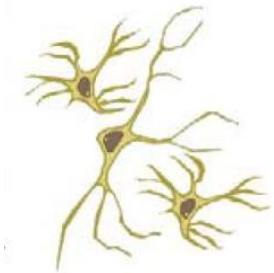
The use of genomic databases to support early drug discovery projects

Sally John

Deriving Drug Discovery Value from Large-Scale Genetic Bioresources.

Workshop 22nd March 2016

Human genetic data can support decision making in target prioritization and validation



Translational

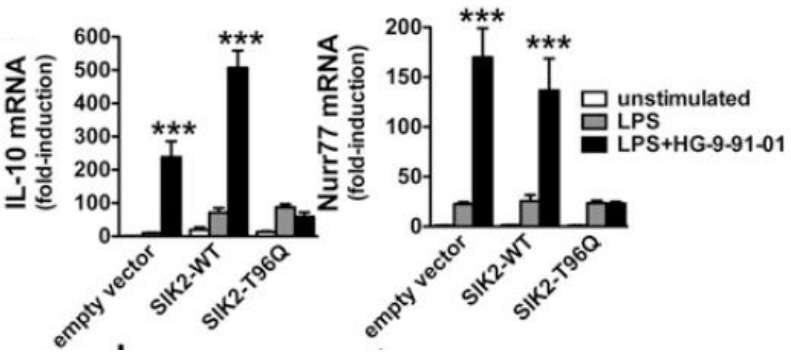
Salt Inducible Kinase inhibitors for the treatment of immune mediated disease

Serine threonine kinases : 3 isoforms (SIK1, SIK2, SIK3)

SIK2 in the immune system

Attenuates LPS-induced TNFa secretion and anti-CD3-induced IL-2 secretion

Enhances LPS-induced IL-10 production



Clark et al PNAS 2012 109: 16986-91

Are there any human genetic data that suggests….
SIK2 has an immune function?
SIK1 SIK2 and SIK3 are associated with potential safety outcomes?

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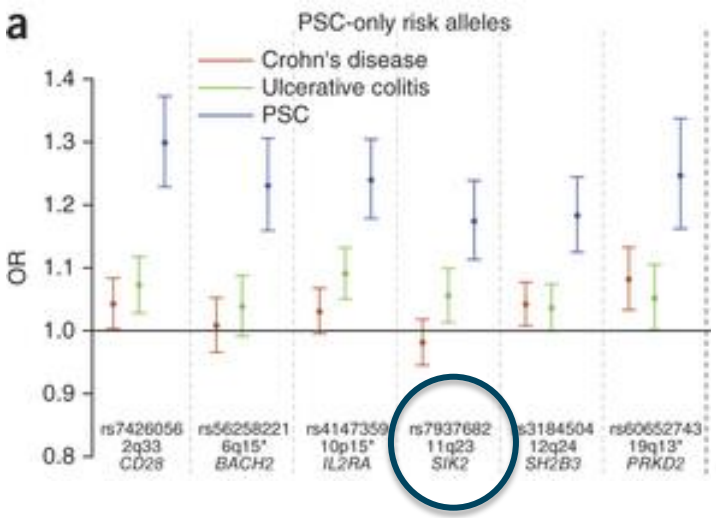
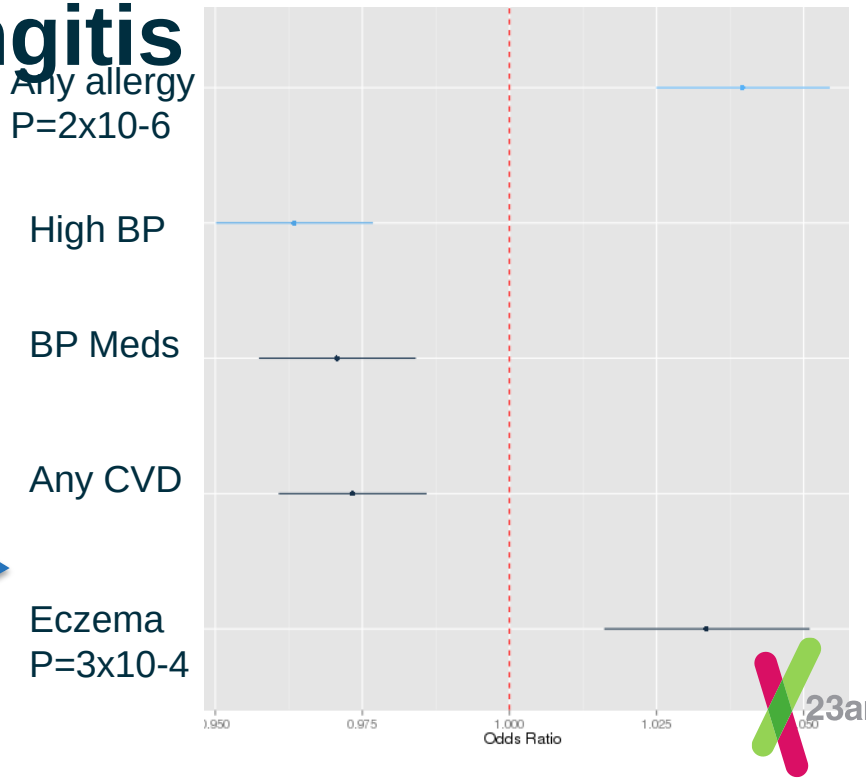
SNPs in SIK2 have a published association with primary sclerosing cholangitis



Liu et al Nature Genetics 2013



Other public data

UNIVERSITY OF CAMBRIDGE — Cardiovascular Epidemiology Unit

MR Catalogue | Information | The Team

Rs7937682 is associated with CVD in the CARDIOgramplusC4D study p = 0.002 OR ~0.97 G allele

http://www.mrcatalogue.medschl.cam.ac.uk/mrcatalogue

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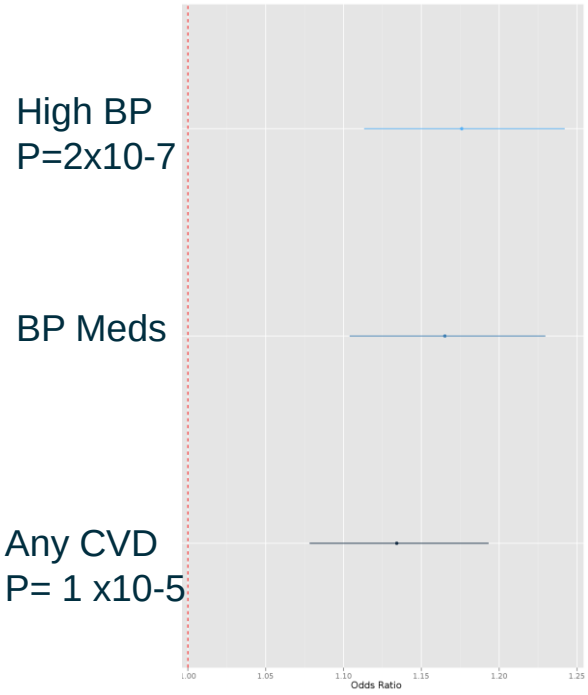
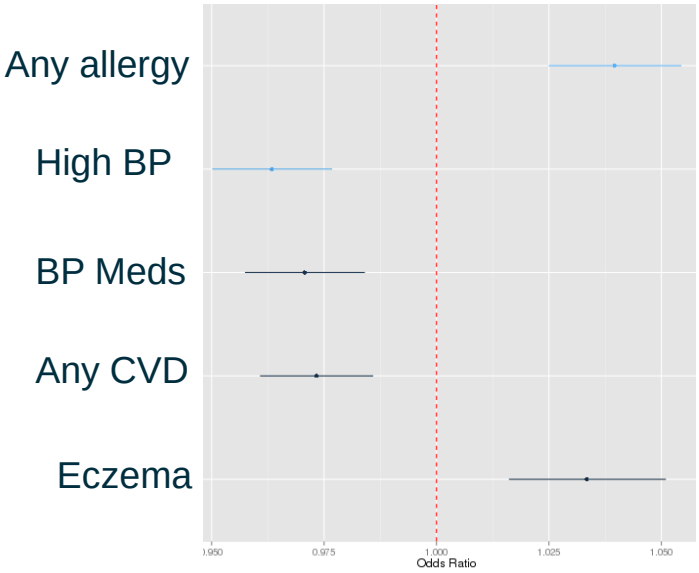
SNPs in all 3 SIK isoforms associated with high blood pressure and CVD

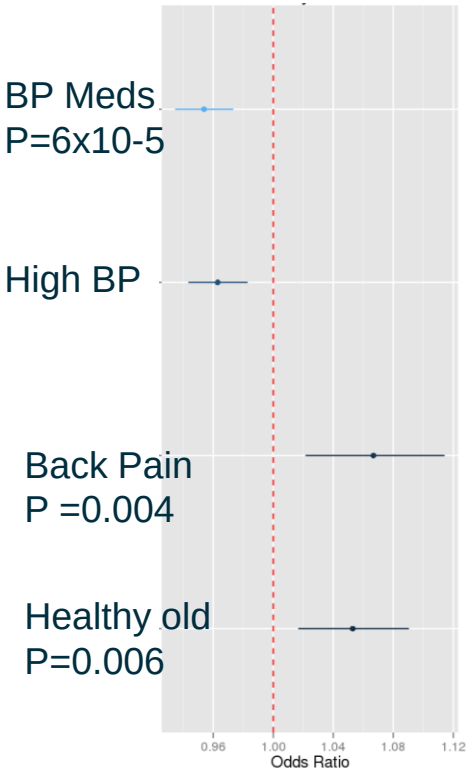
SIK1: rs34487963



SIK2: rs7937682



SIK3: rs10047462



Sample sizes range from 38 – 98K cases and ~200K controls

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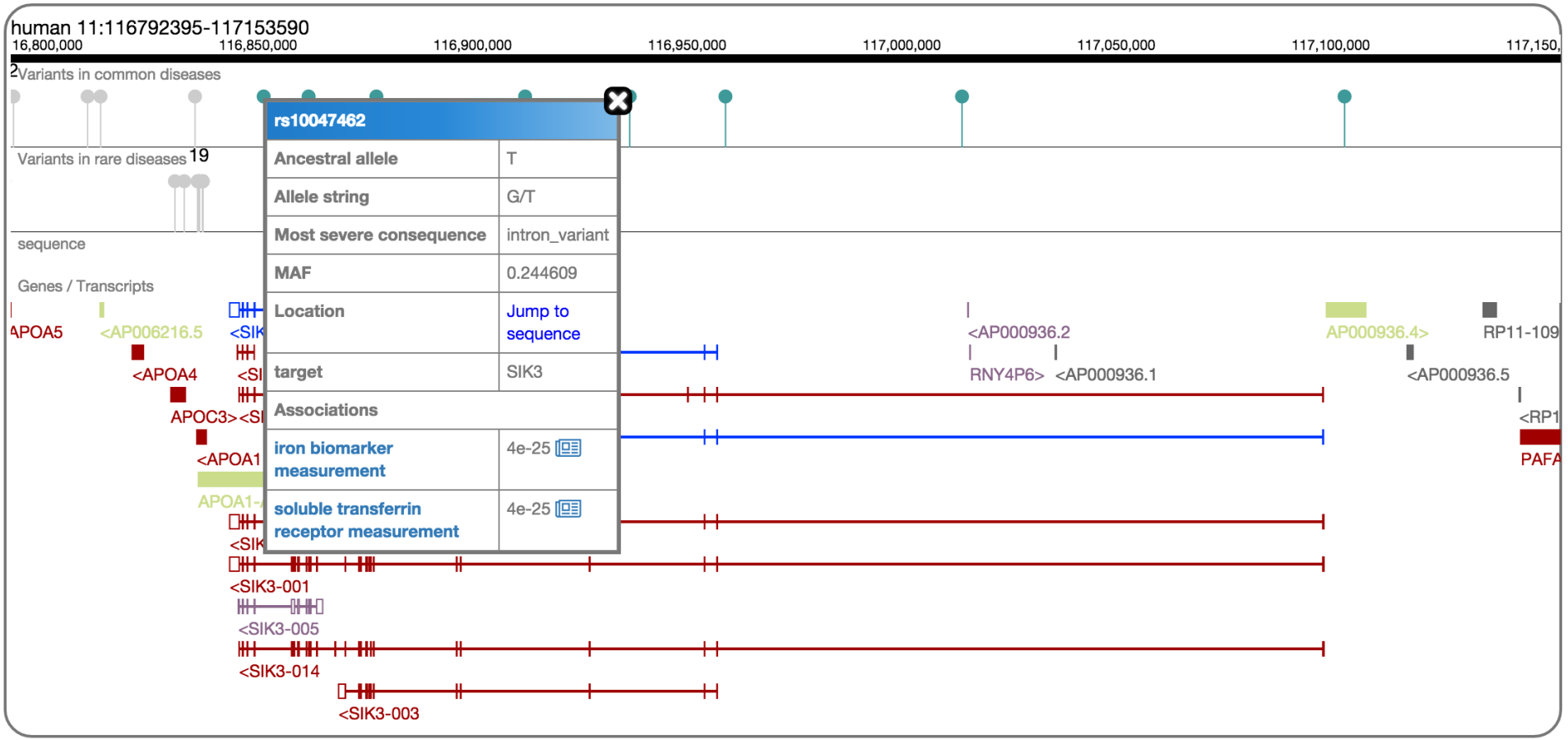
SNPs in SIK3 have multiple effects



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CTTV
Centre for Therapeutic Target Validation

Associations with triglyceride levels: SIK3 or APOC3?

The available human genetic data for the SIK genes ……..

- May support inhibition of SIK2 for immune disease indications ✓
- Supports potential safety concerns for metabolic affects. ✓
- Suggests selective SIK2 inhibition may be important ✓
- *However, these data require replication*
- *Doesn't prove causal gene or direction of effect.*

Functional coding variants may offer more insight

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THL
HELSINGIN YLIOPISTO
BROAD INSTITUTE
FIMM
HUMAN GENE KNOCK OUTS
NEED FOR HUMAN MODELS
Biogen
MERCK
Eisai
Pfizer

Outline of Industry Partnership for Human Genetics (IPHG) proof-of-concept study

Selection of ~50 target genes of interest

a) Early targets of shared interest among IPHG partners

Comprehensive assessment of LoF and GoF and enrichment in Finns across target gene

a) Query phenotypic data following **specific hypotheses** based on each individual target of interest

b) Association analyses of distinct alleles across the entire phenotypic spectrum using a **PheWAS (phenome-wide association study)** approach.

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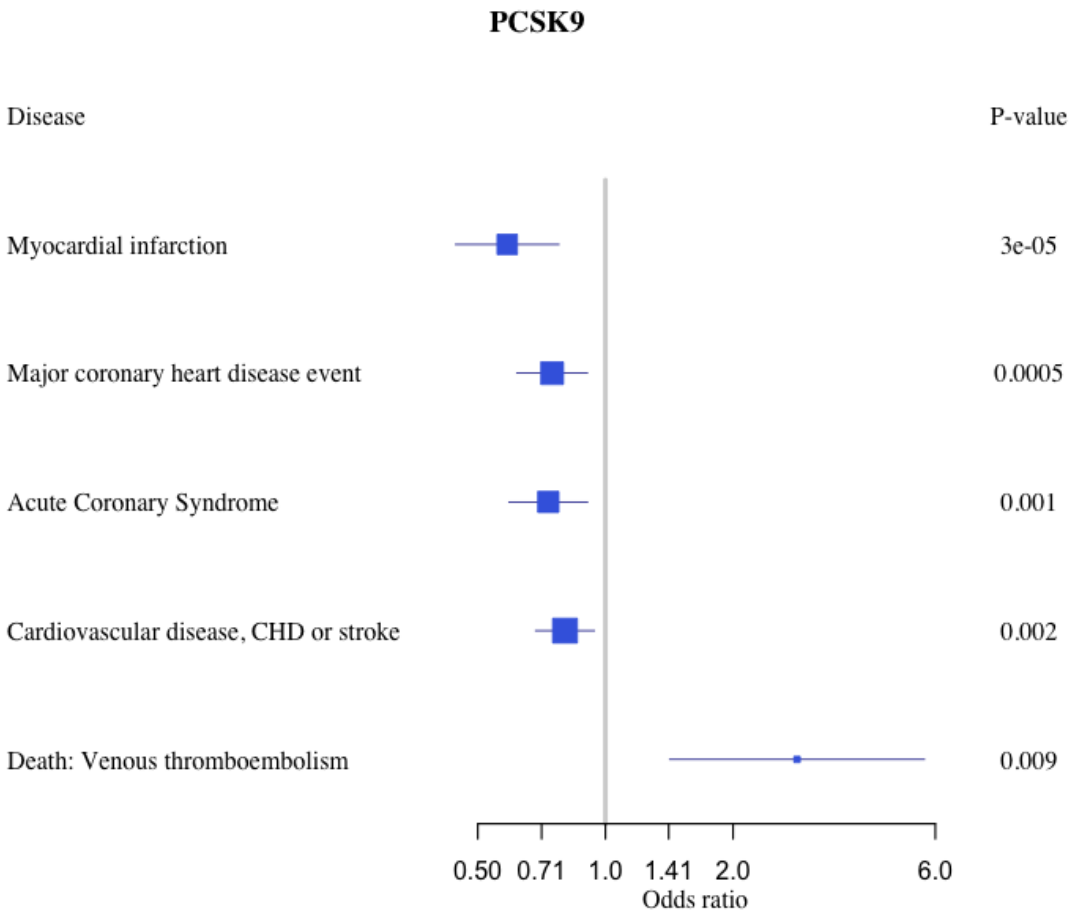
Example results : LoF variant in PCSK9 and disease endpoints in health registers



Association analysis of **Proprotein convertase subtilisin/kexin type 9** PCSK9 LoF variant p.R46L (rs11591147; MAF in Finns 0.0397) with 228 quantitative measurements, 169 disease endpoints, and drug usage in 69 medication categories

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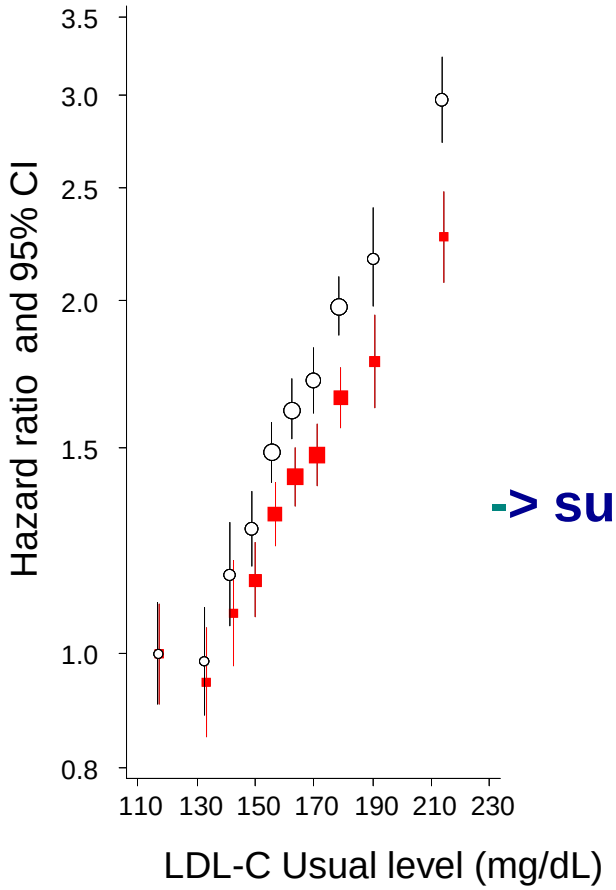
LoF variant in PCSK9 and modifiable intermediate endpoints

Summary of main PCSK9 p.R46L associations:	P-value	Variant allele
LDL-cholesterol calculated (mmol/l)	5.49E-79	Assoc. with lower levels
Total cholesterol (mmol/l)	6.89E-57	Assoc. with lower levels
Apolipoprotein B (g/l)	3.61E-46	Assoc. with lower levels
Ratio HDL/Total cholesterol	3.20E-40	Assoc. with higher levels
Ratio ApoB/ApoA1	1.28E-38	Assoc. with lower levels
LDL-C_measured (mmol/l)	3.69E-24	Assoc. with lower levels



-> support for PCSK9i efficacy

Sarwar et al. ERFC, *JAMA* 2009

Are there any potential side effects from natural PCSK9 inhibition?

Top associations for PCSK9 p.R46L in prescribed medication category:

ATC	Drug category		Allele A	Allele B	# Individuals Users AA/AB/BB	# Individuals Non-users AA/AB/BB	# Individuals Users total / Non-users total	MAF	OR (95% CI)	Additive p-value	Info	Beta	SE
C10A	LIPID MODIFYING AGENTS, PLAIN	rs11591147	G	T	5955/344/4	9997/960/24	6304/10982	0.04	0.60(0.53-0.68)	3.60E-19	1	-0.56	0.06
N06C	PSYCHOLEPTICS AND PSYCHOANALEPTICS IN COMBINATION	rs11591147	G	T	652/73/2	15300/1231/25	728/16558	0.04	1.42(1.13-1.80)	0.008	1	0.33	0.12
C10B	LIPID MODIFYING AGENTS, COMBINATIONS	rs11591147	G	T	82/1/0	15870/1303/28	84/17202	0.04	0.23(0.05-1.10)	0.009	0.87	-1.77	0.98
R03B	OTHER DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES, INHALANTS in ATC	rs11591147	G	T	3069/280/9	12882/1024/18	3360/13926	0.04	1.18(1.03-1.34)	0.012	1	0.17	0.07
C01A	CARDIAC GLYCOSIDES	rs11591147	G	T	456/24/0	15496/1280/28	481/16805	0.04	0.64(0.42-0.95)	0.015	0.99	-0.47	0.21
C02A	ANTIADRENERGIC AGENTS, CENTRALLY ACTING	rs11591147	G	T	203/29/0	15749/1275/28	232/17054	0.04	1.64(1.12-2.40)	0.023	1	0.47	0.19

Causes of hospitalization for 34 Finns homozygote for PCSK9 p.R46L:

ICD group	Variant	# homozygotes	Frequency in homozygotes	# FINRISK individuals	Frequency in FINRISK	P-value	OR (95% CI)
OTHER PSYCHOSES (ICDv9)	1:55505647	3	8.8	219	1.1	0.008	7.84 (1.53-25.24)
Other diseases of upper respiratory tract (ICDv8)	1:55505647	6	17.6	1488	7.6	0.062	2.31 (0.79-5.58)
Neuroses, personality disorders and other nonpsychotic mental disorders (ICDv8)	1:55505647	3	8.8	493	2.5	0.063	3.48 (0.68-11.14)
Pregnancy with abortive outcome (ICDv10)	1:55505647	3	8.8	545	2.8	0.08	3.15 (0.62-10.07)
Other diseases of upper respiratory tract (ICDv10)	1:55505647	4	11.8	939	4.8	0.096	2.44 (0.63-6.86)

-> evidence for potential PCSK9i safety issues?

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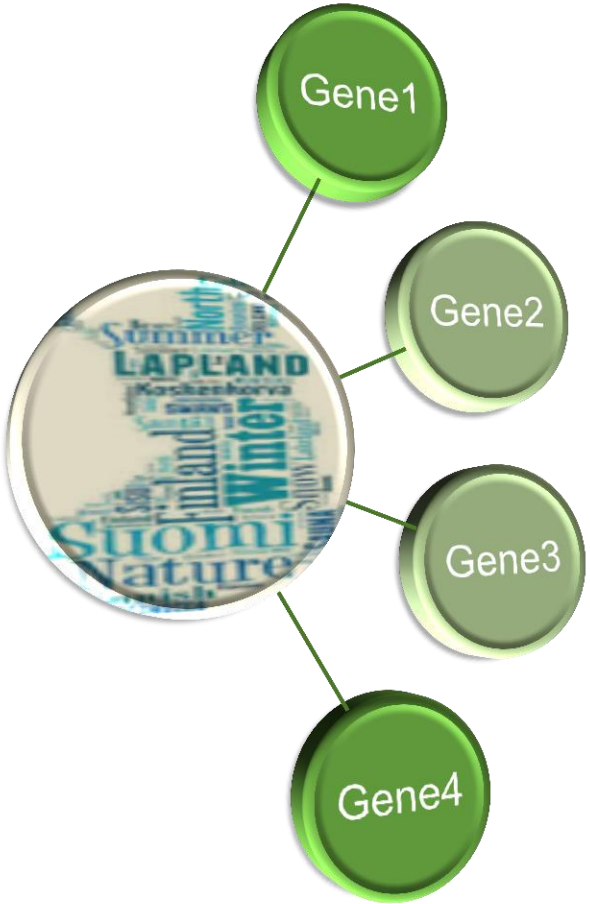
In summary



Getting a complete picture of the role of allelic variation on target genes of interest is critical to improving success in early drug discovery

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