deCODE genetics

Hilma Hólm, MD

Head of Cardiovascular Research at deCODE genetics

Nordic Biobank Conference, September 7th, 2022

deCODE genetics

Conflict of interest statement

- I am an employee of deCODE genetics / Amgen inc.

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deCODE genetics

- Founded in 1998
- Iceland = 360,000 inhabitants
- Population approach:
  - Sample a large fraction of one population to study the genetics of human diversity
  - Data collected independently of questions
  - Can be mined systematically in a model-independent approach

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Advantages of Iceland for genetic research

- Accessible health care data
  - Single payer health care system
  - All health care data linked to a unique personal identifier (kennitala)
- Population structure conducive for genetic research
  - Founder effects
  - Homogeneous population which reduces population stratification issues
- Genealogy database (Book of Icelanders) linking 750,000 Icelanders over several centuries
  - Allows the application of familial analysis
  - Allows determination of parent of origin

Parent-of-origin specific analysis of single variants

Table 1 | Parental-origin-specific analyses of disease-susceptibility variants

Disease, SNP [alleles]*		Standard case-control test		Tests of association with parental origins						
NCBI build 36 position, *N*	*M*, F_{con}	OR	*P*‡	Paternal allele§		Maternal allele§		2-d.f. test‖	Paternal vs maternal (case only)	
				OR	*P*	OR	*P*	*P*	n12:n21¶	*P*
Breast cancer, rs3817198† [C/T]										
C11 1,865,582, 1,803	34,909, 0.303	1.04	0.36	1.17	0.038	0.91	0.11	0.0040	437:339	6.2×10^{-4}
Basal-cell carcinoma, rs157935 [T/G]										
C7 130,236,093, 1,118	37,041, 0.676	1.23	1.8×10^{-5}	1.40	1.5×10^{-6}	1.09	0.19	3.8×10^{-6}	237:182	0.010
T2D, rs2237892 [C/T]										
2,251 (combined)		1.15	0.043	1.03	0.71	1.30	0.0084	0.027	116:149	0.054
T2D, rs231362† [C/T]										
C11 2,648,047, 2,173 (combined)	33,377,	1.10	0.013	0.98	0.73	1.23	6.2×10^{-5}	2.6×10^{-4}	487:592	0.0032
T2D, rs4731702 [C/T]										
C7 130,083,924, 2,251 (combined)	34,706,	1.08	0.039	0.99	0.79	1.17	0.0010	0.0041	498:578	0.022
T2D, rs2334499 [T/C]										
C11 1,653,425, 2,251 (combined)	34,706,	1.08	0.034	1.35	4.7×10^{-10}	0.86	0.0020	5.7×10^{-11}	659:433	4.1×10^{-11}

Variants with parent-of-origin specific effects detected in association analysis

In one case both the paternally transmitted and the maternally transmitted alleles associate with type 2 diabetes but with an opposite effect

› Nature. 2009 Dec 17;462(7275):868-74. doi: 10.1038/nature08625.

Parental origin of sequence variants associated with complex diseases

Augustine Kong [1], Valgerdur Steinthorsdottir, Gisli Masson, Gudmar Thorleifsson, Patrick Sulem, Soren Besenbacher, Aslaug Jonasdottir, Asgeir Sigurdsson, Kari Th Kristinsson, Adalbjorg Jonasdottir, Michael L Frigge, Arnaldur Gylfason, Pall I Olason, Sigurjon A Gudjonsson, Sverrir Sverrisson, Simon N Stacey, Bardur Sigurgeirsson, Kristrun R Benediktsdottir, Helgi Sigurdsson, Thorvaldur Jonsson, Rafn Benediktsson, Jon H Olafsson, Oskar Th Johannsson, Astradur B Hreidarsson, Gunnar Sigurdsson, DIAGRAM Consortium; Anne C Ferguson-Smith, Daniel F Gudbjartsson, Unnur Thorsteinsdottir, Kari Stefansson

deCODE genetics

deCODE facilities

The Research Center

The Recruitment Center

The identity protection service

Provides a communication channel between researchers at deCODE and outside collaborators in Iceland while maintaining privacy for research participants

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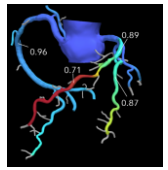
Sources of phenotype data in the Icelandic health care system

- Landspitali – The National University Hospital
- Regional hospitals
- Imaging centers
- Blood laboratories
- Register of primary health care contacts
- Register of contacts with medical specialists in private practice
- Birth register
- Causes of death register
- Cancer register
- Prescription medicines register



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Phenotype data extracted from the Icelandic health care system

- International Classification of Diseases (ICD) codes
- Procedure codes
- Medication prescriptions
- Measurements: height, weight, blood pressure, heart rate etc.
- Clinical biological traits routinely measured in blood, urine
- Clinical test data such as electrocardiogram data, hearing tests results etc
- Imaging test results and actual imaging data, including CTs, MRIs

- The data span decades (electronic and paper data)
- Many longitudinal data points

Complicated phenotypes

Resistant hypertension

Persons who filled ≥3 antihypertensive medications, including one diuretic, for overlapping periods lasting more than six months

and for those taking 3 drugs:

documentation of SBP or DBP >130/90 mmHg after initiation of the determining drug treatment combination (BP measurement taken after the date of prescription of the third drug)

vs

Controlled hypertension

Persons who filled 1 or 2antihypertensive medications, for overlapping periods lasting more than six months

and

documentation of SBP or DBP <130/90 mmHg within 30 days of drugs being dispensed

Exclusion criteria: sleep apnea (ICD-10 code G47.3) 30, chronic kidney disease (CKD) 31 (determined as two independent estimated glomerular filtration rate (eGFR) values below 60 ml/min/1.73 m2 in a 3-month period), secondary hypertension (ICD-10 code I15.*), hyperaldosteronism (ICD-10 code E26), adrenal gland neoplasms (ICD-10 codes C74.0, C79.7), pulmonary heart disease (ICD-10 code I27.*) and coarctation of aorta (ICD-10 code Q25.1

Complicated phenotypes

Resistant hypertension

Persons who filled ≥3 antihypertensive
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Controlled hypertension

Persons who filled 1 or 2antihypertensive
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Data requirement

- Longitudinal drug prescription data with dates
- Longitudinal blood pressure data with dates
- Longitudinal ICD-code data with dates
- Genotypes

Exclusion

independent estimated glomerular filtration rate (eGFR) values below 60 mL/min/1.73 m2 in a 3-month period), secondary hypertension (ICD-10 code I15.*), hyperaldosteronism (ICD-10 code E26), adrenal gland neoplasms (ICD-10 codes C74.0, C79.7), pulmonary heart disease (ICD-10 code I27.*) and coarctation of aorta (ICD-10 code Q25.1

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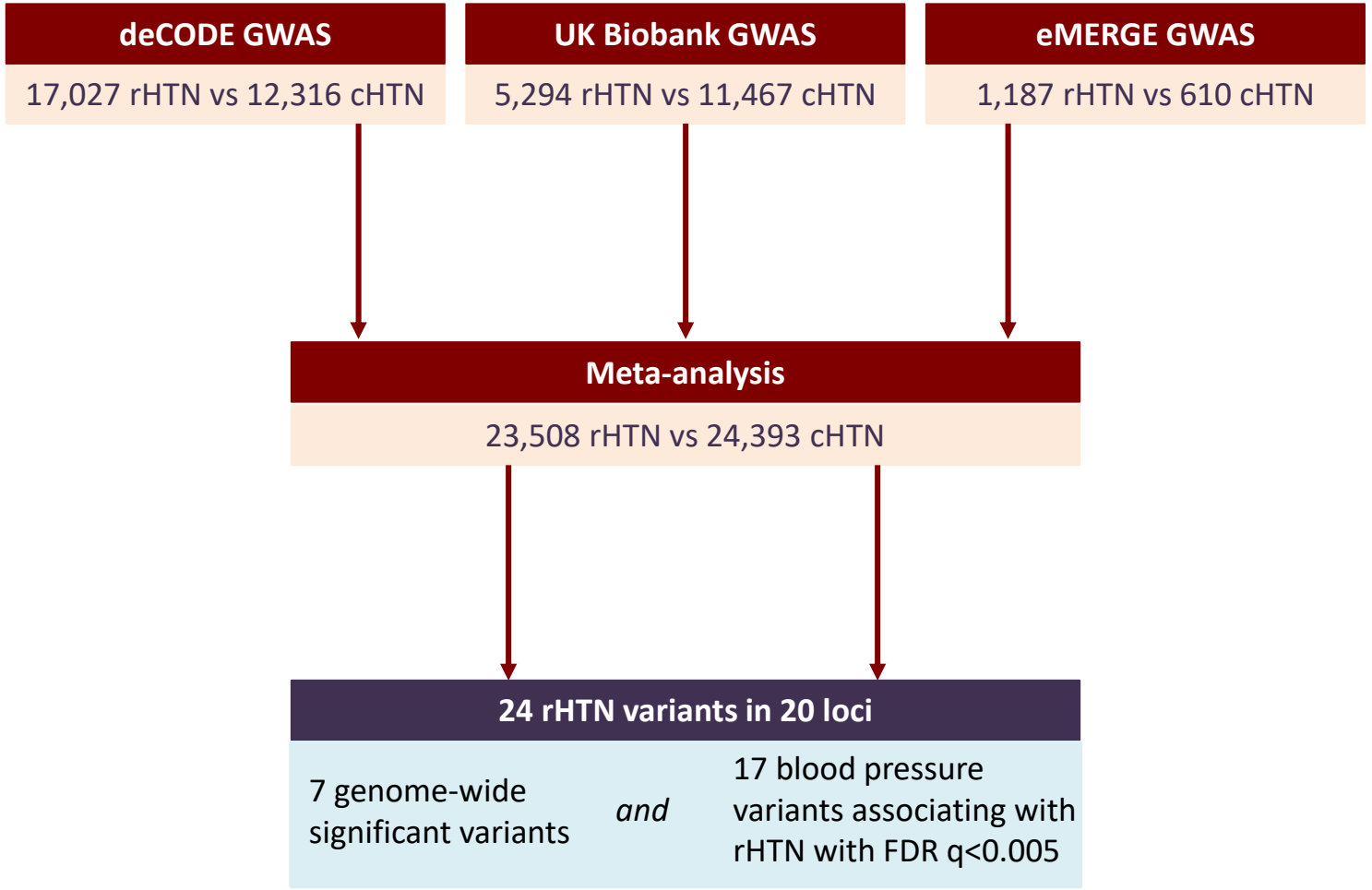
Complicated phenotypes



Submitted

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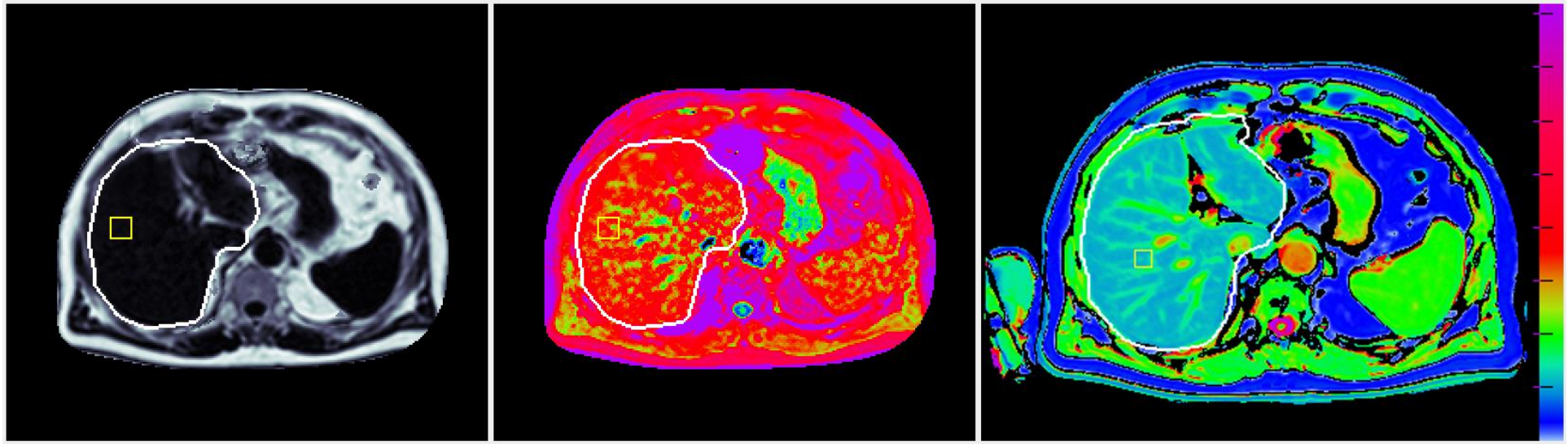
Extraction of information from imaging data by machine learning
Example: Liver fat

- MR allows interrogation of water and fat contribution.
- Deep learning model used to locate the liver in MRIs.
- Enables automatic liver fat fraction, iron content and T1-mapping (measures inflammation) extraction.



Index or ID or PN

	pdff_roi	r2_roi	roi_posx	roi_posy	n_liverMask	n_converged	cT1_median	cT1_roi
0	0.0527190626571932	41.26094184853301	56	114	6513.0	6513.0	628.7497787600158	628.6434947822602

Submitted

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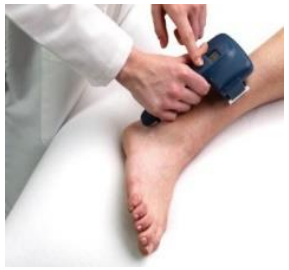
The deCODE health study and other recall studies

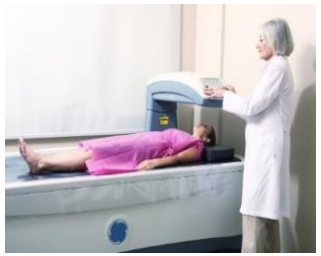
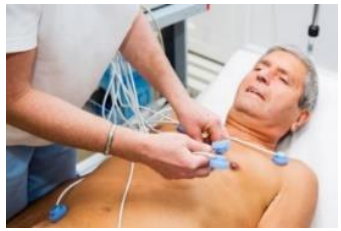


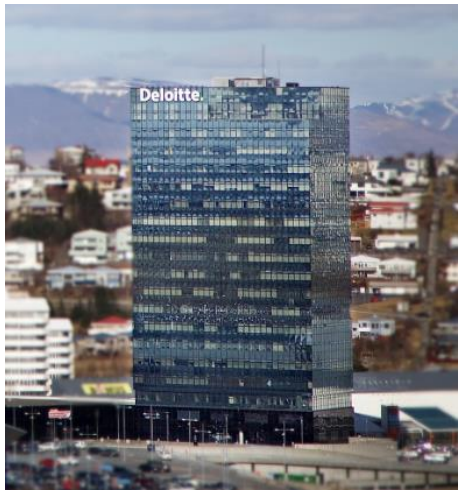








The Recruitment Center

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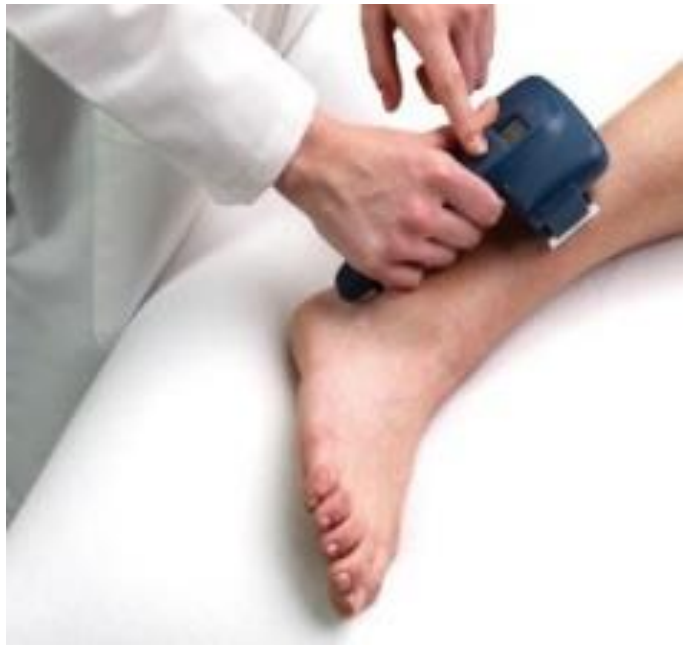
A splice-donor variant in *PRPH* – encoding peripherin - associates with risk of peripheral neuropathy



nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-09719-4 OPEN

A *PRPH* splice-donor variant associates with reduced sural nerve amplitude and risk of peripheral neuropathy

Gyda Bjornsdottir[1], Erna V. Ivarsdottir[1,2], Kristbjorg Bjarnadottir[1], Stefania Benonisdottir[1], Sandra Sif Gylfadottir[3], Gudny A. Arnadottir[1], Rafn Benediktsson[4,5], Gisli Hreinn Halldorsson[1], Anna Helgadottir[1], Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Ingileif Jonsdottir[1,4], Anna Margret Kristinsdottir[1], Olafur Th. Magnusson[1], Gisli Masson[1], Pall Melsted[1,2], Thorunn Rafnar[1], Asgeir Sigurdsson[1], Gunnar Sigurdsson[1,4,5], Astros Skuladottir[1], Valgerdur Steinthorsdottir[1], Unnur Styrkarsdottir[1], Gudmundur Thorgeirsson[1,4,5], Gudmar Thorleifsson[1], Arnor Vikingsson[5], Daniel F. Gudbjartsson[1,2], Hilma Holm[1,4], Hreinn Stefansson[1], Unnur Thorsteinsdottir[1,4], Gudmundur L. Norddahl[1], Patrick Sulem[1], Thorgeir E. Thorgeirsson[1] & Kari Stefansson[1,4]

Nerve conduction (NC) studies generate measures of peripheral nerve function that can reveal underlying pathology due to axonal loss, demyelination or both. We perform a genome-wide association study of sural NC amplitude and velocity in 7045 Icelanders and find a low-frequency splice-donor variant in *PRPH* (c.996+1G>A; MAF = 1.32%) associating with decreased NC amplitude but not velocity. *PRPH* encodes peripherin, an intermediate filament (IF) protein involved in cytoskeletal development and maintenance of neurons. Through RNA and protein studies, we show that the variant leads to loss-of-function (LoF), as when over-expressed in a cell line devoid of other IFs, it does not allow formation of the normal filamentous structure of peripherin, yielding instead punctate protein inclusions. Recall of carriers for neurological assessment confirms that from an early age, homozygotes have significantly lower sural NC amplitude than non-carriers and are at risk of a mild, early-onset, sensory-negative, axonal polyneuropathy.

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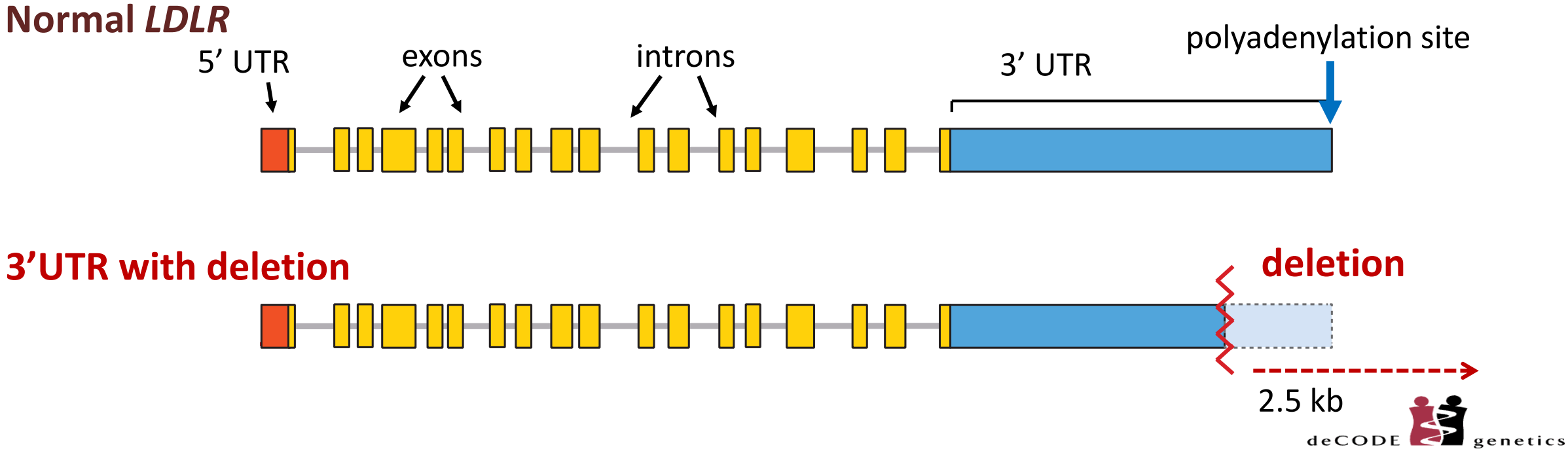
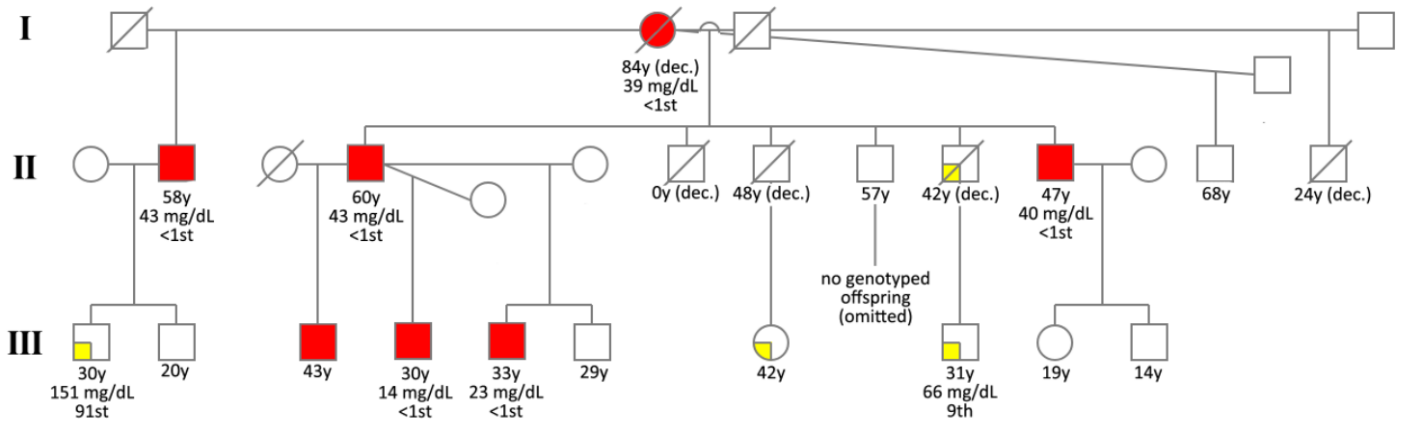
A novel deletion in *LDLR*

- Reported LOF in *LDLR* associate with higher LDL
- Novel 2.5kb deletion in the 3’ UTR that associates with lower LDL



deCODE genetics

Icelandic family with *LDLR* - Gain of function



carrier

non-carrier

Age (y)
Mean LDL-C
LDL-C percentile

- 7 carriers: oldest reached 84
- *De novo* mutation
- Carriers have 74% lower LDL; $P = 1.1 \times 10^{-11}$
  - Lowering similar to that of PCSK9-inhibitors
  - Lifelong very low LDL appears to be well tolerated

Circulation: Genomic and Precision Medicine
Volume 14, Issue 1, February 2021
https://doi.org/10.1161/CIRCGEN.120.003029

2021

ORIGINAL ARTICLE

Lifelong Reduction in LDL (Low-Density Lipoprotein) Cholesterol due to a Gain-of-Function Mutation in *LDLR*

Eythor Bjornsson, MD, Kristbjorg Gunnarsdottir, MSc, Gisli H. Halldorsson, MSc, Asgeir Sigurdsson, BSc, Gudny A. Arnadottir, MSc, Hakon Jonsson, PhD, Eva F. Olafsdottir, MD, Sebastian Niehus, MSc, Birte Kehr, PhD, Gardar Sveinbjörnsson, MSc, Steinunn Gudmundsdottir, MSc, Anna Helgadottir, MD, PhD, Karl Andersen, MD, PhD, Gudmar Thorleifsson, PhD, Gudmundur I. Eyjolfsson, MD, Isleifur Olafsson, MD, PhD, Olof Sigurdardottir, MD, PhD, Jona Saemundsdottir, BSc, Ingileif Jonsdottir, PhD, Olafur Th. Magnusson, PhD, Gisli Masson, PhD, Hreinn Stefansson, PhD, Daniel F. Gudbjartsson, PhD, Gudmundur Thorgeirsson, MD, PhD, Hilma Holm, MD, Bjarni V. Halldorsson, PhD, Pall Melsted, PhD, Gudmundur L. Norddahl, PhD, Patrick Sulem, MD, Unnur Thorsteinsdottir, PhD, and Kari Stefansson, MD, PhD

BACKGROUND: Loss-of-function mutations in the LDL (low-density lipoprotein) receptor gene (*LDLR*) cause elevated levels of LDL cholesterol and premature cardiovascular disease. To date, a gain-of-function mutation in *LDLR* with a large effect on LDL cholesterol levels has not been described. Here, we searched for sequence variants in *LDLR* that have a large effect on LDL cholesterol levels.

METHODS: We analyzed whole-genome sequencing data from 43 202 Icelanders. Single-nucleotide polymorphisms and structural variants including deletions, insertions, and duplications were genotyped using whole-genome sequencing-based data. LDL cholesterol associations were carried out in a sample of >100 000 Icelanders with genetic information (imputed or whole-genome sequencing). Molecular analyses were performed using RNA sequencing and protein expression assays in Epstein-Barr virus-transformed lymphocytes.

RESULTS: We discovered a 2.5-kb deletion (del2.5) overlapping the 3′ untranslated region of *LDLR* in 7 heterozygous carriers from a single family. Mean level of LDL cholesterol was 74% lower in del2.5 carriers than in 101 851 noncarriers, a difference of 2.48 mmol/L (96 mg/dL; $P=8.4\times10^{-8}$). Del2.5 results in production of an alternative mRNA isoform with a truncated 3′ untranslated region. The truncation leads to a loss of target sites for microRNAs known to repress translation of *LDLR*. In Epstein-Barr virus-transformed lymphocytes derived from del2.5 carriers, expression of alternative mRNA isoform was 1.84-fold higher than the wild-type isoform ($P=0.0013$), and there was 1.79-fold higher surface expression of the LDL receptor than in noncarriers ($P=0.0086$). We did not find a highly penetrant detrimental impact of lifelong very low levels of LDL cholesterol due to del2.5 on health of the carriers.

CONCLUSIONS: Del2.5 is the first reported gain-of-function mutation in *LDLR* causing a large reduction in LDL cholesterol. These data point to a role for alternative polyadenylation of *LDLR* mRNA as a potent regulator of LDL receptor expression in humans.

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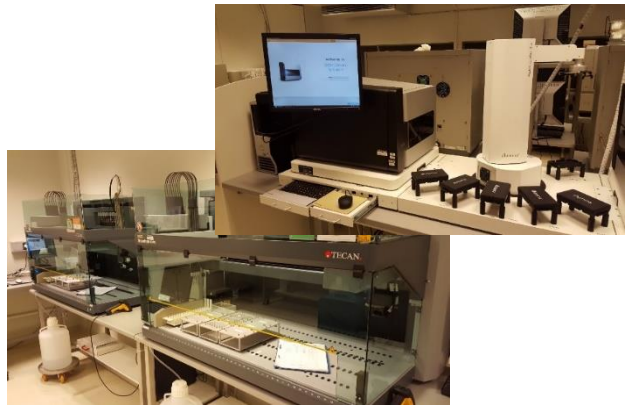
Core laboratories

Biological materials facility
- Sample registration
- DNA/RNA isolation
- Clinical chemistry
- Hematology

Sample storage – robotic freezers
- Hamilton Verso -25°C
- Hamilton BiOS -80°C



Genotyping lab
- Infinium array genotyping
- >1,3M samples genotyped
- OmniExpress24 or GSA

Genome sequencing lab

Whole genome / whole exome /RNA

Illumina
- 18 NovaSeq6000
- 6 MiSeq
- Throughput 14K WGS samples/month

Oxford Nanopore (ONT)
- 3 PromethION P48

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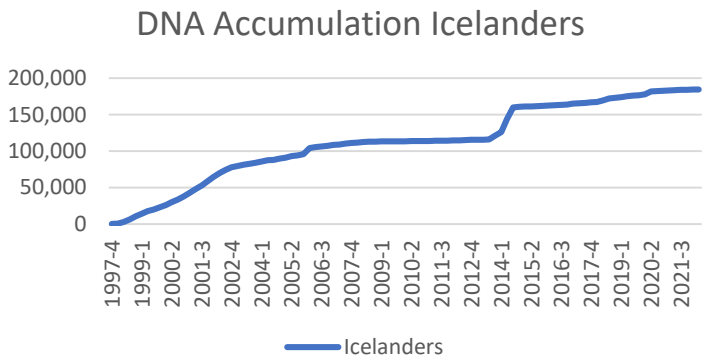
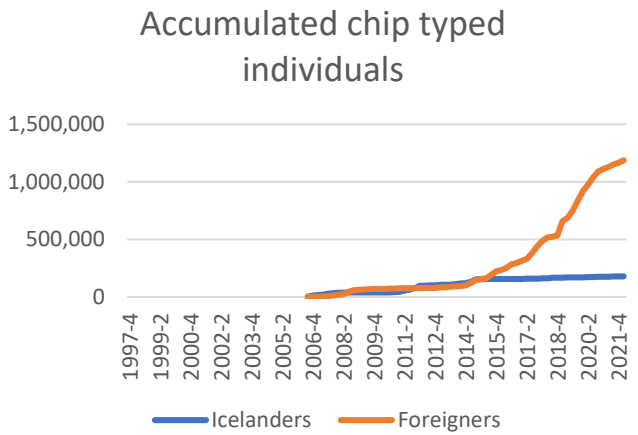
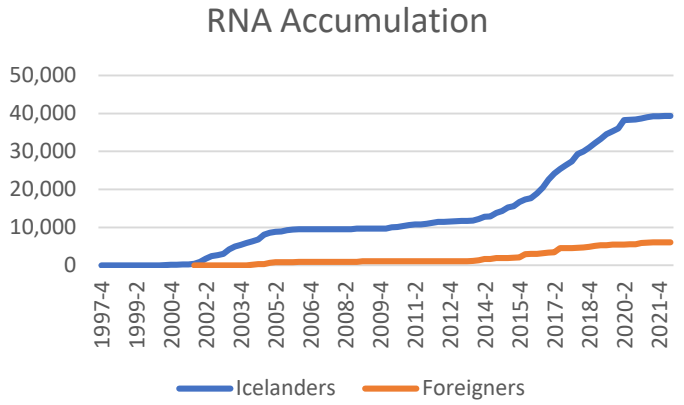
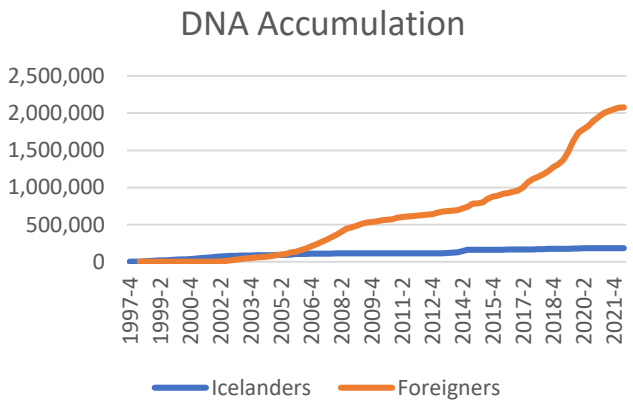
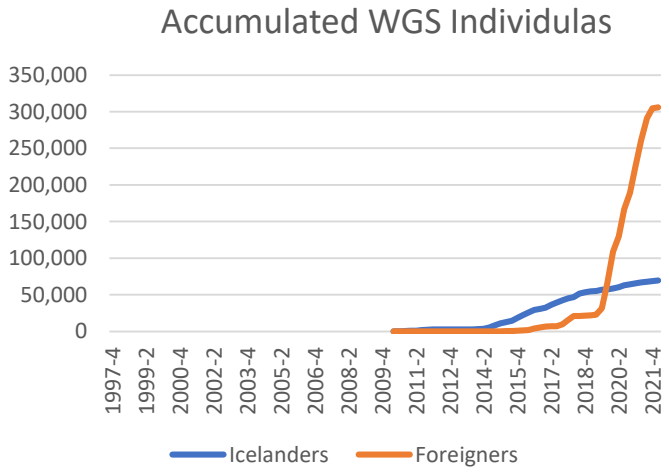
Sample accumulation at deCODE

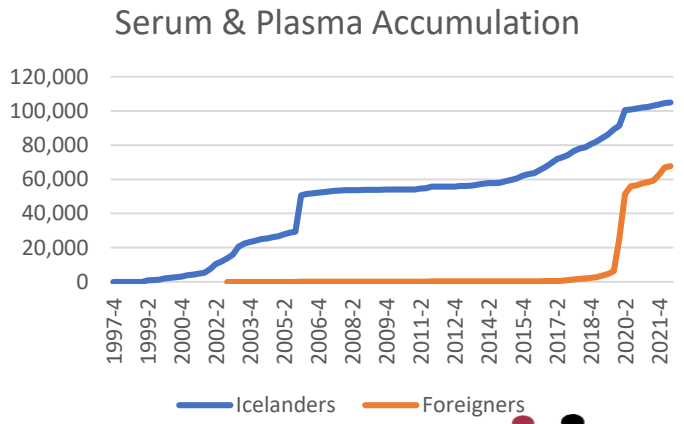












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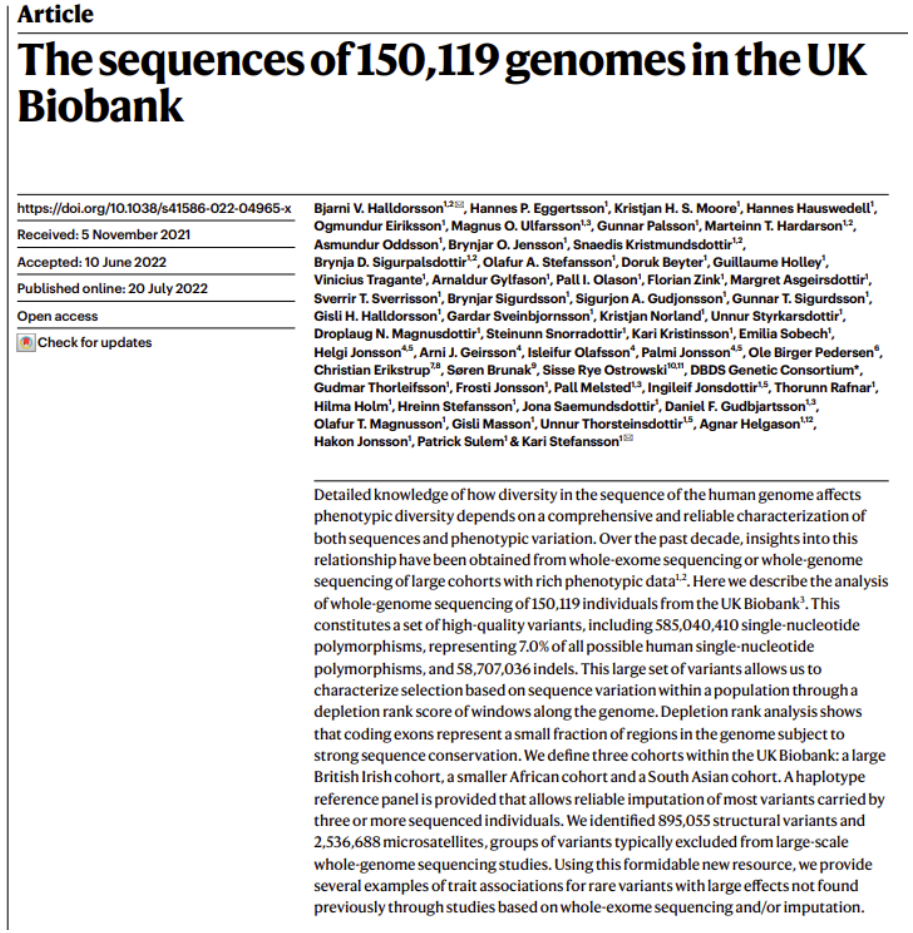
Whole genome sequencing of UK Biobank genomes



Article

The sequences of 150,119 genomes in the UK Biobank

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Open access

Check for updates

Bjarni V. Halldorsson[1,2✉], Hannes P. Eggertsson[1], Kristjan H. S. Moore[1], Hannes Hauswedell[1], Ogmundur Eiriksson[1], Magnus O. Ulfarsson[1,3], Gunnar Palsson[1], Marteinn T. Hardarson[1,2], Asmundur Oddsson[1], Brynjar O. Jensson[1], Snaedis Kristmundsdottir[1,2], Brynja D. Sigurpalsdottir[1,2], Olafur A. Stefansson[1], Doruk Beyter[1], Guillaume Holley[1], Vinicius Tragante[1], Arnaldur Gylfason[1], Pall I. Olason[1], Florian Zink[1], Margret Asgeirsdottir[1], Sverrir T. Sverrisson[1], Brynjar Sigurdsson[1], Sigurjon A. Gudjonsson[1], Gunnar T. Sigurdsson[1], Gisli H. Halldorsson[1], Gardar Sveinbjornsson[1], Kristjan Norland[1], Unnur Styrkarsdottir[1], Droplaug N. Magnusdottir[1], Steinunn Snorradottir[1], Kari Kristinsson[1], Emilia Sobech[1], Helgi Jonsson[4,5], Arni J. Geirsson[4], Isleifur Olafsson[4], Palmi Jonsson[4,5], Ole Birger Pedersen[6], Christian Erikstrup[7,8], Søren Brunak[9], Sisse Rye Ostrowski[10,11], DBDS Genetic Consortium*, Gudmar Thorleifsson[1], Frosti Jonsson[1], Pall Melsted[1,3], Ingileif Jonsdottir[1,5], Thorunn Rafnar[1], Hilma Holm[1], Hreinn Stefansson[1], Jona Saemundsdottir[1], Daniel F. Gudbjartsson[1,3], Olafur T. Magnusson[1], Gisli Masson[1], Unnur Thorsteinsdottir[1,5], Agnar Helgason[1,12], Hakon Jonsson[1], Patrick Sulem[1] & Kari Stefansson[1✉]

Detailed knowledge of how diversity in the sequence of the human genome affects phenotypic diversity depends on a comprehensive and reliable characterization of both sequences and phenotypic variation. Over the past decade, insights into this relationship have been obtained from whole-exome sequencing or whole-genome sequencing of large cohorts with rich phenotypic data[1,2]. Here we describe the analysis of whole-genome sequencing of 150,119 individuals from the UK Biobank[3]. This constitutes a set of high-quality variants, including 585,040,410 single-nucleotide polymorphisms, representing 7.0% of all possible human single-nucleotide polymorphisms, and 58,707,036 indels. This large set of variants allows us to characterize selection based on sequence variation within a population through a depletion rank score of windows along the genome. Depletion rank analysis shows that coding exons represent a small fraction of regions in the genome subject to strong sequence conservation. We define three cohorts within the UK Biobank: a large British Irish cohort, a smaller African cohort and a South Asian cohort. A haplotype reference panel is provided that allows reliable imputation of most variants carried by three or more sequenced individuals. We identified 895,055 structural variants and 2,536,688 microsatellites, groups of variants typically excluded from large-scale whole-genome sequencing studies. Using this formidable new resource, we provide several examples of trait associations for rare variants with large effects not found previously through studies based on whole-exome sequencing and/or imputation.

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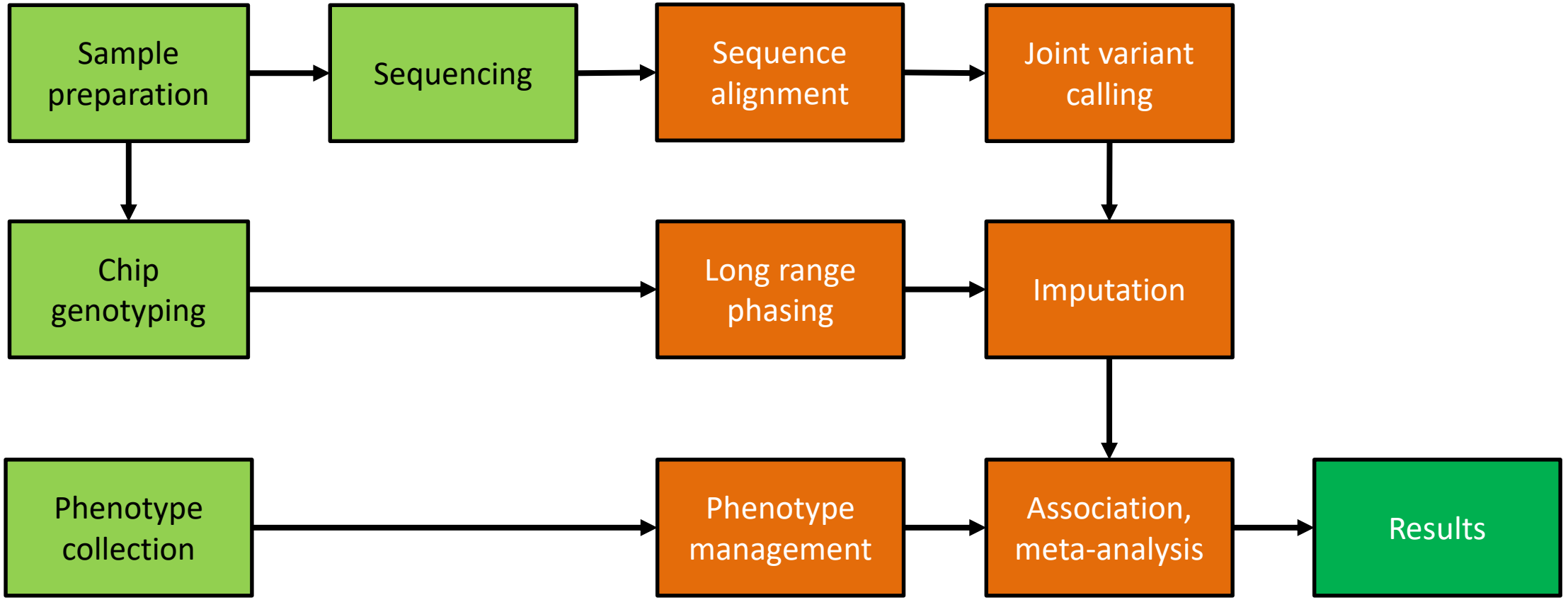
Current main data flow



Sequence diversity in Iceland

- 2015: 2,636 genomes
- The majority of sequenced variants are rare
- More pronounced for protein altering variants
- Fraction of rare increases with N sequenced individuals
- By 2022: 330K WGS including 65K Icelanders

FOCUS ON GENOMES OF ICELANDERS 2015 ARTICLES
nature genetics

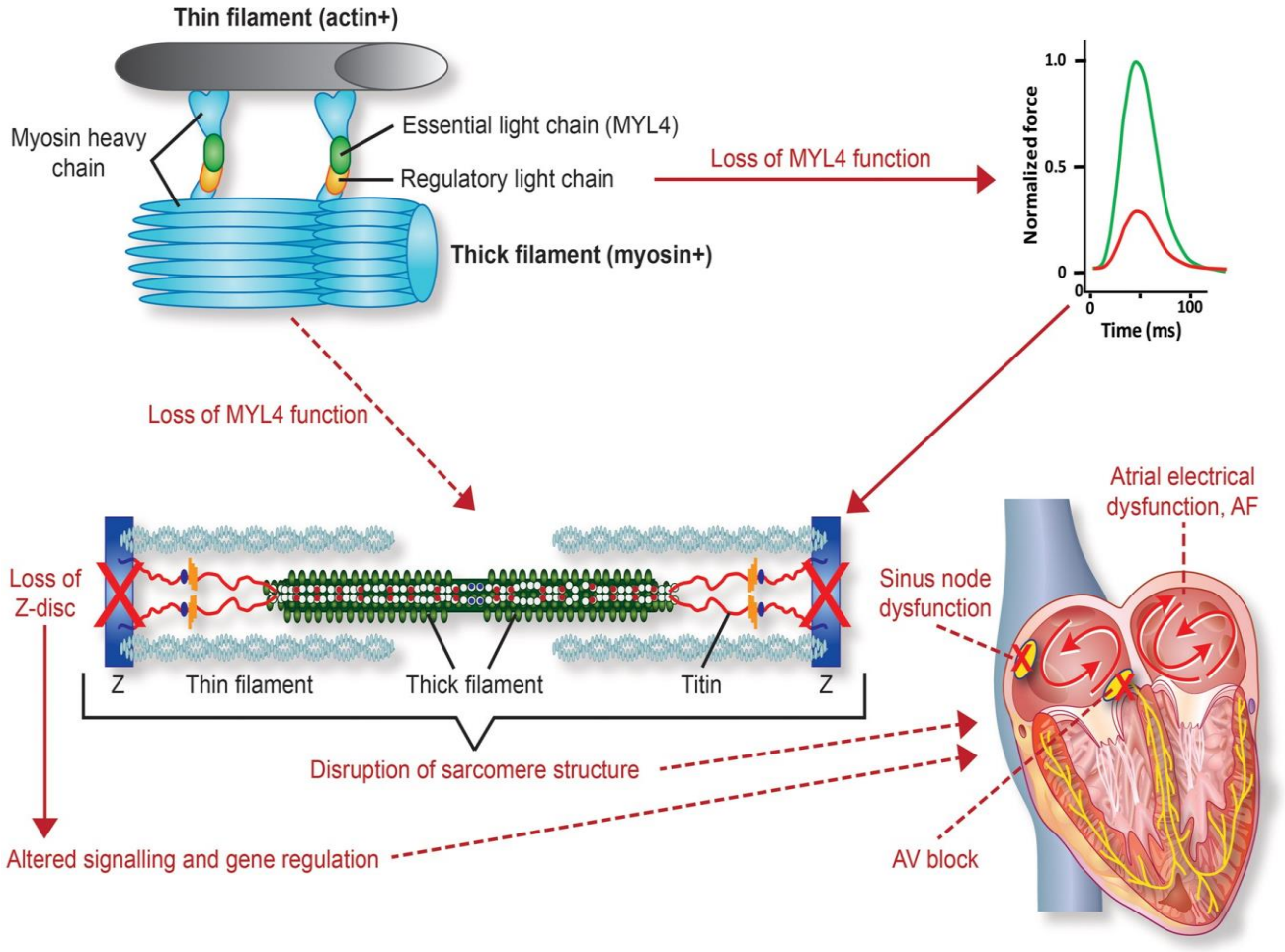
Large-scale whole-genome sequencing of the Icelandic population

Daniel F Gudbjartsson[1,2,21], Hannes Helgason[1,2,21], Sigurjon A Gudjonsson[1], Florian Zink[1], Asmundur Oddson[1], Arnaldur Gylfason[1], Soren Besenbacher[3], Gisli Magnusson[1], Bjarni V Halldorsson[1,4], Eirikur Hjartarson[1], Gunnar Th Sigurdsson[1], Simon N Stacey[1], Michael L Frigge[1], Hilma Holm[1,5], Jona Saemundsdottir[1], Hafdis Th Helgadottir[1], Hrefna Johannsdottir[1], Gunnlaugur Sigfusson[6], Gudmundur Thorgeirsson[7,8], Jon Th Sverrisson[9], Solveig Gretarsdottir[1], G Bragi Walters[1], Thorunn Rafnar[1], Bjarni Thjodleifsson[7], Einar S Bjornsson[8,10], Sigurdur Olafsson[8,10], Hildur Thorarinsdottir[10], Thora Steingrimsdottir[8,11], Thora S Gudmundsdottir[11], Asgeir Theodors[10], Jon G Jonasson[8,12,13], Asgeir Sigurdsson[1], Gyda Bjornsdottir[1], Jon J Jonsson[14,15], Olafur Thorarensen[16], Petur Ludvigsson[16], Hakon Gudbjartsson[1,2], Gudmundur I Eyjolfsson[17], Olof Sigurdardottir[18], Isleifur Olafsson[19], David O Arnar[7,8], Olafur Th Magnusson[1], Augustine Kong[1,2], Gisli Masson[1], Unnur Thorsteinsdottir[1,8], Agnar Helgason[1,20], Patrick Sulem[1] & Kari Stefansson[1,8]

Type	MAF	Loss of function: Frameshift indel, splice acceptor or donor, stop gain or loss, initiator codon	Moderate impact: In-frame indel, missense, splice region	Low impact: Synonymous, stop retained, 3′ or 5′ UTR	Other: Intronic, intergenic	Total
SNP	≥0.5%	602 (0.0070%)	36,282 (0.42%)	108,850 (1.3%)	8,445,855 (98.3%)	8,591,589
	0.1–0.5%	915 (0.023%)	29,659 (0.76%)	59,076 (1.5%)	3,836,528 (97.7%)	3,926,178
	<0.1%	2,462 (0.034%)	57,209 (0.80%)	101,751 (1.4%)	7,010,453 (97.7%)	7,171,875
	All	3,979 (0.020%)	123,150 (0.63%)	269,677 (1.4%)	19,292,836 (98.0%)	19,689,642

deCODE genetics

Disruption of sarcomere integrity in atrial fibrillation



- Rare frameshift deletion (c.234delC) in *MYL4* causes early-onset atrial fibrillation (P=1.7×10^{-14})
- Fully penetrant in the homozygous state
- *MYL4* dysfunction might lead to electrical dysfunction and arrhythmias via impaired contractility and disruption of sarcomere integrity, with loss of co-ordination of contractile, structural, and signaling proteins leading to dramatic electrical consequences

- Causal variants / genes
- Syndromes within common diseases

Eur Heart J, Volume 38, Issue 1, 1 January 2017, Pages 35–37, https://doi.org/10.1093/eurheartj/ehw457

deCODE genetics

Many associations between atrial fibrillation and coding variants in structural genes

Encodes plectin, a cytoskeletal linking protein with a role in maintaining tissue integrity in the heart

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PUBLISHED BY ELSEVIER

A Missense Variant in *PLEC* Increases Risk of Atrial Fibrillation

Rosa B. Thorolfsdottir, MD,[a] Gardar Sveinbjornsson, MSc,[a] Patrick Sulem, MD, PhD,[a] Anna Helgadottir, MD, PhD,[a] Solveig Gretarsdottir, PhD,[a] Stefania Benonisdottir, MSc,[a] Audur Magnusdottir, PhD,[a] Olafur B. Davidsson, MSc,[a] Sridharan Rajamani, PhD,[a] Dan M. Roden, MD,[b] Dawood Darbar, MD,[c] Terje R. Pedersen, MD, PhD,[d] Marc S. Sabatine, MD, MPH,[e] Ingileif Jonsdottir, PhD,[a,f,g] David O. Arnar, MD, PhD, MPH,[a,f,h] Unnur Thorsteinsdottir, PhD,[a,f] Daniel F. Gudbjartsson, PhD,[a,i] Hilma Holm, MD,[a] Kari Stefansson, MD, PhD[a,f]

Encodes a component of the intercalated discs, a highly specialized cell–cell contact structure that enables communication between cardiomyocytes

COMMUNICATIONS BIOLOGY

ARTICLE

DOI: 10.1038/s42003-018-0068-9 OPEN

Coding variants in *RPL3L* and *MYZAP* increase risk of atrial fibrillation

Rosa B. Thorolfsdottir et al.#

Ribosomal protein, expressed exclusively in skeletal muscle and heart; may be a negative regulator of muscle growth

Myosin heavy chain-α, major contractile protein, predominantly expressed in the atria

nature genetics

A rare variant in *MYH6* is associated with high risk of sick sinus syndrome

- also the most significant atrial fibrillation variant in the Icelandic data

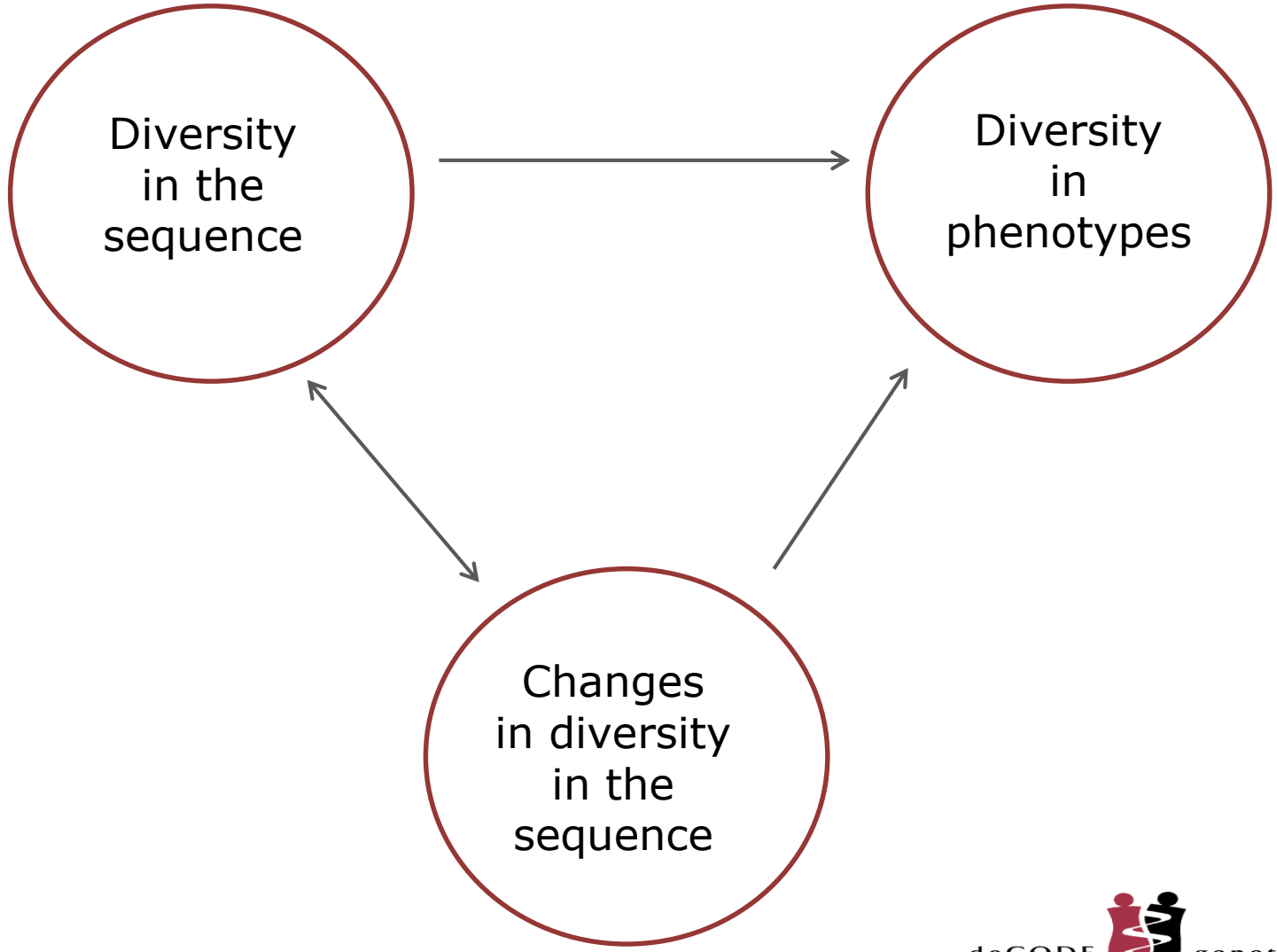
Hilma Holm[1,9], Daniel F Gudbjartsson[1,9], Patrick Sulem[1], Gisli Masson[1], Hafdis Th Helgadottir[1], Carlo Zanon[1], Olafur Th Magnusson[1], Agnar Helgason[1], Jona Saemundsdottir[1], Arnaldur Gylfason[1], Hrafnhildur Stefansdottir[2], Solveig Gretarsdottir[1], Stefan E Matthiasson[3], Guðmundur Thorgeirsson[2,4], Aslaug Jonasdottir[1], Asgeir Sigurdsson[1], Hreinn Stefansson[1], Thomas Werge[5], Thorunn Rafnar[1], Lambertus A Kiemeney[6,7], Babar Parvez[8], Raafia Muhammad[8], Dan M Roden[8], Dawood Darbar[8], Gudmar Thorleifsson[1], G Bragi Walters[1], Augustine Kong[1], Unnur Thorsteinsdottir[1,4], David O Arnar[2,4] & Kari Stefansson[1,4]

Causal variants / genes

deCODE genetics

Understanding the processes that generate sequence diversity in the human genome

- Recombinations
- Gene conversions
- De novo mutations



deCODE genetics

deCODE genetic map: 2002

article

A high-resolution recombination map of the human genome

Augustine Kong, Daniel F. Gudbjartsson, Jesus Sainz, Gudrun M. Jonsdottir, Sigurjon A. Gudjonsson, Bjorgvin Richardsson, Sigrun Sigurdardottir, John Barnard, Bjorn Hallbeck, Gisli Masson, Adam Shlien, Stefan T. Palsson, Michael L. Frigge, Thorgeir E. Thorgeirsson, Jeffrey R. Gulcher & Kari Stefansson

Published online: 10 June 2002, doi:10.1038/ng917

Determination of recombination rates across the human genome has been constrained by the limited resolution and accuracy of existing genetic maps and the draft genome sequence. We have genotyped 5,136 microsatellite markers for 146 families, with a total of 1,257 meiotic events, to build a high-resolution genetic map meant to: (i) improve the genetic order of polymorphic markers; (ii) improve the precision of estimates of genetic distances; (iii) correct portions of the sequence assembly and SNP map of the human genome; and (iv) build a map of recombination rates. Recombination rates are significantly correlated with both cytogenetic structures (staining intensity of G bands) and sequence (GC content, CpG motifs and poly(A)/poly(T) stretches). Maternal and paternal chromosomes show many differences in locations of recombination maxima. We detected systematic differences in recombination rates between mothers and between gametes from the same mother, suggesting that there is some underlying component determined by both genetic and environmental factors that affects maternal recombination rates.

Introduction

The draft sequence of the human genome[1] has markedly advanced the understanding of human genetics. Because the available sequence is that of a reference genome, however, it does not provide insight into the genomic variability that is responsible for much of human diversity. Along with mutation, a major mechanism generating variability in the eukaryotic genome is intergenerational mixing of DNA through meiotic recombination of homologous chromosomes. The standard approach to studying rates of recombination across the genome is to build a genetic map by genotyping, with a high density of markers, a large number of individuals in families and then match this to physical map together provide better estimates of recombination rates with respect to physical distances, which are essential to understanding the intergenerational variability of the genome. Thus, our results should facilitate the formulation and testing of hypotheses about the relationships between sequence content and recombination rate and between recombination rate and the degree of linkage disequilibrium.

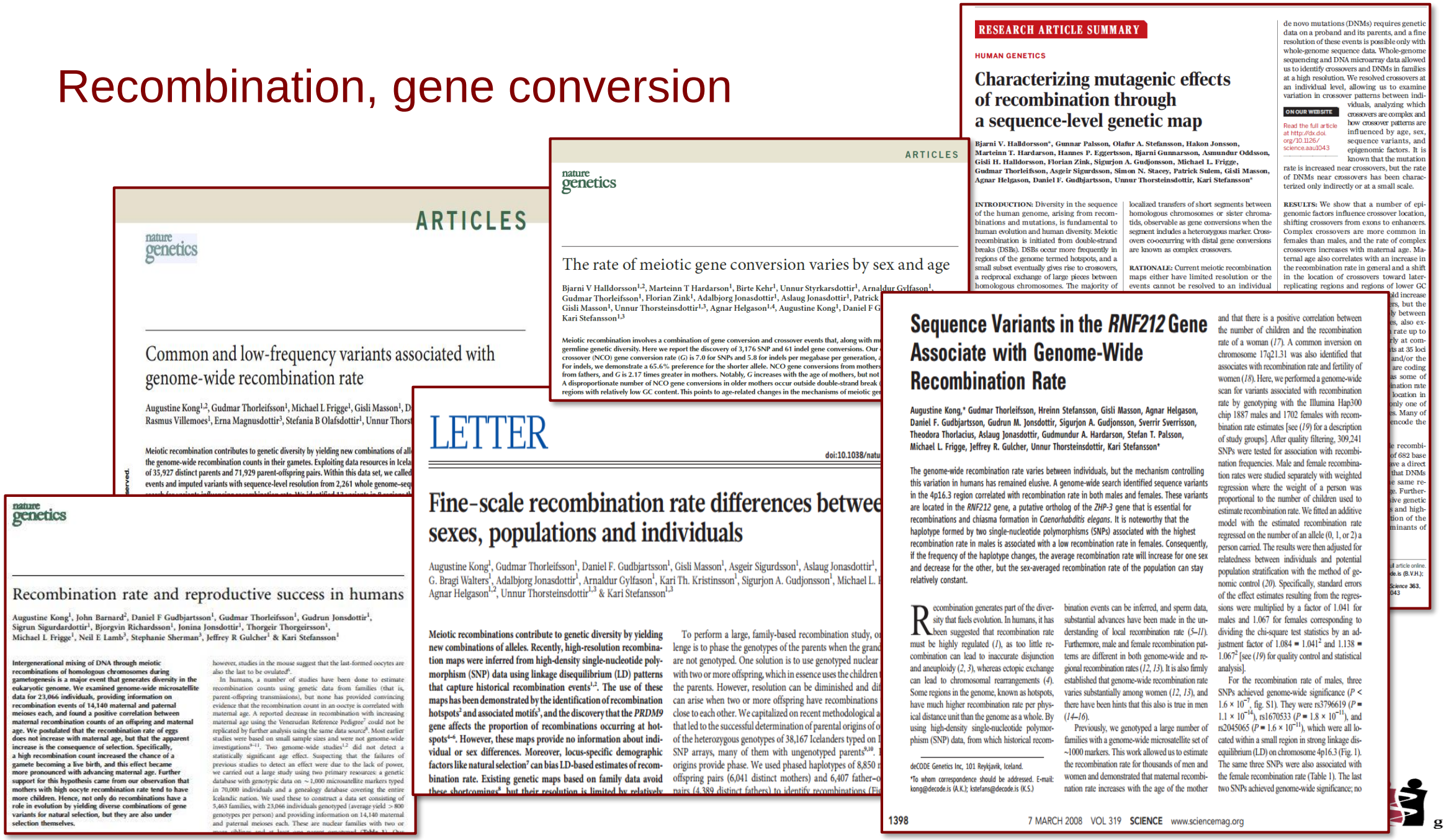
Results

Data collection

We genotyped 869 individuals in 146 Icelandic families, consisting of 149 sibships and providing information on 628 male/paternal and 629 female/maternal meioses, with 5,136

deCODE genetics

Recombination, gene conversion



RESEARCH ARTICLE SUMMARY

HUMAN GENETICS

Characterizing mutagenic effects of recombination through a sequence-level genetic map

Bjarni V. Halldorsson*, Gunnar Palsson, Olafur A. Stefansson, Hakon Jonsson, Marteinn T. Hardarson, Hannes P. Eggertsson, Bjarni Gunnarsson, Asmundur Oddsson, Gisli H. Halldorsson, Florian Zink, Sigurjon A. Gudjonsson, Michael L. Frigge, Gudmar Thorleifsson, Asgeir Sigurdsson, Simon N. Stacey, Patrick Sulem, Gisli Masson, Agnar Helgason, Daniel F. Gudbjartsson, Unnur Thorsteinsdottir, Kari Stefansson*

ON OUR WEBSITE

Read the full article at http://dx.doi.org/10.1126/science.aau1043

ARTICLES

nature genetics

The rate of meiotic gene conversion varies by sex and age

ARTICLES

nature genetics

Common and low-frequency variants associated with genome-wide recombination rate

LETTER

Fine-scale recombination rate differences between sexes, populations and individuals

nature genetics

Recombination rate and reproductive success in humans

Sequence Variants in the *RNF212* Gene Associate with Genome-Wide Recombination Rate

Augustine Kong,* Gudmar Thorleifsson, Hreinn Stefansson, Gisli Masson, Agnar Helgason, Daniel F. Gudbjartsson, Gudrun M. Jonsdottir, Sigurjon A. Gudjonsson, Sverrir Sverrisson, Theodora Thorlacius, Aslaug Jonasdottir, Gudmundur A. Hardarson, Stefan T. Palsson, Michael L. Frigge, Jeffrey R. Gulcher, Unnur Thorsteinsdottir, Kari Stefansson*

1398 7 MARCH 2008 VOL 319 SCIENCE www.sciencemag.org

genetics

De novo mutations

ARTICLE

doi:10.1038/nature11396

Rate of *de novo* mutations and the importance of father's age to disease risk

Augustine Kong[1], Michael L. Frigge[1], Gisli Masson[1], Soren Besenbacher[1,2], Patrick Sulem[1], Gisli Magnusson[1], Sigurjon A. Gudjonsson[1], Asgeir Sigurdsson[1], Aslaug Jonasdottir[1], Adalbjorg Jonasdottir[1], Wendy S. W. Wong[3], Gunnar Sigurdsson[1], G. Bragi Walters[1], Stacy Steinberg[1], Hannes Helgason[1], Gudmar Thorleifsson[1], Daniel F. Gudbjartsson[1], Agnar Helgason[1,4], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,5] & Kari Stefansson[1,5]

Mutations gen
major import
genomes of 7
father's age o
diversity in m
child. The eff
doubling ever
the remaining
age on the ris

LETTERS

https://doi.org/10.1038/s41588-018-0259-9

nature genetics

Multiple transmissions of de novo mutations in families

Hákon Jónsson[1], Patrick Sulem[1], Gudny A. Arnadottir[1], Gunnar Pálsson[1], Hannes P. Eggertsson[1], Snaedis Kristmundsdottir[1], Florian Zink[1], Birte Kehr[1], Kristjan E. Hjorleifsson[1], Brynjar Ö. Jensson[1], Ingileif Jonsdottir[1], Sigurdur Einar Marelsson[2], Sigurjon Axel Gudjonsson[1], Arnaldur Gylfason[1], Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Simon N. Stacey[1], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,3], Gisli Masson[1], Augustine Kong[1,4], Bjarni V. Halldorsson[1,5], Agnar Helg

De novo muta
rare diseases
in mosaicism
tions can caus
ling pairs fro
by siblings (s
DNM recurre

LETTER

doi:10.10

Parental influence on human germline *de novo* mutations in 1,548 trios from Iceland

Hákon Jónsson[1], Patrick Sulem[1], Birte Kehr[1], Snaedis Kristmundsdottir[1], Florian Zink[1], Eirikur Hjartarson[1], Marteinn T. Hardarson[1], Kristjan E. Hjorleifsson[1], Hannes P. Eggertsson[1], Sigurjon Axel Gudjonsson[1], Lucas D. Ward, Gudny A. Arnadottir[1], Einar A. Helgason[1], Hannes Helgason[1], Arnaldur Gylfason[1], Adalbjorg Jonasdottir[1], Aslaug Jo, Thorunn Rafnar[1], Mike Frigge[1], Simon N. Stacey[1], Olafur Th. Magnusson[1], Unnur Thorsteinsdottir[1,2], Gisli Masson[1], Augustine Kong[1,3], Bjarni V. Halldorsson[1,4], Agnar Helgason[1,5], Daniel F. Gudbjartsson[1,3] & Kari Stefansson[1,2]

The characterization of mutational processes that generate sequence diversity in the human genome is of paramount importance both to medical genetics[1,2] and to evolutionary studies[3]. To understand how the age and sex of transmitting parents affect *de novo* mutations, here we sequence 1,548 Icelanders, their parents, and, for a subset of 225, at least one child, to 35× genome-wide coverage. We find 108,778 *de novo* mutations, both single nucleotide polymorphisms and indels, and determine the parent of origin of 42,961. The number of *de novo* mutations from mothers increases by 0.37 per year of age (95% CI 0.32–0.43), a quarter of the 1.51 per year from maternal origin[17], and show strand concordance[18]. advances, our knowledge on how sex differences in g opment and maintenance affect their mutability is lir differences in the rate and class of DNMs transmitted fathers, we analysed whole-genome sequencing (W 14,688 Icelanders with an average of 35× coverage (Dat This set contained 1,548 trios, used to identify 108,778 high-quality DNMs (101,377 single nucleotide polymorphisms (SNPs); Methods and Fig. 1), resulting in an average of 70.3 DNMs per proband.

nature genetics

ARTICLES

https://doi.org/10.1038/s41588-020-00755-1

Check for updates

Differences between germline genomes of monozygotic twins

Hakon Jonsson[1]✉, Erna Magnusdottir[2], Hannes P. Eggertsson[1], Olafur A. Stefansson[1], Gudny A. Arnadottir[1], Ogmundur Eiriksson[1], Florian Zink[1], Einar A. Helgason[1], Ingileif Jonsdottir[1], Arnaldur Gylfason[1], Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Doruk Beyter[1], Thora Steingrimsdottir[2], Gudmundur L. Norddahl[1], Olafur Th. Magnusson[1], Gisli Masson[1], Bjarni V. Halldorsson[1,3], Unnur Thorsteinsdottir[1,2], Agnar Helgason[1,4], Patrick Sulem[1], Daniel F. Gudbjartsson[1,5]✉ and Kari Stefansson[1,2]✉

Despite the important role that monozygotic twins have played in genetics research, little is known about their genomic differences. Here we show that monozygotic twins differ on average by 5.2 early developmental mutations and that approximately 15% of monozygotic twins have a substantial number of these early developmental mutations specific to one of them. Using the parents and offspring of twins, we identified pre-twinning mutations. We observed instances where a twin was formed from a single cell lineage in the pre-twinning cell mass and instances where a twin was formed from several cell lineages. CpG>TpG mutations increased in frequency with embryonic development, coinciding with an increase in DNA methylation. Our results indicate that allocations of cells during development shapes genomic differences between monozygotic twins.

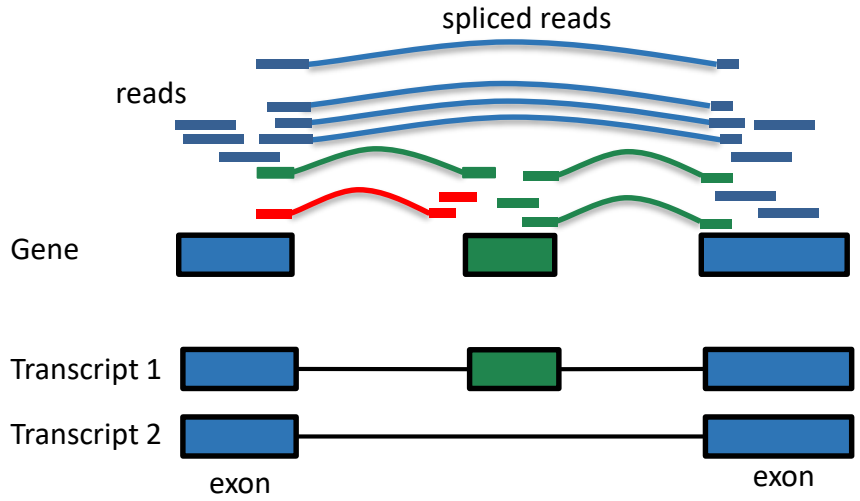
deCODE genetics

RNA sequencing at deCODE (transcriptomics)

- Whole blood (n=17,848) – 88% of individuals have WGS data
- Adipose (n=770)
- Lymphoblast (n=235)
- Heart (n=182)
- Cell sorted whole blood (n=935 individuals, n=557 with all subtypes)
  - CD4+ T-cells (n=837)
  - CD8+ T-cells (n=807)
  - B cells (n=758)
  - Neutrophils (n=730)
  - Monocytes (n=884)

Molecular phenotypes from RNA-sequencing

- Phenotypes from RNA-seq reads
- Expression (eQTLs): How much RNA is observed for each gene
- Splicing (sQTLs): What is the fraction of reads that use a specific junction



Total expression = 15 reads

Red junction = 1/8
Green junction 3/8
Blue junction = 4/8

Proteomics

ARTICLES
https://doi.org/10.1038/s41588-021-00978-w
nature genetics

Large-scale integration of the plasma proteome with genetics and disease

Egil Ferkingstad[1], Patrick Sulem[1]✉, Bjarni A. Atlason[1], Gardar Sveinbjornsson[1], Magnus I. Magnusson[1], Edda L. Styrmisdottir[1], Kristbjorg Gunnarsdottir[1], Agnar Helgason[1,2], V. Halldorsson[1,3], Brynjar O. Jensson[1], Florian Zink[1], lasson[1], Gudny A. Arnadottir[1], Hildigunnur Katrinardottir[1], Magnusson[1,4], Olafur Th. Magnusson[1], Run Fridriksdottir[1], rjon A. Gudjonsson[1], Simon N. Stacey[1], Solvi Rognvaldsson[1], runn A. Olafsdottir[1,4], Valgerdur Steinthorsdottir[1], Vinicius Tragante[1], nn Stefansson[1], Ingileif Jonsdottir[1,4], Hilma Holm[1], d[1,6], Jona Saemundsdottir[1], Gudmundur L. Norddahl[1], Sigrun H. Lund[1], nur Thorsteinsdottir[1,4] and Kari Stefansson[1,4]✉

the gap between the genome and diseases. Here we describe genome-wide association vels measured with 4,907 aptamers in 35,559 Icelanders. We found 18,084 associations of proteins in plasma (protein quantitative trait loci; pQTL), of which 19% were with rare AF) < 1%). We tested plasma protein levels for association with 373 diseases and other tions. We integrated pQTL and genetic associations with diseases and other traits and iations in the GWAS Catalog are with variants in high linkage disequilibrium with pQTL. ential drug targets with variants that influence levels of possible biomarkers. Combining omics, we provide a valuable resource that can be used to improve understanding of dis- drug discovery and development.

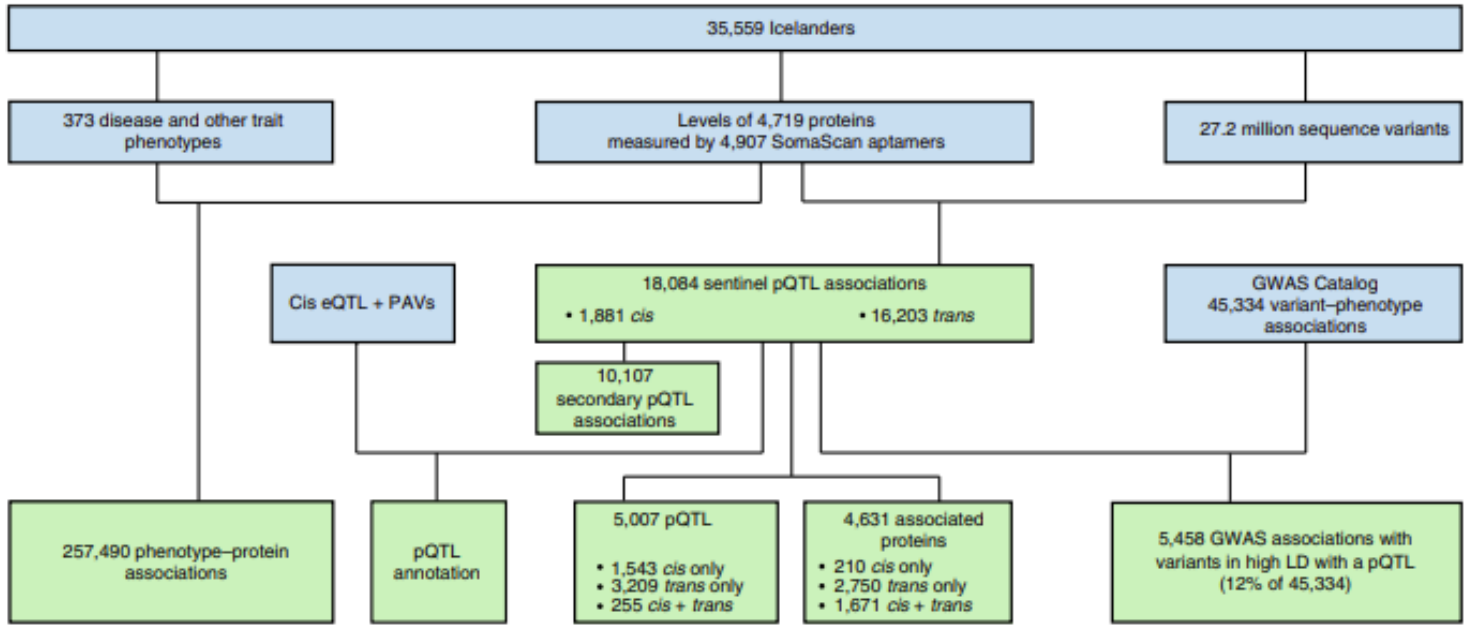


Fig. 1 | Study design and main results. Sentinel variant, most significant variant for a given protein in the region; pQTL, set of variants in high LD ($r^2 > 0.80$) with associations with levels of one or more proteins; eQTL, variants associated with gene expression. Blue boxes show input data, while green boxes show results.

deCODE genetics

Integration of genomic, transcriptomic, and proteomic data

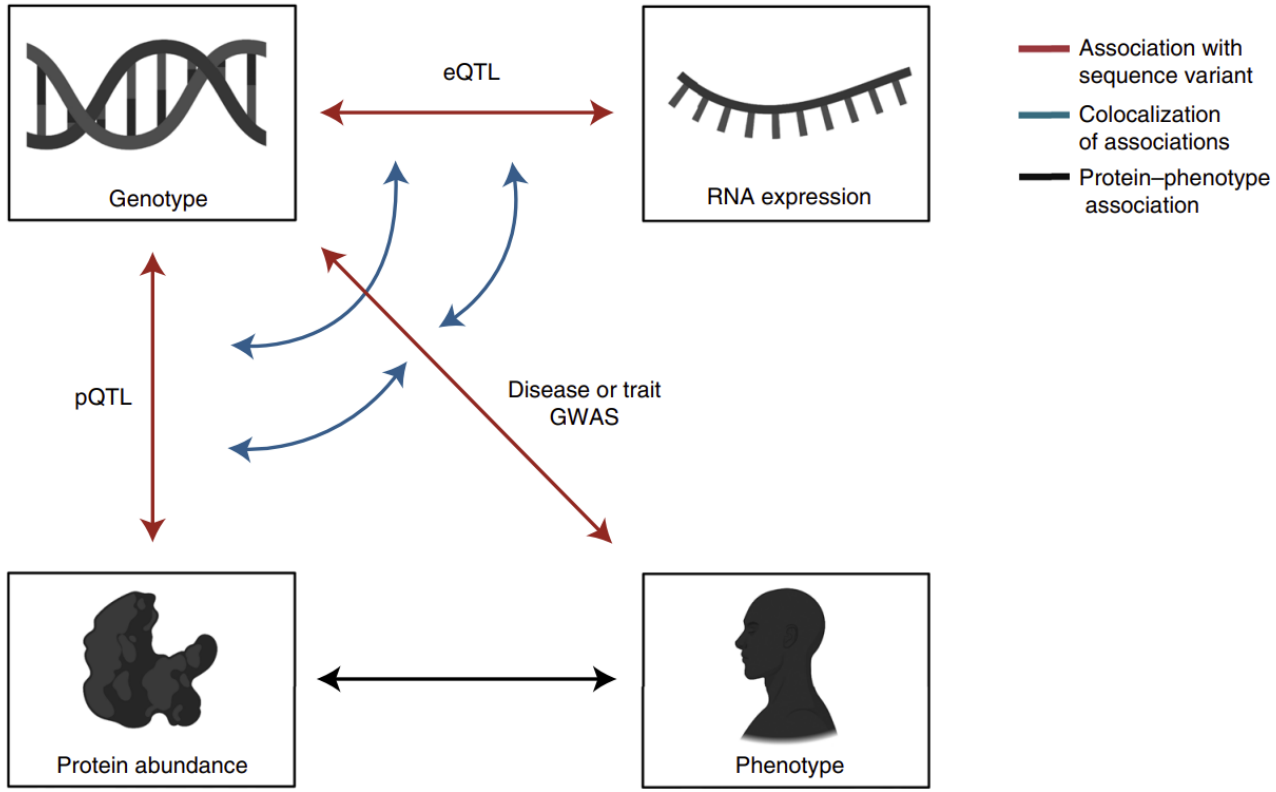
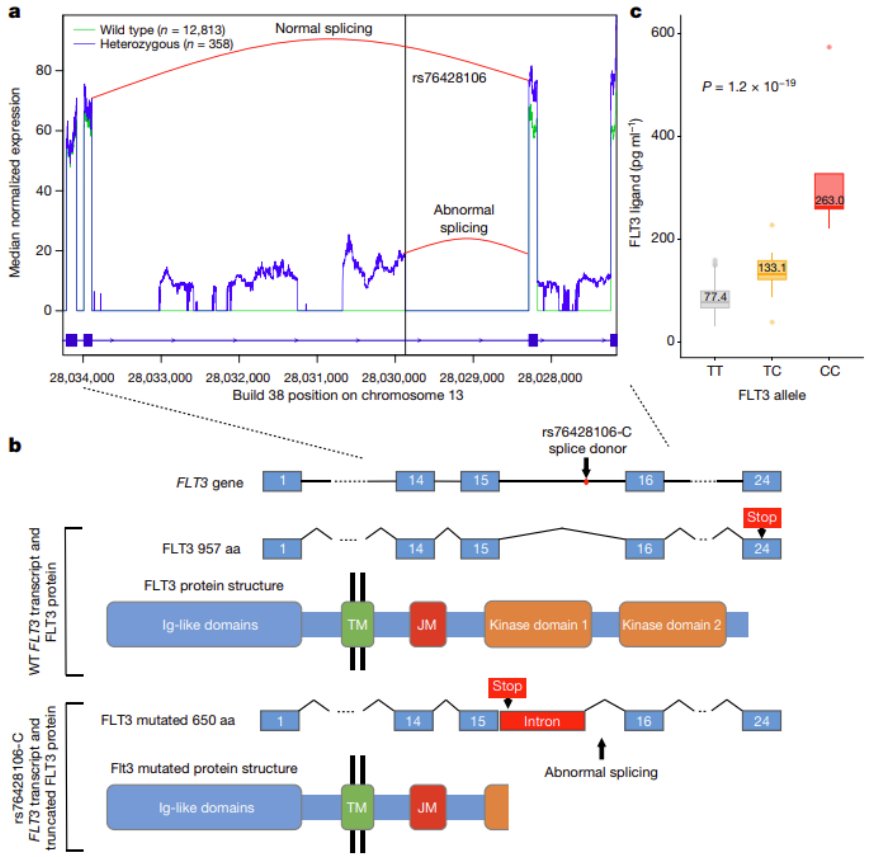


Fig. 2 | The concepts of pQTL, eQTL and colocalization with disease-associated variants. Schematic in which associations between sequence variants and protein level, RNA expression and phenotypes are shown as red arrows. Colocalization of associations are shown as blue arrows. Protein–phenotype associations are shown as black arrows.

deCODE genetics

FLT3 stop mutation increases FLT3 ligand level and risk of autoimmune thyroid disease



- *FLT3* intron variant rs76428106-C (AF 1.4%) associates with AITD
- The variant also associates with other autoimmune diseases (SLE, RF/anti-CCP+, celiac disease)
- RNA sequencing data demonstrated that the variant creates a novel splice site that generates a truncated protein (loss of function effect)
- The variant is is associated with higher plasma levels of the FLT3 ligand (effect=0.49 SD, P=3.8×10^{-47}), seen in Somascan data and replicated with ELISA

Nature 2020, Saedis Saevarsdottir

deCODE genetics

Proteins for prediction

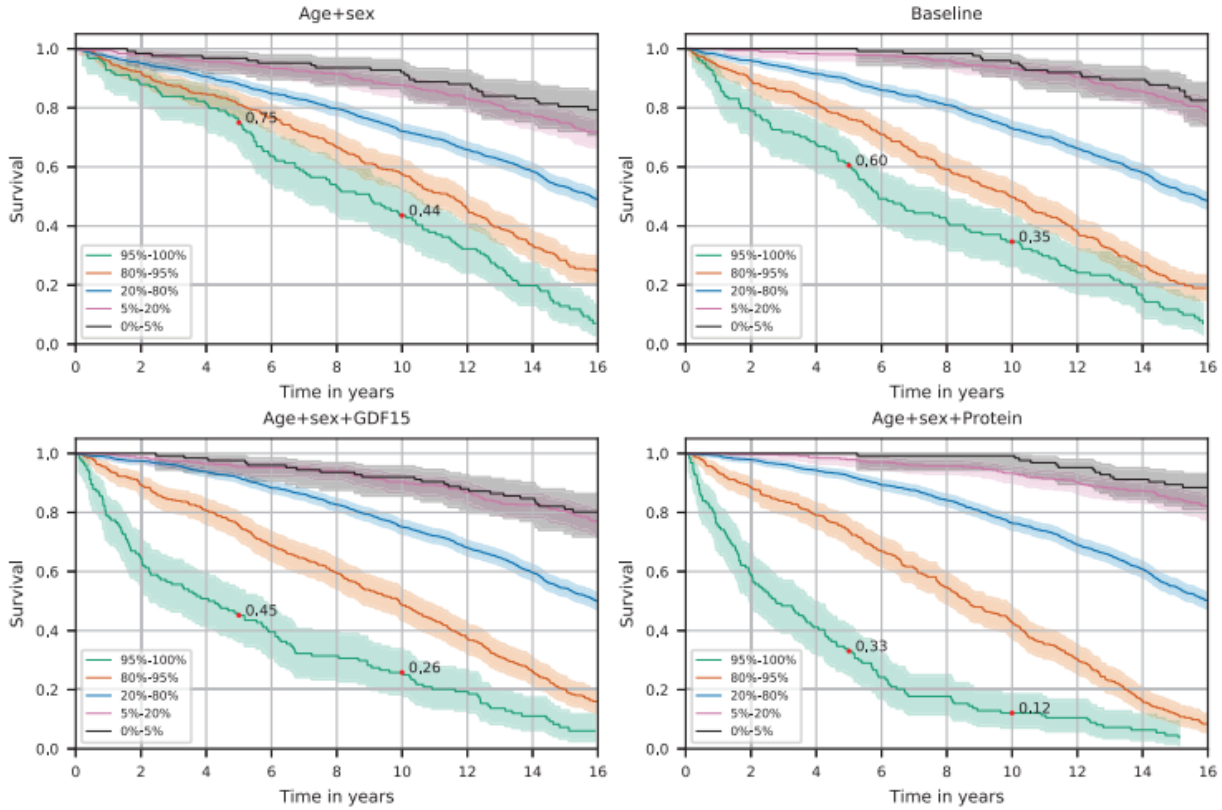


Fig. 2 Survival of 60–80 years old participants. The Kaplan–Meier curves for 2488 participants are split by quantiles of predicted 10-year risk by each model, demonstrating the different survival rates in the different risk groups. The colored areas represent 95% confidence intervals. The red dots show survival after 5 and 10 years.

communications biology

ARTICLE

https://doi.org/10.1038/s42003-021-02289-6 OPEN

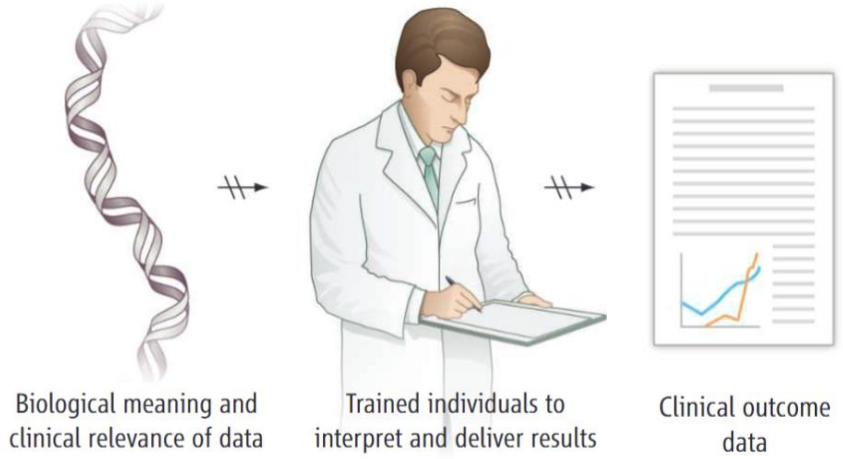
Predicting the probability of death using proteomics

Thjodbjorg Eiriksdottir[1], Steinthor Ardal[1], Benedikt A. Jonsson[1], Sigrun H. Lund[1], Erna V. Ivarsdottir[1], Kristjan Norland[1], Egil Ferkingstad[1], Hreinn Stefansson[1], Ingileif Jonsdottir[1,2,3], Hilma Holm[1], Thorunn Rafnar[1], Jona Saemundsdottir[1], Gudmundur L. Norddahl[1], Gudmundur Thorgeirsson[1,2,3], Daniel F. Gudbjartsson[1,2], Patrick Sulem[1], Unnur Thorsteinsdottir[1,2], Kari Stefansson[1,2✉] & Magnus O. Ulfarsson[1,2✉]

deCODE genetics

Clinical sequencing at deCODE

- Benefits from ongoing research at deCODE
  - Large normative set
- 1200 families of rare disease cases referrals received
  - Clinical whole genome sequencing (30x)
  - WGS of trios (affected offspring + both parents)
- Solved 1/3 of cases: Half *de novo*, half recessive
- Clinical sequencing report
  - Detailed interpretation (extensive report)
  - Detection of pathogenic/likely pathogenic variants for the relevant condition

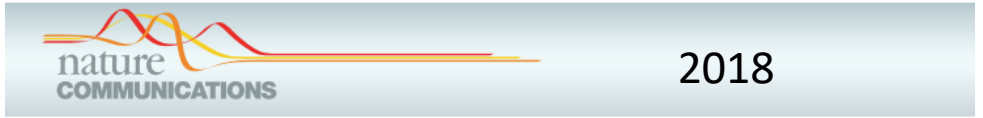


Adapted from Science, 2012

deCODE genetics

Homozygous for LOF in *CYBC1*

- Stop-gained Tyr2Ter in *CYBC1*
  - Associates with risk of inflammatory bowel disease (IBD) under recessive model in Iceland
  - Novel cause of chronic granulomatous disease (colitis + infections)
- *CYBC1*
  - An uncharacterized gene in humans at the time
  - Homozygous knockout mice die from infections



ARTICLE
DOI: 10.1038/s41467-018-06964-x OPEN

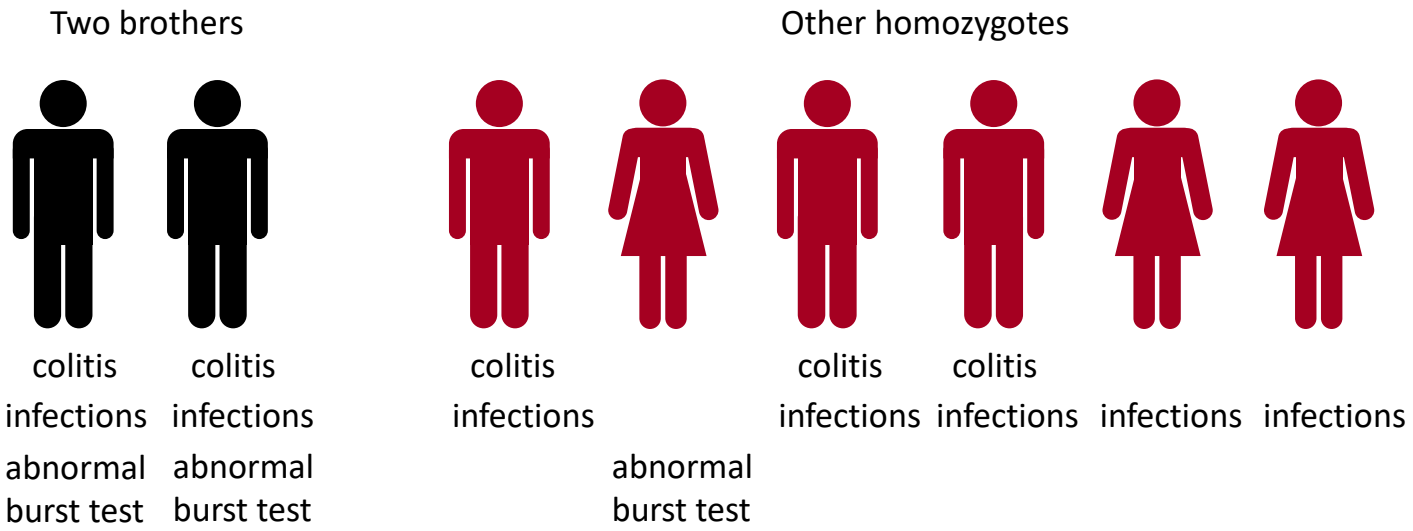
A homozygous loss-of-function mutation leading to CYBC1 deficiency causes chronic granulomatous disease

Gudny A. Arnadottir[1], Gudmundur L. Norddahl[1], Steinunn Gudmundsdottir[1], Arna B. Agustsdottir[1], Snaevar Sigurdsson[1], Brynjar O. Jensson[1], Kristbjorg Bjarnadottir[1], Fannar Theodors[1], Stefania Benonisdottir[1], Erna V. Ivarsdottir[1,2], Asmundur Oddsson[1], Ragnar P. Kristjansson[1], Gerald Sulem[1], Kristjan F. Alexandersson[1], Thorhildur Juliusdottir[1], Kjartan R. Gudmundsson[1], Jona Saemundsdottir[1], Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Asgeir Sigurdsson[1], Paolo Manzanillo[1], Sigurjon A. Gudjonsson[1], Gudmundur A. Thorisson[1], Olafur Th. Magnusson[1], Gisli Masson[1], Kjartan B. Orvar[3,4], Hilma Holm[1], Sigurdur Bjornsson[3,4], Reynir Arngrimsson[5,6], Daniel F. Gudbjartsson[1,2], Unnur Thorsteinsdottir[1,6], Ingileif Jonsdottir[1,6], Asgeir Haraldsson[6,7], Patrick Sulem[1] & Kari Stefansson[1,6]

Gene	Position (hg38)	Mutation	AF Iceland	Phenotype	P-value (recessive)	OR/effect (recessive)
CYBC1	Chr17:82449249	P.Tyr2Ter	0.76%	IBD	8.3×10^{-8}	67.6

Eight homozygous Icelanders

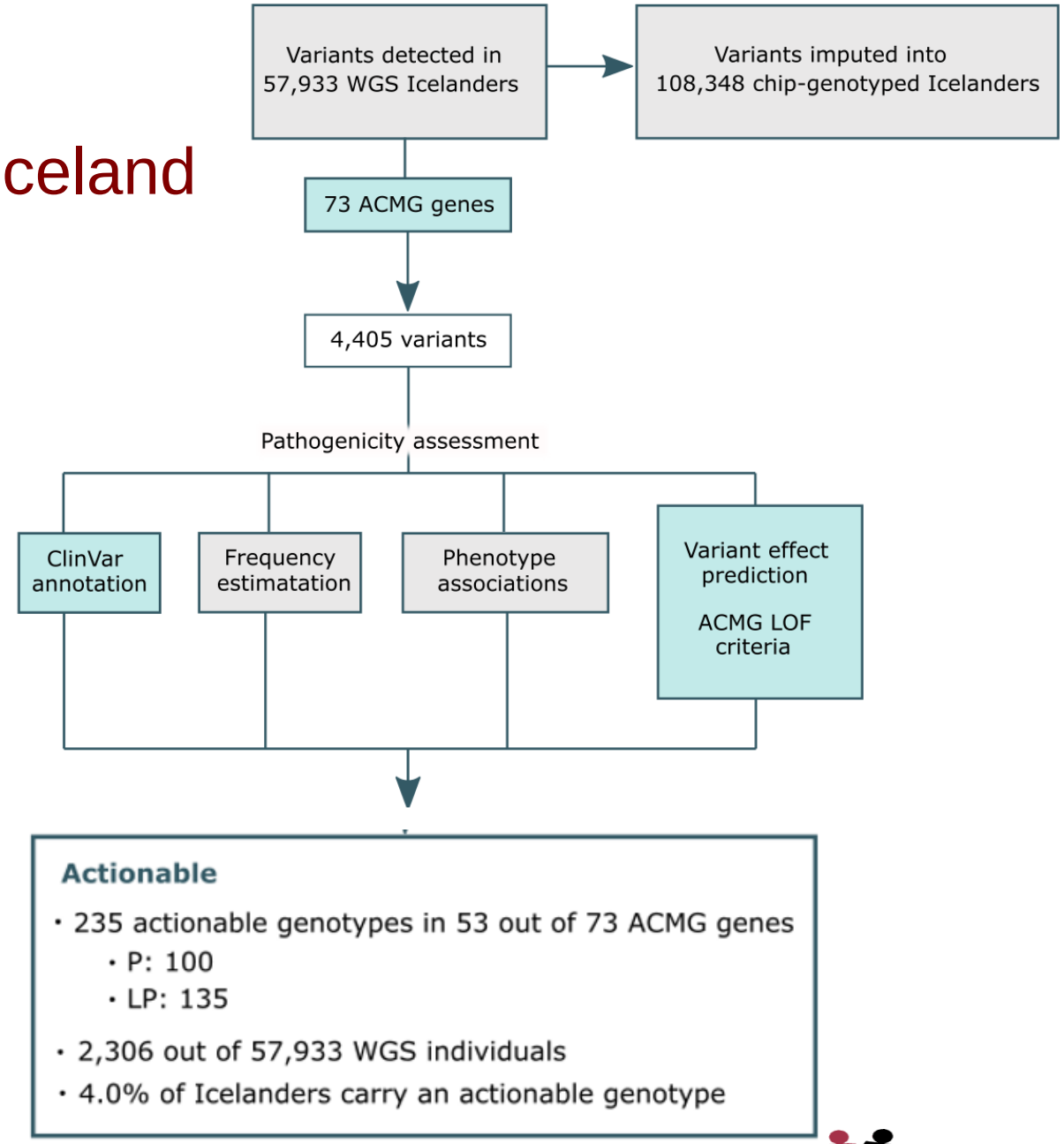
- Phenotyping of homozygous Icelanders identified from genotype dataset allows:
  - Collection of samples to confirm abnormal burst test
  - Deep phenotyping



deCODE genetics

Medically actionable genotypes in Iceland

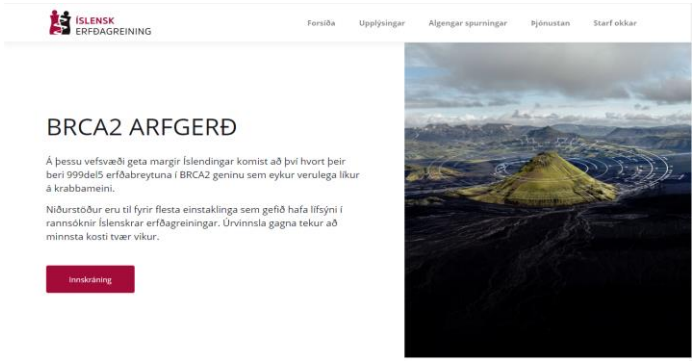
- Coding or splice variants from 57,933 WGS Icelanders
- Individual inspection of variants in 73 genes (ACMG)
- Manual curation and classification
- 1 in 25 WGS Icelanders (4%) carry an actionable genotype



Submitted

deCODE genetics

The Icelandic *BRCA2* founder mutation Return of results of actionable findings



- One founder mutation in *BRCA2* - 999del5 has reached a high frequency in Iceland
- 1 in 140 Icelanders
- Returning genotype since 2018
- Confirmed by two genotyping methods
- More request from women than men

Age	Women Neg	Women Pos	Men Neg	Men Pos
20-29	1703	27	405	15
30-39	5818	50	1559	32
40-49	6976	77	2079	38
50-59	6502	34	1999	45
60-69	4938	26	1755	45
70-79	1595	11	914	20
80+	141	1	130	2
Total	27.673	226	8.841	197
Positive	**423**			
Total	**37 K**			

deCODE genetics

COMMUNICATIONS BIOLOGY

REVIEW ARTICLE

https://doi.org/10.1038/s42003-018-0261-x OPEN

A scientometric review of genome-wide association studies

Melinda C. Mills [1] & Charles Rahal [1]

This scientometric review of genome-wide association studies (GWAS) from 2005 to 2018 (3639 studies; 3508 traits) reveals extraordinary increases in sample sizes, rates of discovery and traits studied. A longitudinal examination shows fluctuating ancestral diversity, still predominantly European Ancestry (88% in 2017) with 72% of discoveries from participants recruited from three countries (US, UK, Iceland). US agencies, primarily NIH, fund 85% and women are less often senior authors. We generate a unique GWAS H-Index and reveal a tight social network of prominent authors and frequently used data sets. We conclude with 10 evidence-based policy recommendations for scientists, research bodies, funders, and editors.

Table 4 The top 10 most prominent GWAS authors

Name author	N-papers	Citation count	GWAS H-index	Network betweenness	Network centrality	Country	Institution
Kári Stefánsson	177	27568	84	0.020	0.308	Iceland	deCODE genetics
Unnur Þorsteinsdóttir	142	23633	77	0.006	0.241	Iceland	deCODE genetics
Albert Hofman	267	25534	76	0.013	0.345	U.S.	University of Harvard
André G. Uitterlinden	280	23337	76	0.018	0.367	Netherlands	Erasmus MC
Cornelia M van Duijn	188	20879	71	0.008	0.294	Netherlands	Erasmus MC
Gudmar Thorleifsson	119	20408	70	0.006	0.232	Iceland	deCODE Genetics
Christian Gieger	166	22562	70	0.011	0.272	Germany	Helmholtz Zentrum München
Panos Deloukas	109	20323	68	0.009	0.233	U.K.	Queen Mary University of London
H-Erich Wichmann	112	20266	68	0.007	0.220	Germany	Helmholtz Zentrum München
Fernando Rivadeneira	198	17976	65	0.009	0.282	Netherlands	Erasmus MC

Automated and manual (web search) curation of details regarding authors ranked within the 10 highest GWAS H-Index (an estimate of the importance, significance, and broad impact of a scientist's cumulative GWAS-related research contributions). N-Papers refer to the number of times the author features as an author (at any position) within the Catalog. Information on citations comes from PubMed Central. Betweenness and Degree centrality calculated with Network-X. All characters converted to ASCII to ensure maximum matches of the same authors across papers

In terms of the ratio of the number of observations contributed by a country relative to the population of the country[26], Iceland is by far the largest (19.13), followed by the United Kingdom (0.32).

deCODE genetics

Genetics of cardiovascular disease at deCODE for 25 years

DISEASES
Hypertension
Resistant hypertension
Type 2 diabetes
Coronary artery disease
Atrial fibrillation
Heart failure
Abdominal aortic aneurysm
Ischemic stroke
Intracranial aneurysm
Aortic stenosis
Venous thromboembolism
Sick sinus syndrome
Hypertrophic cardiomyopathy
Dilated cardiomyopathy
Familial hypercholesterolemia
Coarctation of the aorta
Sudden cardiac death

TRAITS
Systolic pressure
Diastolic pressure
Blood sugar
Non-HDL-C
LDL-C
Triglycerides
HDL-C
Plant sterols
Lp(a)
Heart rate
PR traits
QRS traits
QT interval
BMI
Lean mass
Fat mass
Fat distribution
Smoking

Common — rare diseases

Common — rare variants

Causal variants / genes

Causal relationships between traits

Causal components

Disease correlations

New syndromes

Syndromes within common diseases

Interaction with the environment

Clinical versus research approach

True penetrance

deCODE genetics

Genetic data suggest that both dietary cholesterol and dietary phytosterol contribute directly to atherogenesis

Table 3 Disparate effects of genetic risk scores for non-high density lipoprotein cholesterol on the risk of coronary artery disease

		GRS-other			GRS-*ABCG5/8*			GRS-*NPC1L1*		
		Non-HDL cholesterol variants, outside *ABCG5/8* and *NPC1L1* loci			Non-HDL cholesterol variants at *ABCG5/8* locus			Non-HDL cholesterol variants at *NPC1L1* locus		
	Cases/controls	OR	95% CI	*P*	OR	95% CI	*P*	OR	95% CI	*P*
Iceland	19 074/124 037	1.47	(1.37, 1.59)	1.3×10^{-23}	1.96	(1.48, 2.58)	2.0×10^{-6}	1.89	(1.18, 3.01)	0.0079
Denmark	33 603/148 707	1.64	(1.54, 1.75)	7.3×10^{-55}	2.30	(1.63, 3.26)	2.5×10^{-6}	2.94	(1.73, 5.00)	7.2×10^{-5}
UK Biobank	32 867/375 698	1.51	(1.45, 1.58)	3.3×10^{-81}	1.96	(1.63, 2.35)	4.9×10^{-13}	1.64	(1.13, 2.37)	0.0087
Combined	85 544/648 442	1.54	(1.49, 1.59)	1.1×10^{-154}	2.01	(1.75, 2.31)	9.8×10^{-23}	1.95	(1.51, 2.52)	2.6×10^{-7}
								P_{het} (for difference in effects on CAD)		
GRS-*ABCG5/8* vs. GRS-other								2.4×10^{-4}		
GRS-*NPC1L1* vs. GRS-other								0.067		

The effects on CAD are given per 1 mmol/L of genetically elevated non-HDL cholesterol levels.
CAD, coronary artery disease; CI, confidence interval; GRS, genetic risk score; HDL, high-density lipoprotein; OR, odds ratio.
P_{het}: *P*-value for heterogeneity in effects.

Helgadottir et al, European Heart Journal 2020

Understanding the behaviour of SARS-CoV-2

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Spread of SARS-CoV-2 in the Icelandic Population

D.F. Gudbjartsson, A. Helgason, H. Jonsson, O.T. Magnusson, P. Melsted, G.L. Norddahl, J. Saemundsdottir, A. Sigurdsson, P. Sulem, A.B. Agustsdottir, B. Eiriksdottir, R. Fridriksdottir, E.E. Gardarsdottir, G. Georgsson, O.S. Gretarsdottir, K.R. Gudmundsson, T.R. Gunnarsdottir, A. Gylfason, H. Holm, B.O. Jensson, A. Jonasdottir, F. Jonsson, K.S. Josefsdottir, T. Kristjansson, D.N. Magnusdottir, L. le Roux, G. Sigmundsdottir, G. Sveinbjornsson, K.E. Sveinsdottir, M. Sveinsdottir, E.A. Thorarensen, B. Thorbjornsson, A. Löve, G. Masson, I. Jonsdottir, A.D. Möller, T. Gudnason, K.G. Kristinsson, U. Thorsteinsdottir, and K. Stefansson

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Humoral Immune Response to SARS-CoV-2 in Iceland

D.F. Gudbjartsson, G.L. Norddahl, P. Melsted, K. Gunnarsdottir, H. Holm, E. Eythorsson, A.O. Arnthorsson, D. Helgason, K. Bjarnadottir, R.F. Ingvarsson, B. Thorsteinsdottir, S. Kristjansdottir, K. Birgisdottir, A.M. Kristinsdottir, M.I. Sigurdsson, G.A. Arnadottir, E.V. Ivarsdottir, M. Andresdottir, F. Jonsson, A.B. Agustsdottir, J. Berglund, B. Eiriksdottir, R. Fridriksdottir, E.E. Gardarsdottir, M. Gottfredsson, O.S. Gretarsdottir, S. Gudmundsdottir, K.R. Gudmundsson, T.R. Gunnarsdottir, A. Gylfason, A. Helgason, B.O. Jensson, A. Jonasdottir, H. Jonsson, T. Kristjansson, K.G. Kristinsson, D.N. Magnusdottir, O.T. Magnusson, L.B. Olafsdottir, S. Rognvaldsson, L. le Roux, G. Sigmundsdottir, A. Sigurdsson, G. Sveinbjornsson, K.E. Sveinsdottir, M. Sveinsdottir, E.A. Thorarensen, B. Thorbjornsson, M. Thordardottir, J. Saemundsdottir, S.H. Kristjansson, K.S. Josefsdottir, G. Masson, G. Georgsson, M. Kristjansson, A. Moller, R. Palsson, T. Gudnason, U. Thorsteinsdottir, I. Jonsdottir, P. Sulem, and K. Stefansson

ABSTRACT

deCODE genetics

Symptoms, physical measures and cognitive tests after SARS-CoV-2 infection in a large population-based case-control study

Case – control study

Cases
1706 persons with prior SARS-CoV-2 infection
September 2020 – November 2021

vs

Historical controls
13,779 persons that participated in the dHS before the pandemic
June 2016 – March 2020

Contemporary controls
619 persons without prior SARS-CoV-2 infection
September 2020 – November 2021

Assessment of longitudinal measures

125 **cases** that participated twice in the dHS
First visit: June 2016 – March 2020
Second visit: Sept 2020 – Nov 2021

vs

295 **controls** that participated twice in the dHS
First visit: June 2016 – March 2020
Second visit: Sept 2020 – Nov 2021

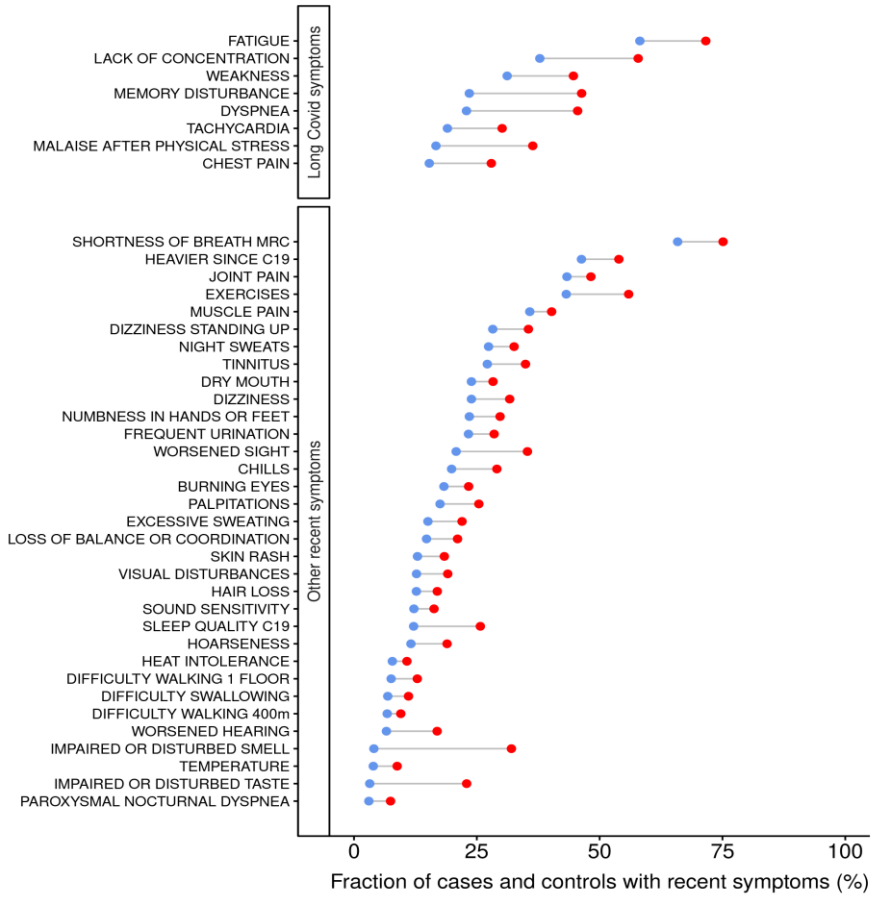
Overview of data collected for cases and controls in the study

Self-reported data	Questionnaires		General health and lifestyle factors GAD-7* (anxiety), PHQ-9* (depression) PSS* (stress), SHAI* (health anxiety) SWLS* (life satisfaction), 36-SF* (health measure), SIQR*(fatigue) C19Q*: Symptoms during last 4 weeks
Objective measures	Measurements		Height, Weight, BMI Blood pressure, Heart rate Oxygen saturation Body composition, Grip strength Smell test, Taste test*, Hearing test Spirometry, Ambulatory sleep test Cardiopulmonary exercise test
	Cognitive tests		Digit coding Letter and category fluency WMS logical memory* Spatial working memory Trail making tests WMS reasoning & word comprehension
	Blood tests		Complete blood count Electrolytes, CRP Thyroid function tests Liver and kidney tests Cardiac biomarkers Lipids, glucose Sex hormones

deCODE genetics

Symptoms, physical measures and cognitive tests after SARS-CoV-2 infection in a large population-based case-control study

Subjective measures



Objective measures

Cases were more likely than controls to have

- measured impairment in smell and taste
- lower grip strength
- poorer immediate and delayed memory recall

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Thank you

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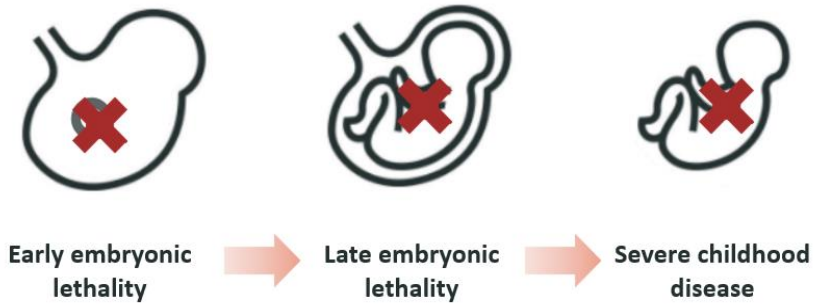
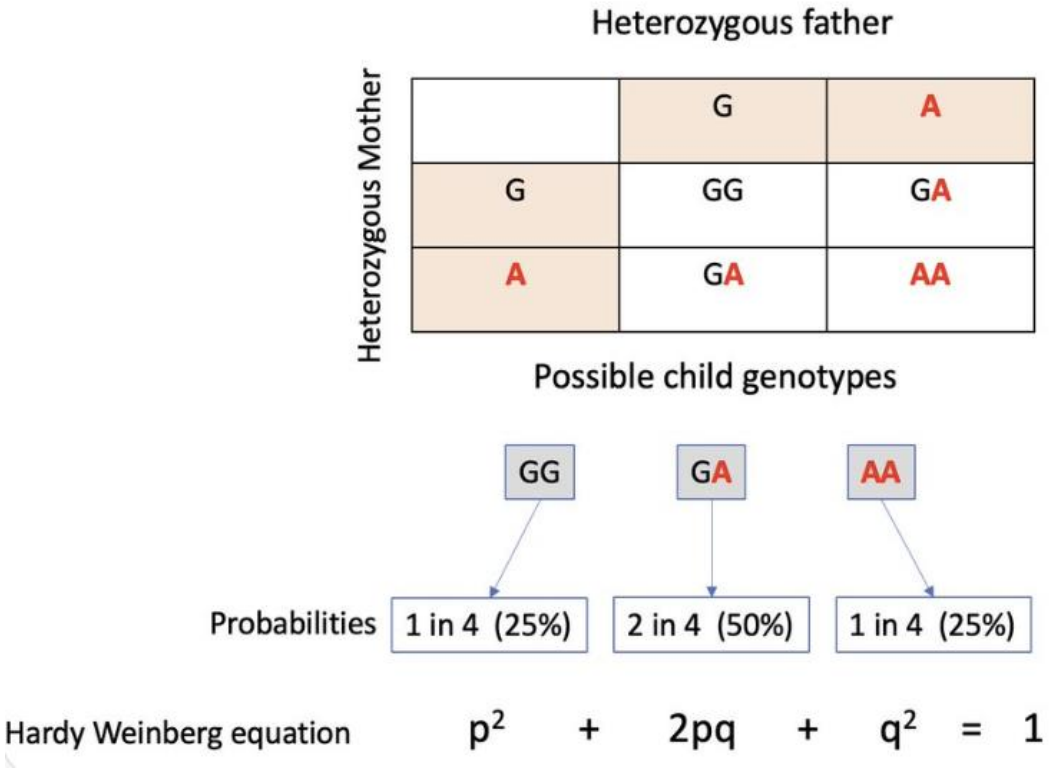
Deficit of homozygous loss-of-function genotypes

- A deficit of homozygous genotypes will appear if associated with:
  - Incompatibility with early embryonic development (early miscarriage)
  - Incompatibility with late embryonic/fetal development (late miscarriage, stillbirth)
  - A severe condition (early death; severe disease)

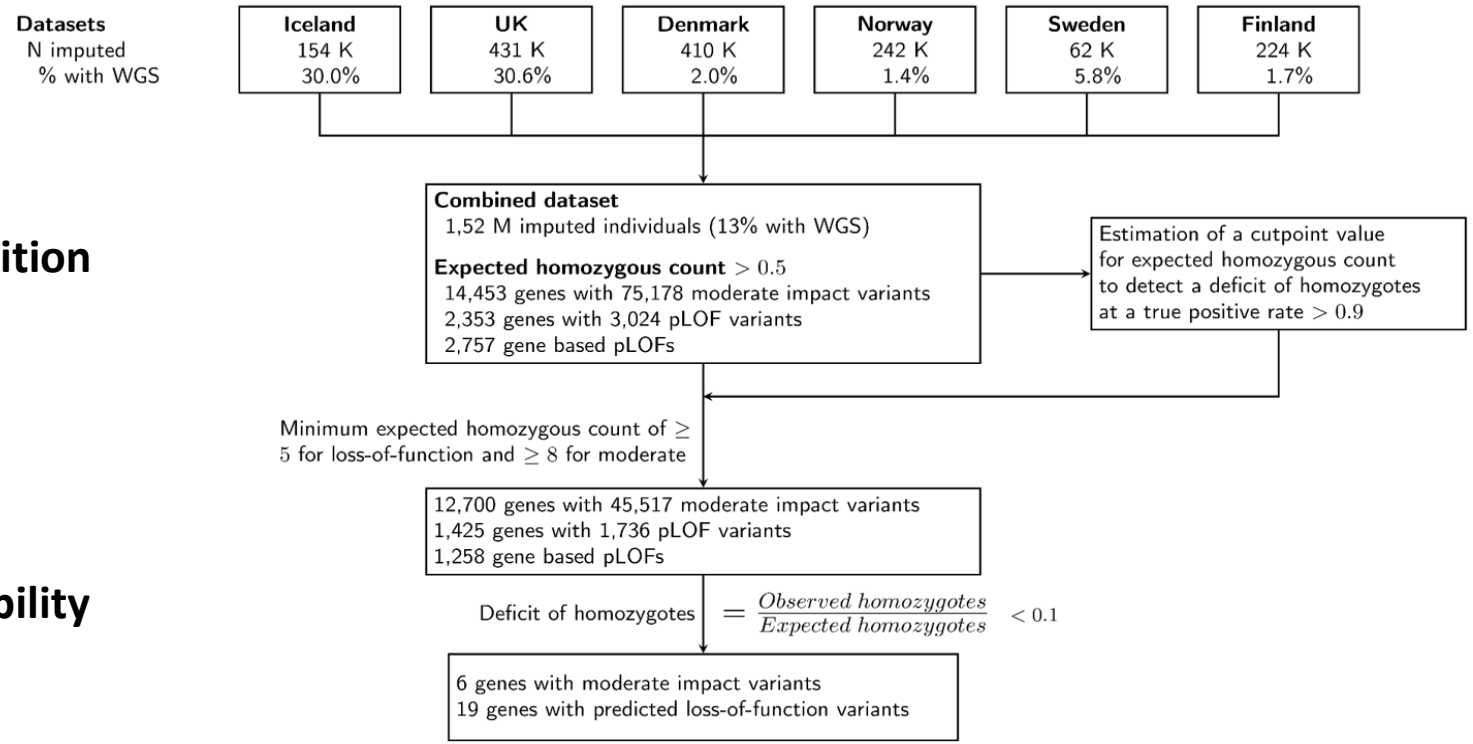




deCODE genetics

Deficit of homozygosity among 1.5 million individuals and causes of recessive lethality

- **1.5 M genotyped individuals in 6 countries**
- **25 genes for lethality of homozygotes**
  - **Including 13 not known for recessive condition**
- **Genes with deficit of homozygosity are over-represented among genes**
  - **Essential for growth of human cell lines**
  - **Orthologous to mouse genes affecting viability**



LETTERS 2015 FOCUS ON GENOMES OF ICELANDERS

nature genetics

Identification of a large set of rare complete human knockouts

Patrick Sulem[1,6], Hannes Helgason[1,2,6], Asmundur Oddson[1], Hreinn Stefansson[1], Sigurjon A Gudjonsson[1], Florian Zink[1], Eirikur Hjartarson[1], Gunnar Th Sigurdsson[1], Adalbjorg Jonasdottir[1], Aslaug Jonasdottir[1], Asgeir Sigurdsson[1], Olafur Th Magnusson[1], Augustine Kong[1,2], Agnar Helgason[1,3], Hilma Holm[1,4], Unnur Thorsteinsdottir[1,5], Gisli Masson[1], Daniel F Gudbjartsson[1,2] & Kari Stefansson[1,5]

Submitted 2022

deCODE genetics