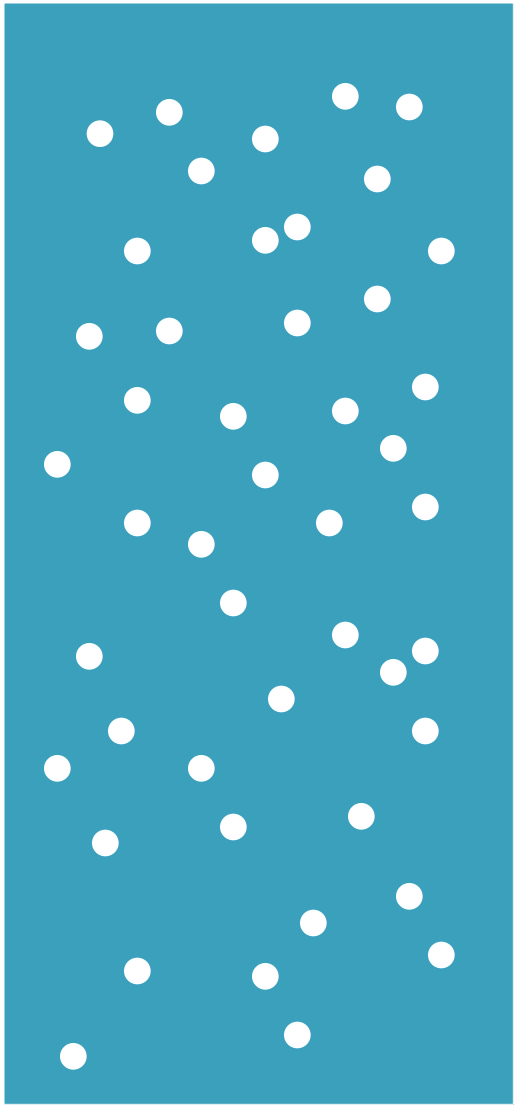

Kári Stefánsson
from deCODE
genetics that
serves as the
genetics engine
for AMGEN

Dataset on diversity
in the sequence

Dataset on diversity
in the phenotype



Dataset on diversity
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Dataset on diversity
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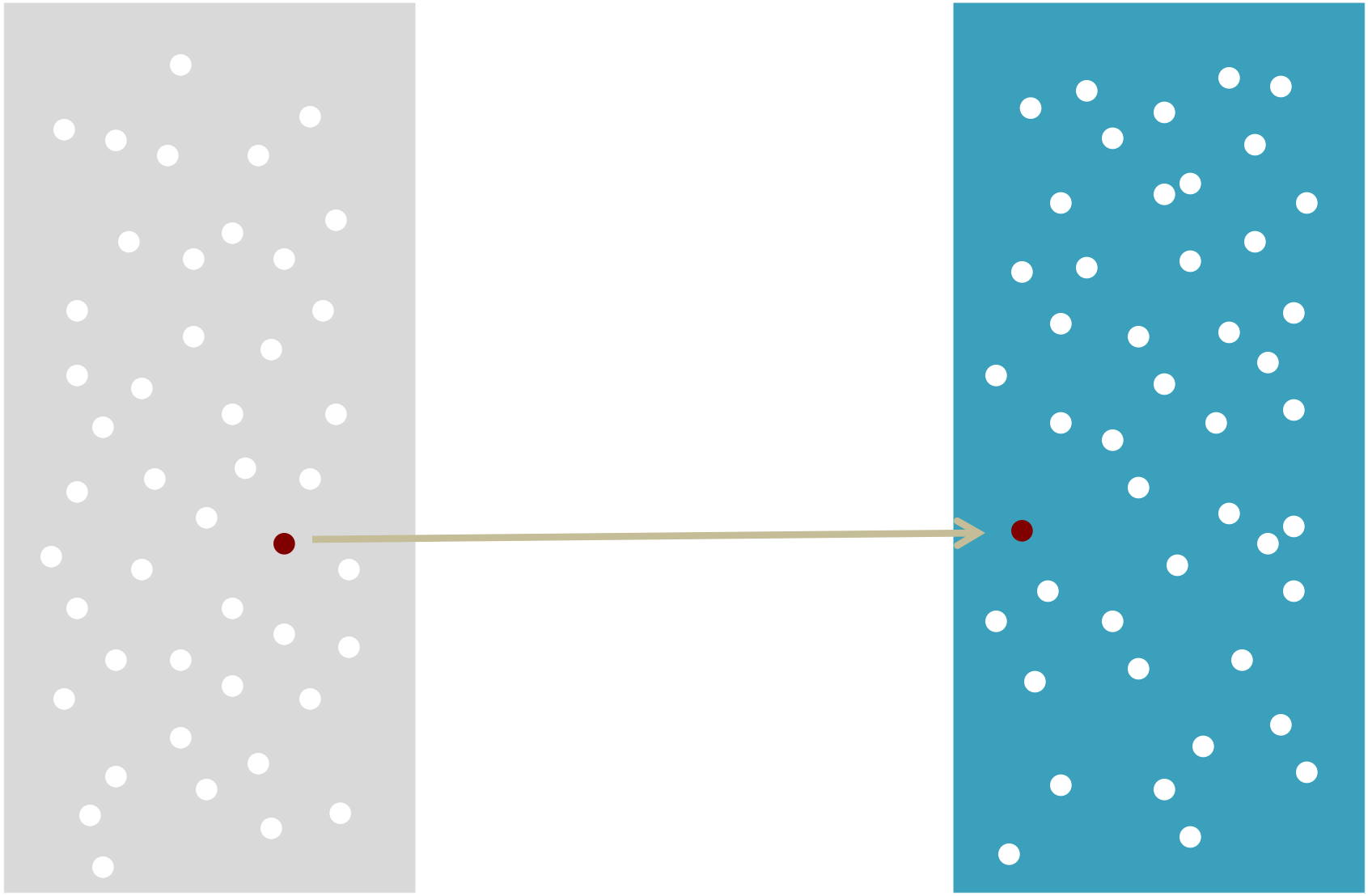


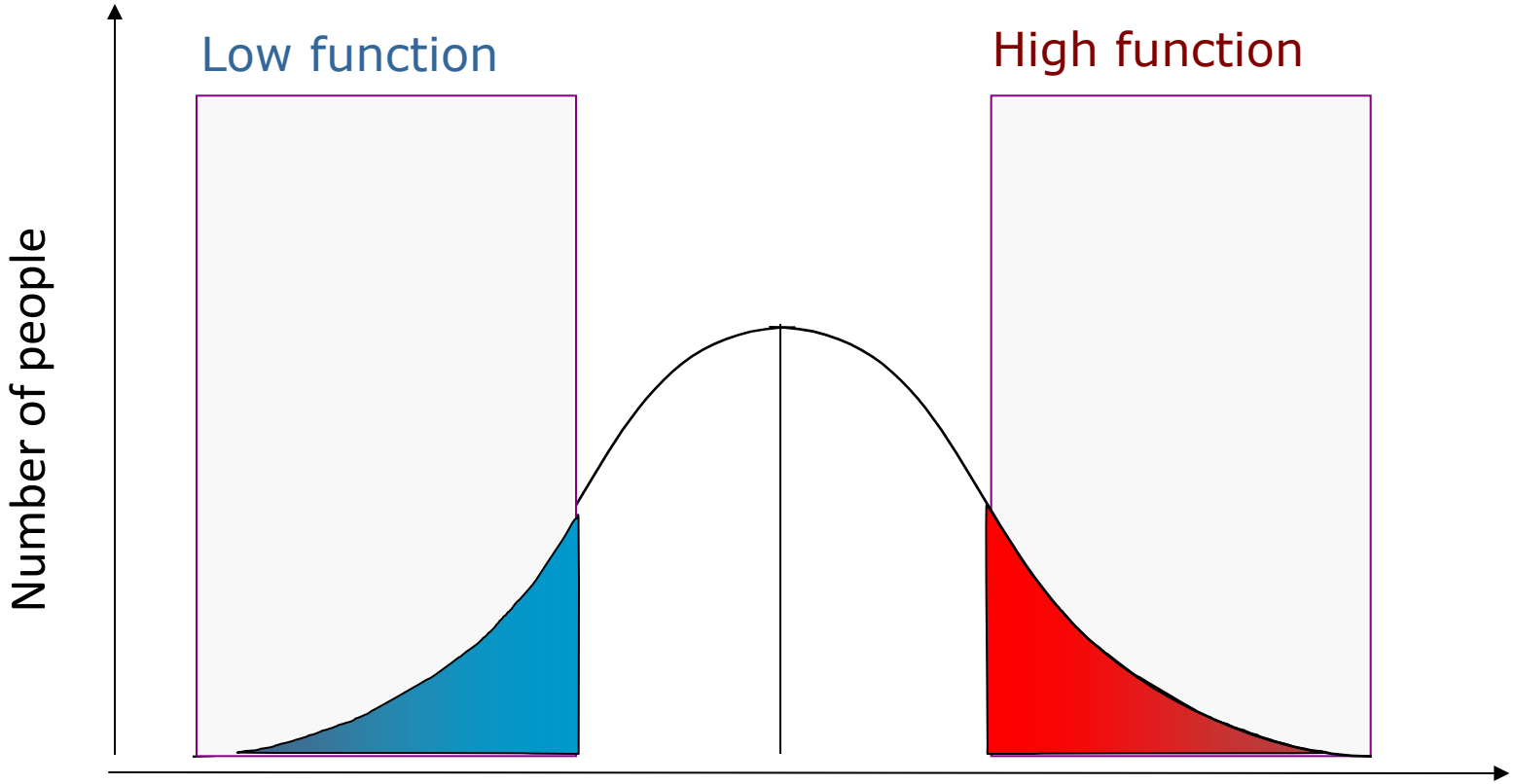
Data on diversity in the sequence of Icelandic genomes

- Genotyped 160.000 Icelanders or about half the nation with one of the Illumina chips
- Whole genome (?) sequenced over 20.000 Icelanders to the median depth of 30x
- Documented genealogy (phasing instrument) of the entire nation centuries back in time
- Imputed variants down to a frequency of 0.01% into 390.000 Icelanders dead or alive
- List of 16000 Icelanders who are homozygous for a loss of function mutation in at least one of 1800 genes

Data on diversity in phenotypes of Icelandic genomes

- 5000+ phenotypes including
- All cancer diagnosed in Iceland since 1950
- All CADs and myocardial infarctions since 1980
- All artificial hips and knees since the procedures came to Iceland
- All cases of asthma and COPD since 1970
- All cases of schizophrenia and bipolar disease since 1970
- Birthweight and length of the entire nation as weel as annual measures of weight and height from age 6 to 12.
- National database on all drug prescriptions
- Educational attainment and results of standardized exams for the entire nation over 60 years
- Socioeconomic status of the entire nation
- All cases of chronic kidney disease since 1970
- Rheumatoid arthritis, psoriasis, atopic dermatidis and MS
- All cases of Type I and II diabetes ever diagnosed in Iceland
- BMI of ca 100.000 Icelanders
- Memberships in all associations of the creative professions

Normal distribution of physiologic function



Complex Traits that deCODE Has Associated with Common Variants in the Sequence

Type 2 diabetes
Myocardial infarction/CAD
Abdominal aortic aneurysm
Intracranial aneurysm
Atrial fibrillation
dementia
Stroke
Nicotine addiction
Lung cancer
Peripheral arterial disease
Prostate cancer
Breast cancer
Exfoliation Glaucoma
Restless leg syndrome
Osteoporosis/BMD
Open angle glaucoma
Height
Pigmentation
Recombination rate

Melanoma
Squamous cell carcinoma
Schizophrenia
Urinary bladder cancer
Asthma
Basal cell carcinoma
BMI
Menarch
Thyroid cancer
Essential tremor
Chronic renal failure
Heart block
Primary open angle glaucoma
Coffee consumption
Love of crossword puzzles

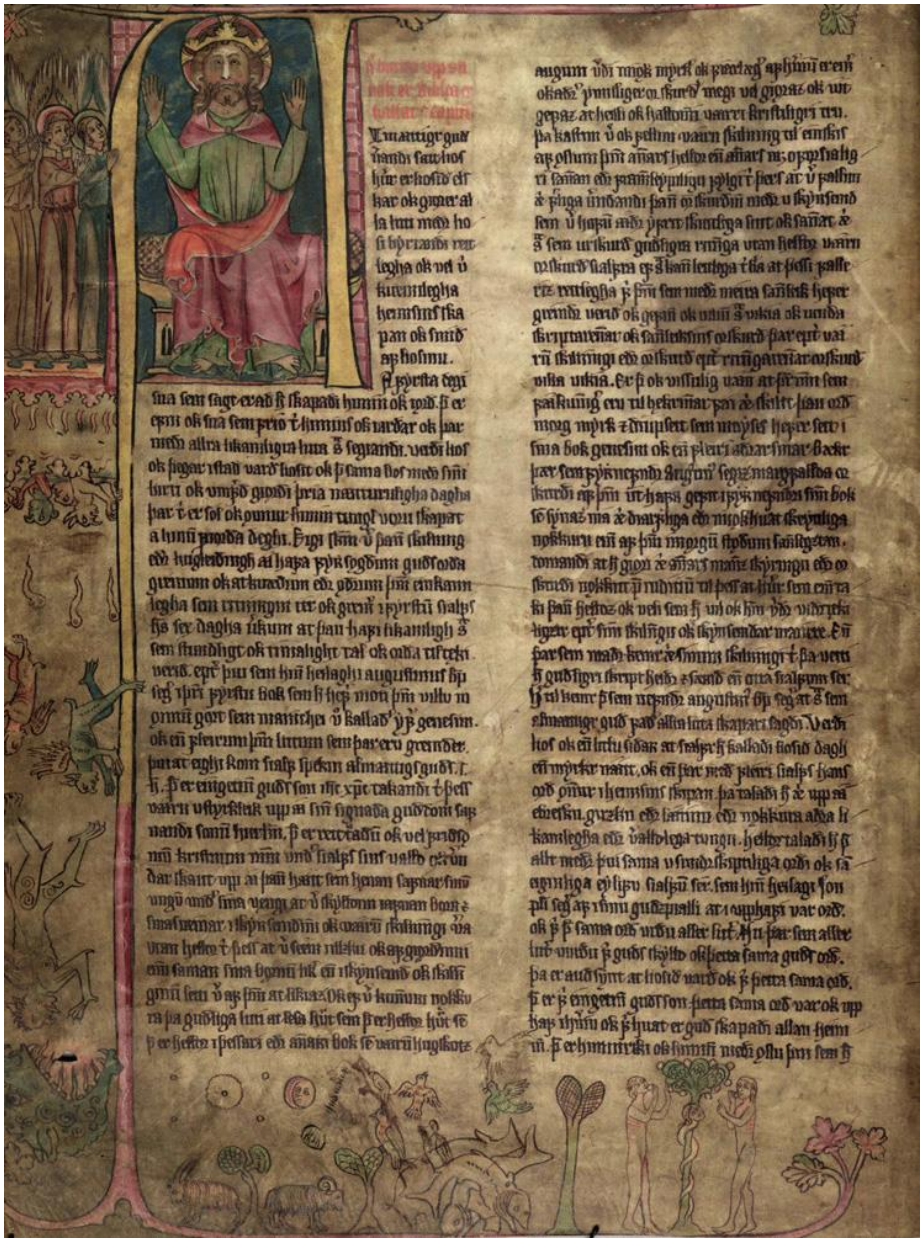
And this list is growing

Complex Traits that deCODE Has Associated with Rare Variants in the Sequence

Ovarian cancer
Glioma
Basal cell carcinoma of the skin
Prostate cancer
Cancer of the biliary tract
Chronic lymphocytic lymphoma
Alzheimer's Disease
Osteoporosis
ADHD
Type 2 Diabetes
Sudden cardiac death
Atrial fibrillation
Osteoarthritis
Gout
Age Related Macular Degeneration
Height
Dyslexia
Schizophrenia
Autism

Stomach cancer
Waldenström's macroglobulinemia
MGUS
Lung cancer

SSStom



How we use these data to serve drug discovery and development

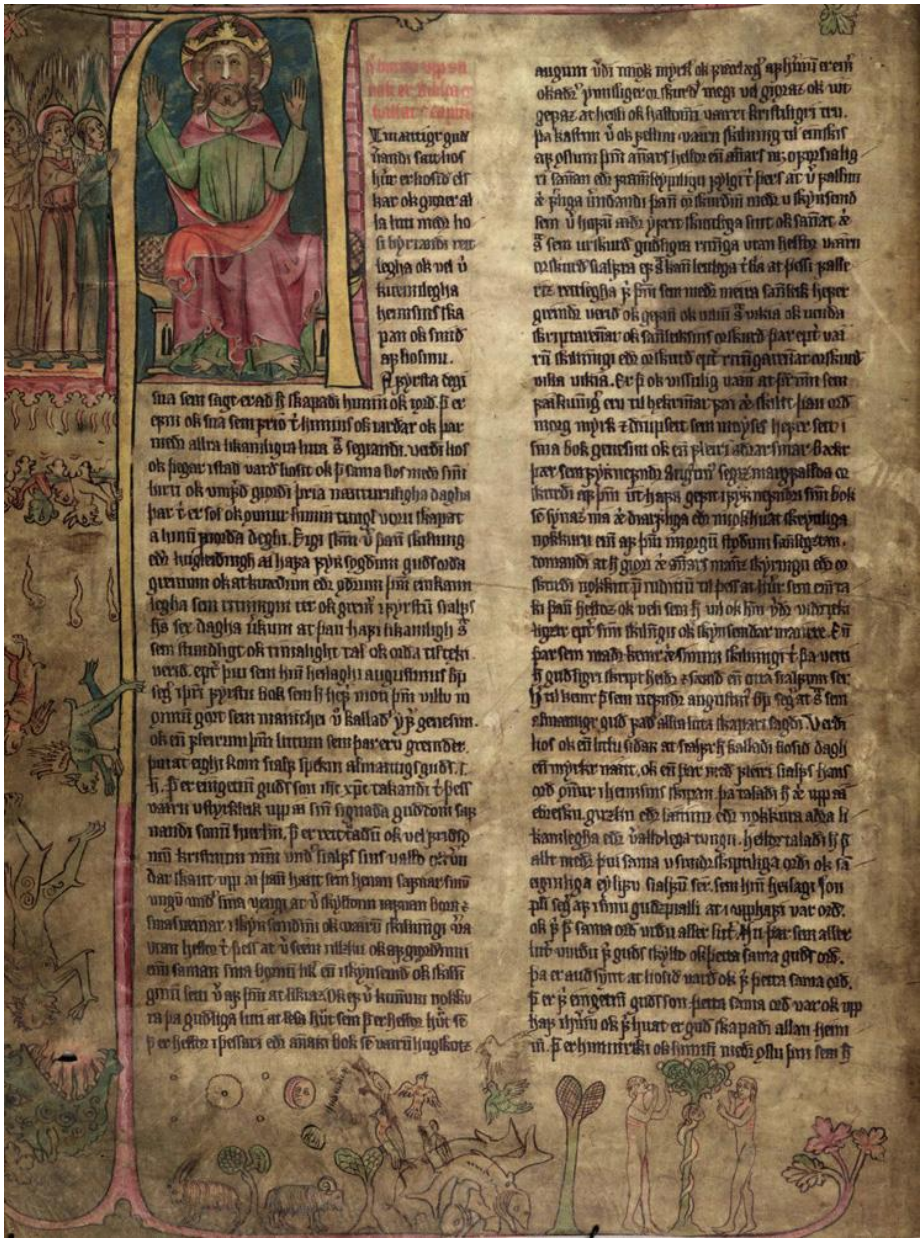
PCSK9 Arg46Leu associates with lower non-HDL and protects against CAD

			Non-HDL cholesterol (N=136,261)		CAD all (N=36,886)		CAD early onset (N=5,196)	
rsID	**PCSK9 effect**	**Allele freq.**	**Effect (mg/dl)**	**P**	**OR**	**P**	**OR**	**P**
rs11591147	Arg46Leu	1.2%	-17.9	2.3E-73	0.73	2.8E-7	0.60	1.9E-4

- Arg46Leu variant is predicted through functional studies to be a loss of function mutation
- Arg46Leu variant is associated with 2.3 years older age at diagnosis of CAD and 3 years for MI

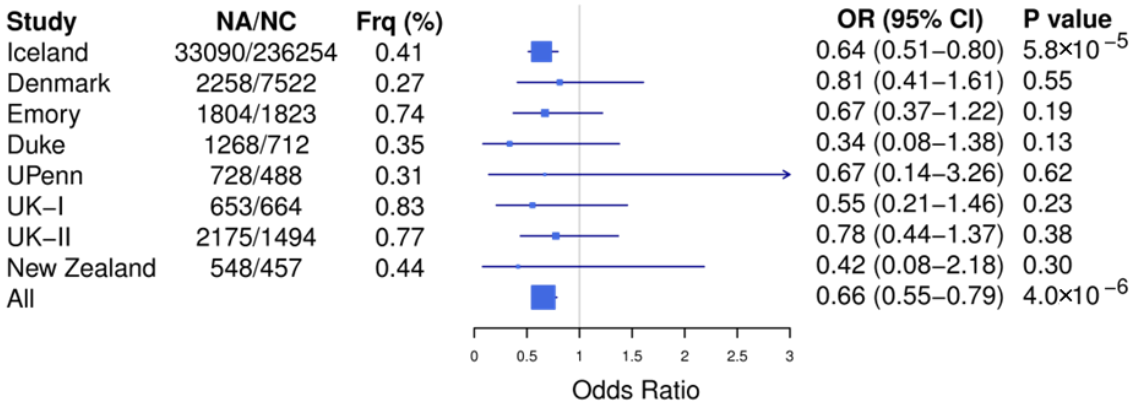
Screening for potential side effects of PCSK9 inhibitor

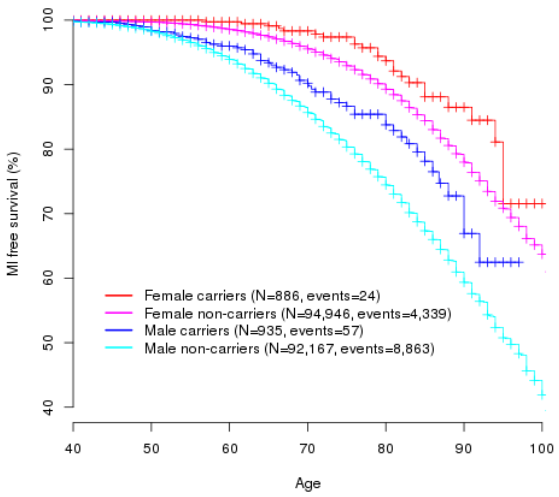
Phenotype	N cases/contr	P value	OR
Alzheimer	3,754/163,803	0.37	0.89
Other dementia	2,176/82,025	0.66	0.93
Type 2 diabetes	11,206/269,139	0.54	1.05
Lifespan	118,626	0.11	+8 months



Another CAD target coming out of our genetics

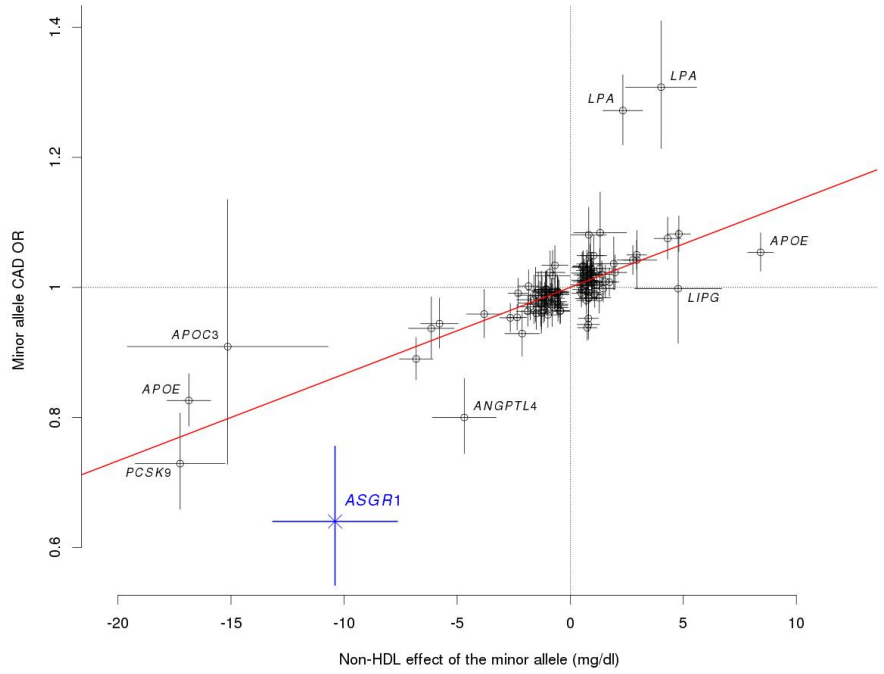
The del12 protects against coronary artery disease and delays the onset myocardial infraction

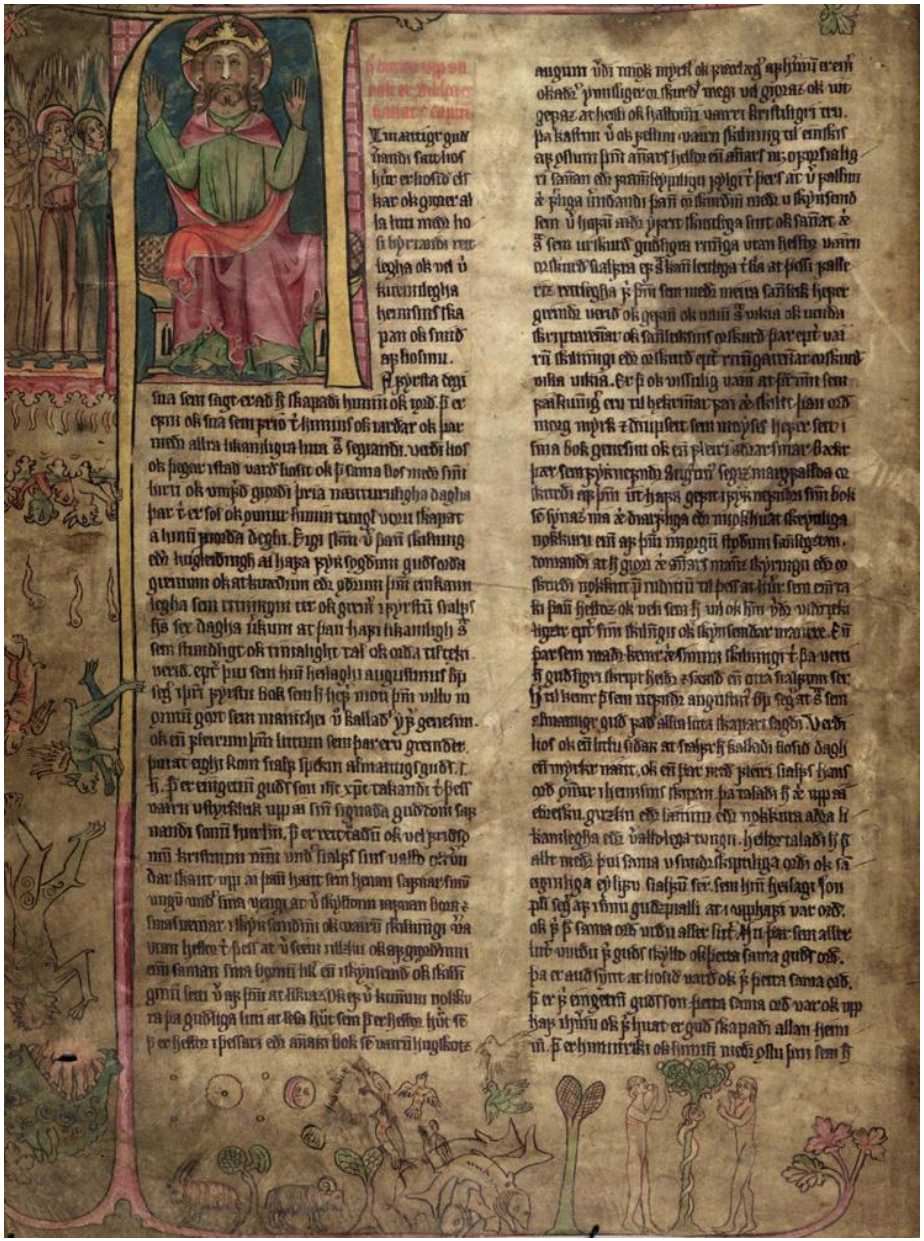




Trait	Variant	
	PCSK9 (Arg46Leu), MAF=1.2%	*(del12),* MAF=0.41%
Non-HDL cholesterol	**-0,49 (SD)** (P=1.2x10^{-64})	-0,19 (SD) (P=1.4x10^{-9})
CAD	0.75 (OR) (P=1.9x10^{-5})	**0.62 (OR)** (P=2.6x10^{-5})
MI	0.74 (OR) (P=1.7x10^{-4})	**0.56 (OR)** (P=2.0x10^{-5})
Lifespan	+8 months (P=0.11)	**+18 months** (P=0.04)

The relationship between the effect of sequence variants on non-HDL cholesterol and their effect on CAD risk





Alzheimer´s

LETTER

doi:10.1038/nature11283

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

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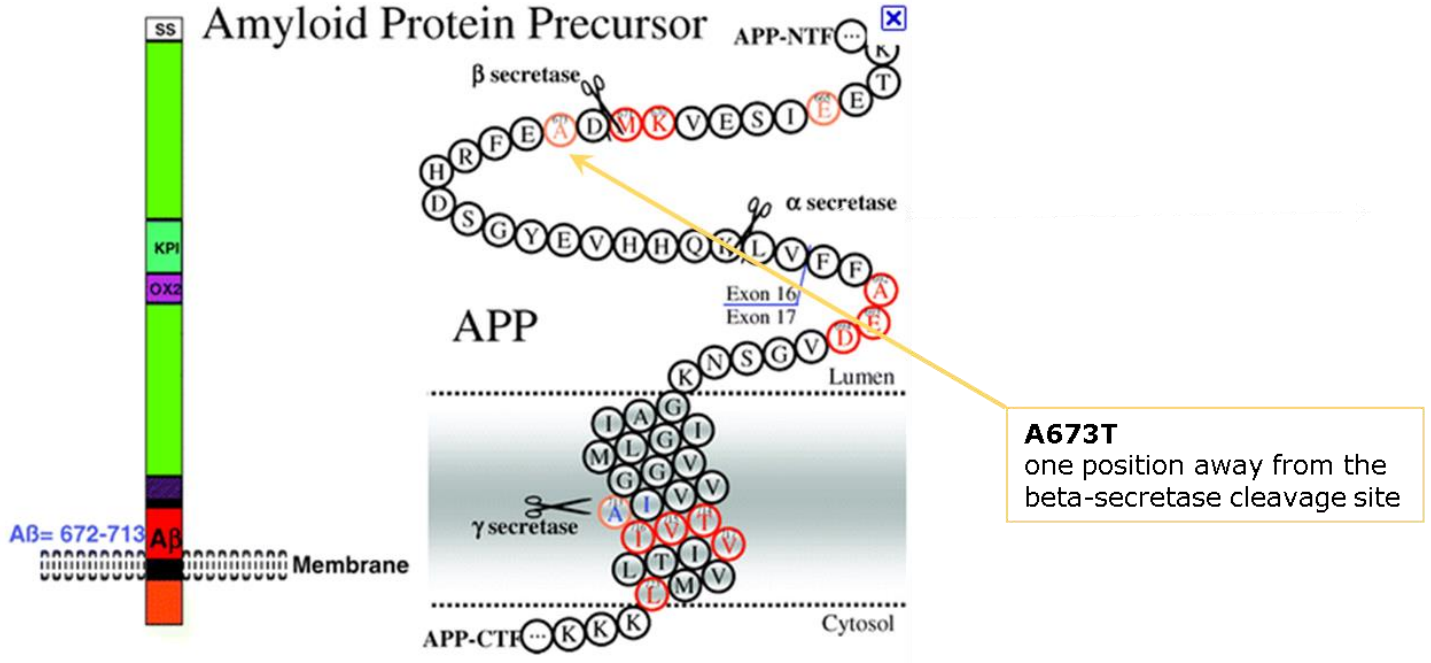

Alzheimer's

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 10, 2013 VOL. 368 NO. 2

Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

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ABSTRACT

BACKGROUND

Sequence variants, including the ε4 allele of apolipoprotein E, have been associated with the risk of the common late-onset form of Alzheimer's disease. Few rare variants affecting the risk of late-onset Alzheimer's disease have been found.

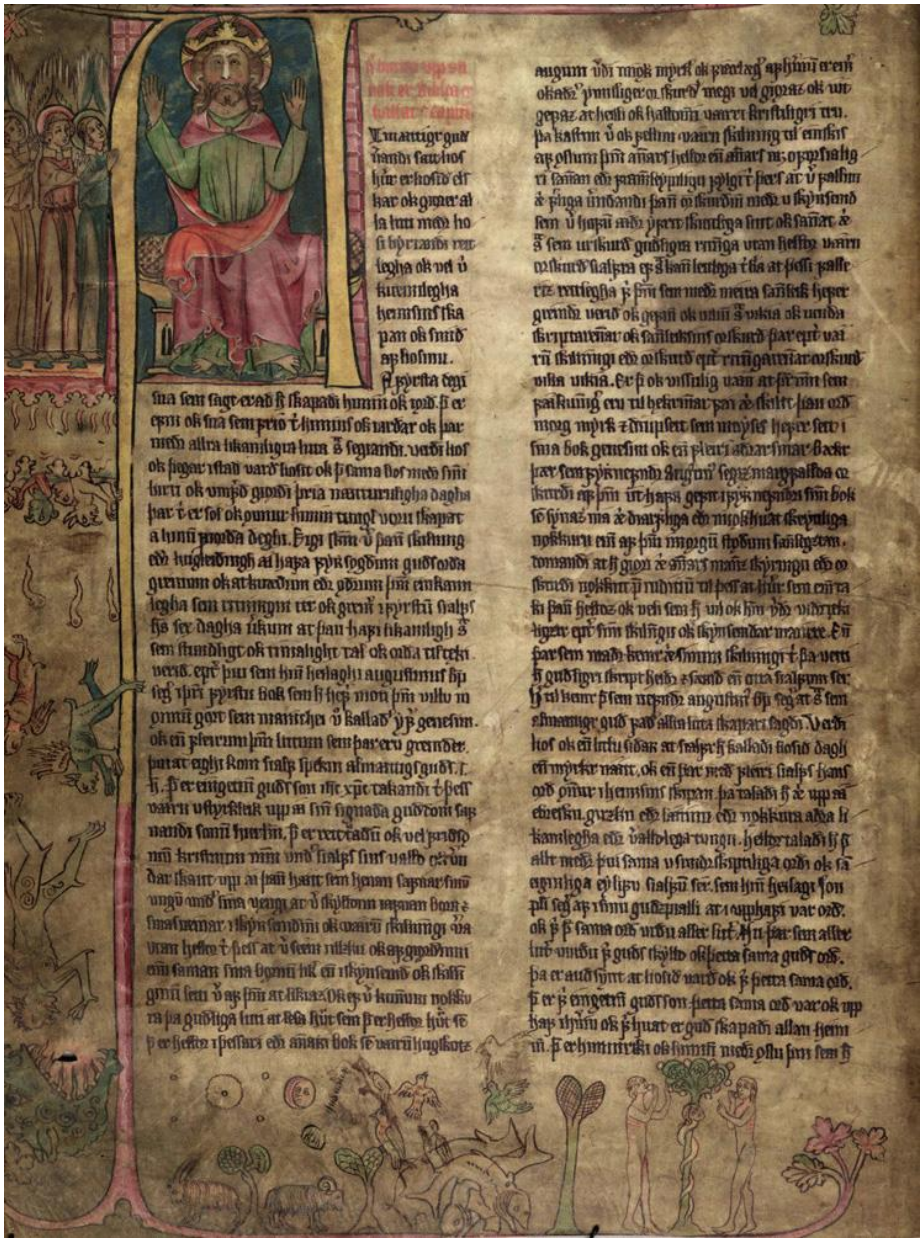
METHODS

We obtained the genome sequences of 2261 Icelanders and identified sequence variants that were likely to affect protein function. We imputed these variants into the genomes of patients with Alzheimer's disease and control participants and then tested for an association with Alzheimer's disease. We performed replication tests using case–control series from the United States, Norway, the Netherlands, and Germany. We also tested for a genetic association with cognitive function in a population of unaffected elderly persons.

RESULTS

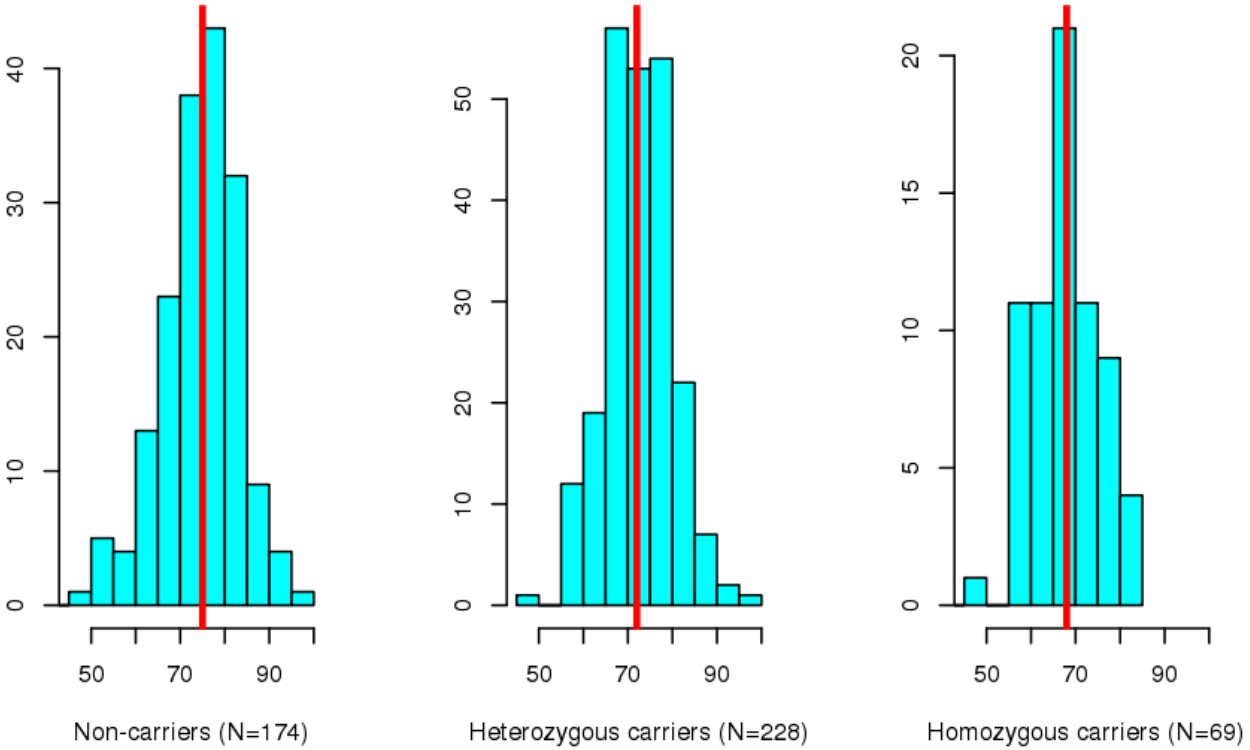
A rare missense mutation (rs75932628-T) in the gene encoding the triggering receptor expressed on myeloid cells 2 (*TREM2*), which was predicted to result in an R47H substitution, was found to confer a significant risk of Alzheimer's disease in Iceland (odds ratio, 2.92; 95% confidence interval [CI], 2.09 to 4.09; $P=3.42\times10^{-10}$). The mutation had a frequency of 0.46% in controls 85 years of age or older. We observed the association in additional sample sets (odds ratio, 2.90; 95% CI, 2.16 to 3.91; $P=2.1\times10^{-12}$ in combined discovery and replication samples). We also found that carriers of rs75932628-T between the ages of 80 and 100 years without Alzheimer's disease had poorer cognitive function than noncarriers ($P=0.003$).

From deCODE Genetics (T.J., H.S., S.S., I.J., U.T., A.K., K.S.), the University of Iceland, Faculty of Medicine (I.J., P.V.J., U.T., K.S.), and Landspitali University Hospital (P.V.J., J.S., S.B.) — all in Reykjavik, Iceland; the Department of Medical Genetics, Institute of Human Genetics, Tübingen (J.H.), Division of Molecular and Clinical Neurobiology, Department of Psychiatry, University of Munich, Munich (L.M.U.) and University of Halle, Halle (D.R., I.G.), and the Department of Psychiatry, University of Frankfurt am Main, Frankfurt am Main (H.H.) — all in Germany; the Department of Neurology, Alzheimer's Disease Center, Emory University School of Medicine, Atlanta (A.I.L., J.J.L.); K.G. Jebsen Center for Psychosis Research, Division of Mental Health and Addiction (O.A.A., S.D.), and the Geriatric Department, Norwegian Center for Aging and Health (K.E., I.U.), Oslo University Hospital, and the Institute of Clinical Medicine, University of Oslo (O.A.A., K.E., S.D.) — all in Oslo; and the Department of Epidemiology, Erasmus Medical Center, Rotterdam, the Netherlands, (C.I.-V., A.H., M.A.I., C.M.D.). Address reprint requests to Dr. K. Stefansson at deCODE Genetics, Stur-

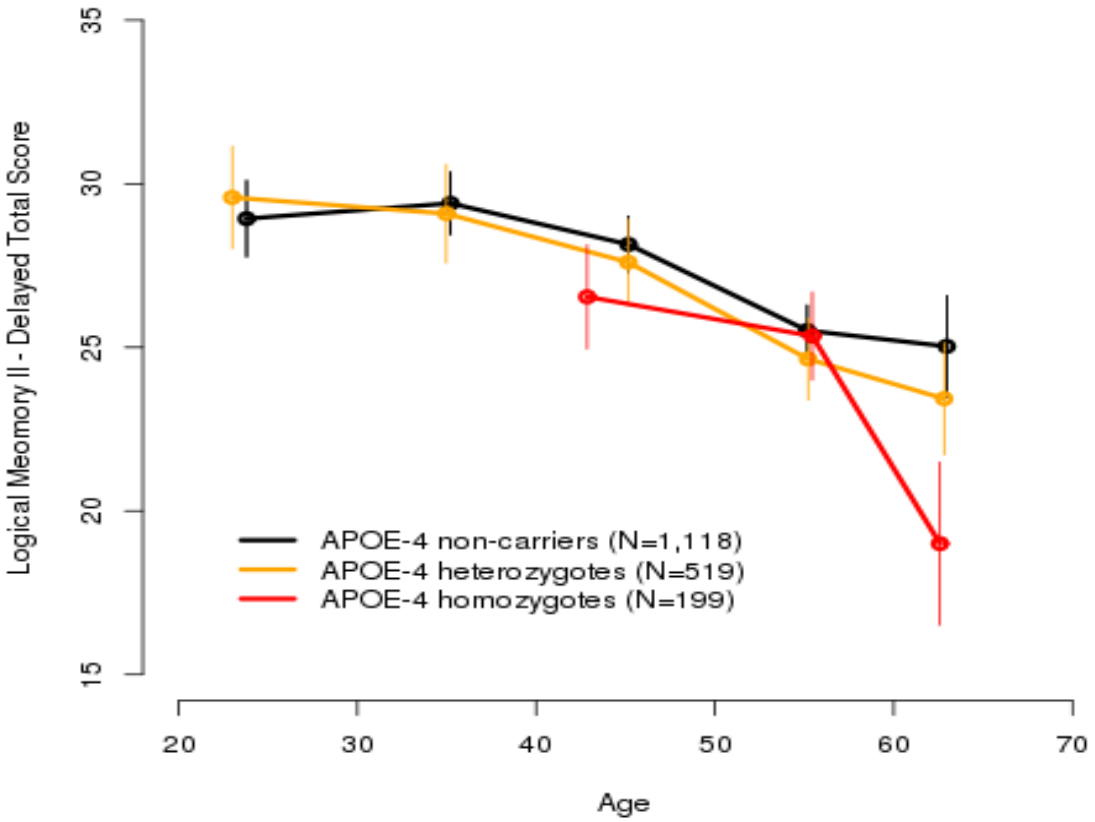


When to begin to treat in Alzheimer´s

Alzheimer‘s disease age at onset by *APOE* genotype



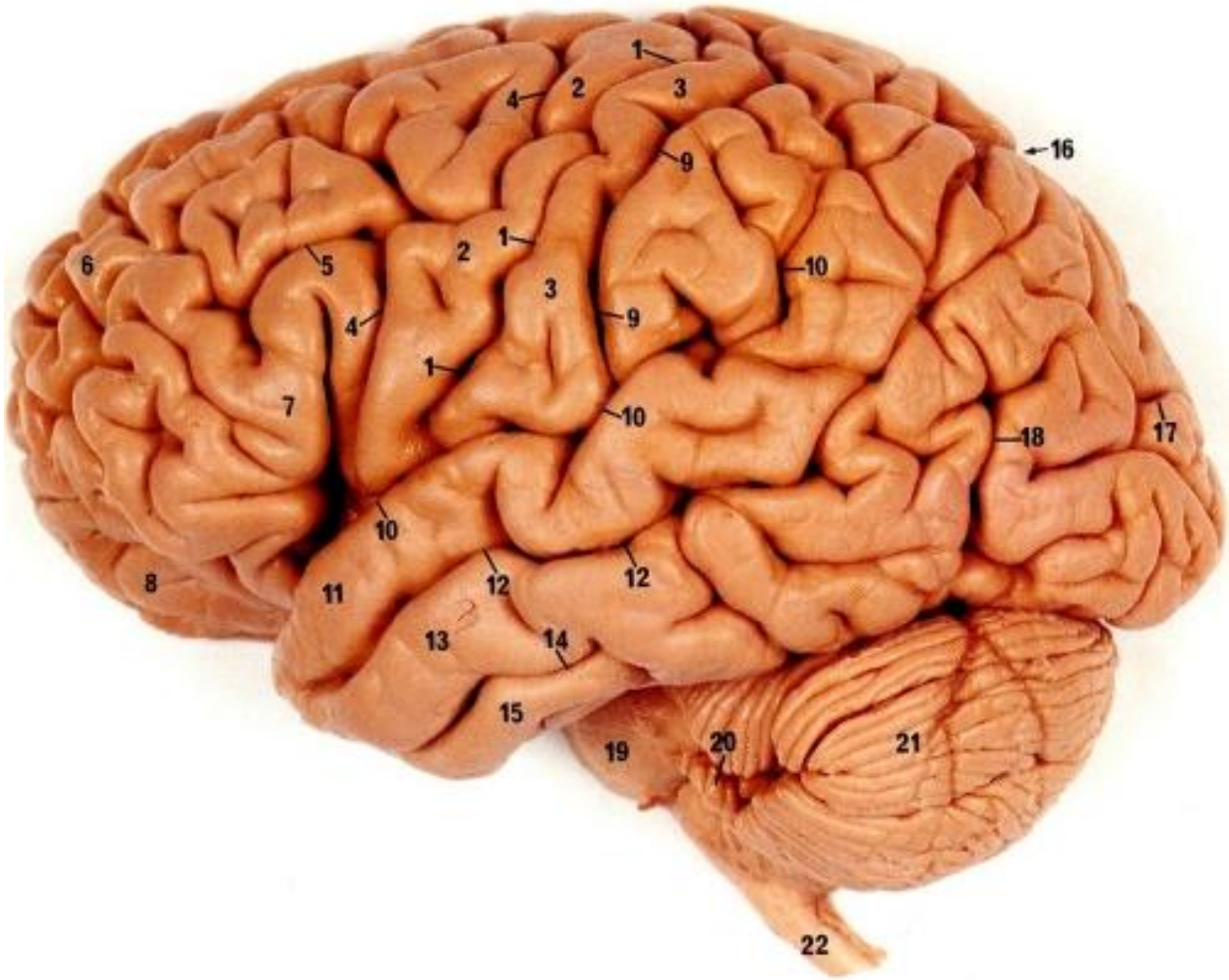
Wechsler Memory Scale decline with age



Vertical bars indicate 95% CIs

Gaps to be filled

- Much better annotation of intergenic sequences
- Societal acceptance of the duty to contribute data in return for access to healthcare
- Longer reads on whole genomes of populations
- Somatic sequencing of all organs in a large numbers of people
- Figuring out how the brain work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Erfðafræði reykinga og sjúkdóma sem Þeim tengjast

LETTERS

A variant associated with nicotine dependence, lung cancer and peripheral arterial disease

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Smoking is a leading cause of preventable death, causing about 5 million premature deaths worldwide each year[1,2]. Evidence for genetic influence on smoking behaviour and nicotine dependence (ND)[3–8] has prompted a search for susceptibility genes. Furthermore, assessing the impact of sequence variants on smoking-related diseases is important to public health[9,10]. Smoking is the major risk factor for lung cancer (LC)[11–14] and is one of the main risk factors for peripheral arterial disease (PAD)[15–17]. Here we identify a common variant in the nicotinic acetylcholine receptor

smoking, with SQ reported as cigarettes per day. All SQ data were clustered into categories (see Supplementary Information) and we refer to them as 'SQ levels'. The SQ levels were 0 (1–10 cigarettes per day), 1 (11–20), 2 (21–30) and 3 (31 or more). Each increment represents an increase in SQ of 10 cigarettes per day. Allele T of the SNP rs1051730 was most strongly associated with SQ, and the association was highly significant ($P = 5 \times 10^{-16}$). The SNP is within the *CHRNA3* gene in a linkage disequilibrium block also containing two other genes, *CHRNA5* and *CHRNB4*, that encode nicotinic acetyl-