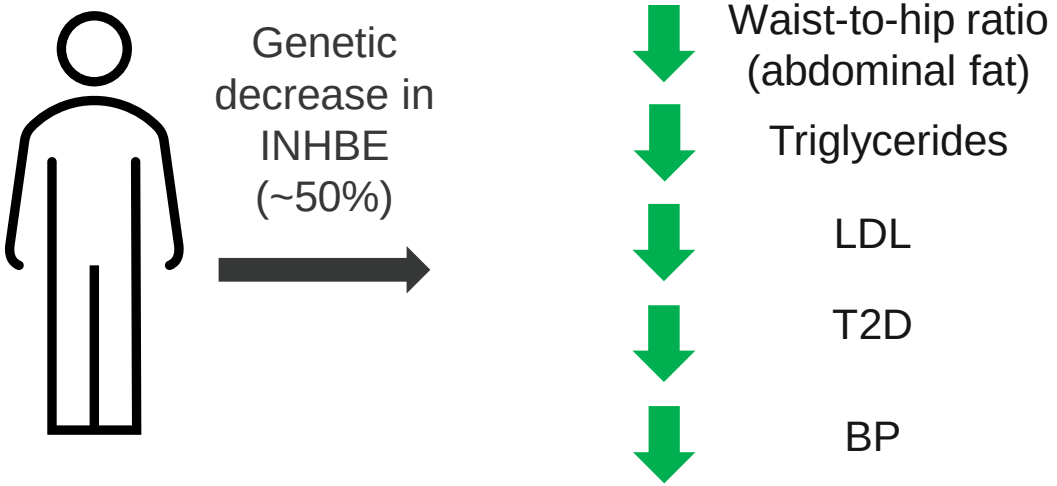
Activin E

Inhibin E

Source: GTex

INHBE Loss of Function Protects from MetS

- Alnylam discovered target in UK Biobank
- *INHBE* loss of function improves waist-to-hip ratio, a surrogate for abdominal fat that impacts risk for type 2 diabetes and heart disease



We are now pursuing an annual or bi-annual RNA-therapeutic to knockdown INHBE