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**

- **Phase 3 2000-2009**
  - Efficacy: 52%
  - Safety: 30%
  - Commercial: 16%
  - Other: 2%

**Genetic support tracks with success**

*Likelihood of success/phase for genetic vs. non-genetic drug targets (OR)*

- Preclinical
- Phase I
- Phase II
- Phase III
- Approved

*Tuft Center for the Study of Drug Development.. 2013*

*Nelson et al. Nat Genet. 2015*
Drug targets with human genetic support have higher success rates

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

**Spinal muscular atrophy**
- cause: homozygous delSMN1
- SMN2 nonfunctional due to alternative splicing

**Therapeutic hypothesis:**
- SMN2Δ7 splicing \(\rightarrow\) 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 \(\uparrow\), event-free survival \(\uparrow\)
- NURTURE Ph2 pre-symptomatic study: all participants reach motor milestones
- 1000s SMA patients on treatment
- newborn screening implemented
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Ivliev et al., unpublished
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. Yet: Data have yet been missing to directly study the genome and the proteome.
Genomic atlas of the human plasma proteome

Benjamin B. Sun\textsuperscript{1,22}, Joseph C. Marazwili\textsuperscript{2,20,21}, James E. Peters\textsuperscript{1,22}, David Stacey\textsuperscript{1}, James R. Staley\textsuperscript{1}, James Blackshaw\textsuperscript{1}, Stephen Burgess\textsuperscript{1,3}, Tao Jiang\textsuperscript{1}, Ellie Page\textsuperscript{1,3}, Praveen Surendran\textsuperscript{1}, Clare Oliver-Williams\textsuperscript{1,8}, Mihir A. Kamat\textsuperscript{1}, Bram F. Prins\textsuperscript{1}, Sheri K. Wilcox\textsuperscript{2}, Erik S. Zimmerman\textsuperscript{1}, An Chi\textsuperscript{2}, Narinder Bansal\textsuperscript{1,8}, Sarah L. Spain\textsuperscript{5}, Angela M. Wood\textsuperscript{1}, Nicholas W. Morrell\textsuperscript{1,10}, John R. Bradley\textsuperscript{1}, Nebojsa Janjic\textsuperscript{1}, David J. Roberts\textsuperscript{1,13}, Willem H. Ouwehand\textsuperscript{3,13,14}, John A. Todd\textsuperscript{1}, Nicole Soranzo\textsuperscript{3,14,16,17}, Karsten Sohre\textsuperscript{1}, Dirk S. Paul\textsuperscript{1}, Caroline S. Fox\textsuperscript{1}, Robert M. Flint\textsuperscript{1,18}, John Danesh\textsuperscript{1,3,13}, Hekto Runz\textsuperscript{2,13} & Adam S. Butterworth\textsuperscript{1,3,13}

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

\begin{itemize}
  \item 88 sentinel pQTLs in high LD ($r^2 \geq 0.8$)
\end{itemize}

with sentinel GWAS variants

\begin{itemize}
  \item 30 with cis, 54 with trans, and 4 with both
  \item 253 distinct genotype–disease associations
  \item 96 PP>0.8 for shared causal variants
\end{itemize}
Myostatin (*GDF8*), a plasma protein and drug target for neuromuscular disease

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

\( \Delta GDF8 \) causes muscle hypertrophy

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

Therapeutic hypothesis:

GDF8 in plasma \( \downarrow \) -> muscle growth \( \uparrow \)

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

GDF8/11 \( \rightarrow \) Activin A/B \( \rightarrow \) BMP9

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

BIIB110 is currently in a **Phase 1a** 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**

GDF8 \(\xrightarrow{\text{trans-pQTL}}\) GDF11 \(\xrightarrow{\text{GASP1}}\) GDF8

rs11079936 rs7225465

rs11079936-C \(\xrightarrow{\text{myostatin}}\)

**GASP1 regulates GDF8/11 at the protein level**

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

In silico prediction of protein complex

GDF8/11 \(\xrightarrow{\text{Activin A/B}}\) GDF8/11

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.

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. "Real-World phenotypic Data" can be used in conjunction with Genetics. Phenome-wide association studies (PheWAS) test the association of selected SNPs with a large list of phenotypic endpoints. SNP X is associated with risk for efficacy and surrogate for toxicity.
Is all this data of any concrete use for drug discovery and development?
Can we inform on drug target safety / efficacy through meta-PheWAS across multiple large real-world biobank cohorts?

Study outline: 25 SNPs in 19 drug targets across indication -> 4 RWD cohorts + 44 GWAS
Phenotype mapping for „meta-PheWAS“ in 700k individuals

- Phenotype mapping for "meta-PheWAS" in 700k individuals

- 23andMe: 654 disease endpoints
- UK Biobank: 90 disease endpoints
- FINRISK: 278 disease endpoints

145 mapped endpoints
1,538 cohort-specific and unmapped endpoints

PheWAS + meta-analysis
PheWAS
27,611 tests: 1,683 endpoints, 25 SNPs

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:

- **Neurological**
  - Parkinson’s disease
  - Headaches
  - Speech/language disorder

- **Autoimmune**
  - Autoimmune disease
  - Ankylosing spondylitis
  - Crohn’s disease
  - IBD
  - Ulcerative colitis
  - SLE

- **Endocrine & metabolic**
  - Heart/metabolic disease

- **Cardiovascular**
  - Hypertension
  - Dyslipidemia

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

Aim: To sequence the exomes of 500k UKBB participants

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

GWAS on family history of Alzheimer’s disease

Riccardo E. Marioni, Sarah E. Harris, Qian Zhang, Allan F. McRae, Saskia P. Hagaenaars, 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

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?

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

ICD code: G12 - Spinal muscular atrophy and related syndromes

MSTN\textsubscript{wt}  \hspace{1cm} MSTN\Delta

SMN1\Delta/MSTN\textsubscript{wt}  \hspace{1cm} SMN1\Delta/MSTN\Delta

RiSTEYES (Andrea Ganna, FIMM)
Acknowledgements

Biogen team

Jimmy Liu
Ellen Tsai
Chris Whelan
Chia-Yen Chen
et al.

Sally John

pQTL study

Joe Maranville
Ben Sun
Jimmy Peters
John Danesh
Adam Butterworth
et al.

Finnish academic partners

Aarno Palotie (Director General)
Mark Daly (Scientific Lead)
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... THE PARTICIPANTS !!!
... AND MANY OTHERS

FinnGen partners

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Positions open!!