hvorfor blir vi **syke** ?

hvordan blir vi **friske** ?

Blodlipider er arvelige risikofaktorer for hjerte- og karsykdom som kan behandles

Lipoproteiner frakter kolesterol rundt i kroppen

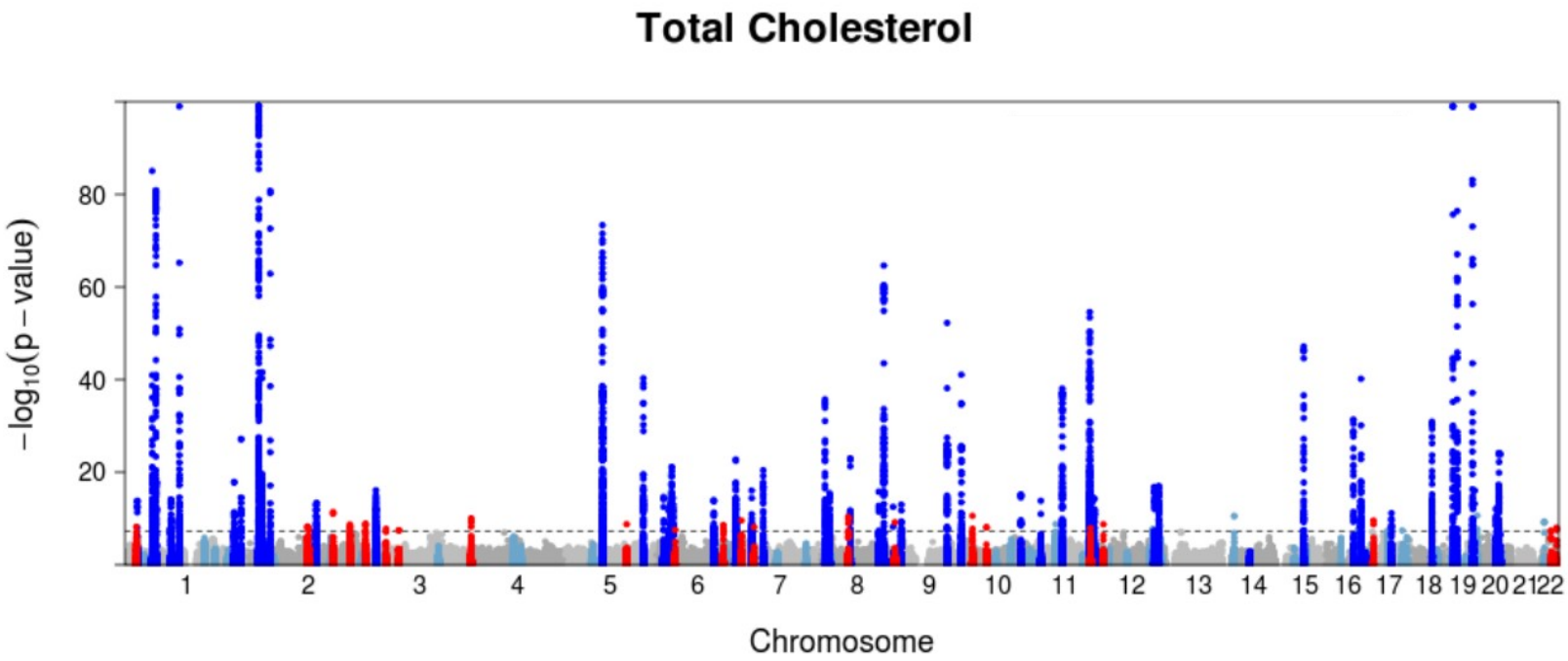
Table 1 | Meta-analysis of plasma lipid concentrations in >100,000 individuals of European descent.

Locus	Chr	Lead SNP	Lead trait	Other traits	Alleles/MAF	Effect size	P	eQTL	CAD	Ethnic
LDLRAP1	1	rs12027135	TC	LDL	T/A/0.45	−1.22	4×10^{-11}	Y		+++?
PABPC4	1	rs4660293	HDL		A/G/0.23	−0.48	4×10^{-10}	Y		++++
PCSK9	1	rs2479409	LDL	TC	A/G/0.30	+2.01	2×10^{-28}			++++
ANGPTL3	1	rs2131925	TG	TC, LDL	T/G/0.32	−4.94	9×10^{-43}	Y		++++
EVI5	1	rs7515577	TC		A/C/0.21	−1.18	3×10^{-8}			+++?
SORT1	1	rs629301	LDL	TC	T/G/0.22	−5.65	1×10^{-170}	Y	Y	++++
ZNF	1	rs168	HDL		A/G/0.35	−0.47	1×10^{-10}			++?−
MO	1	rs6	TC							++?
GALNT2	1	rs4846914	HDL	TG	A/G/0.40	−0.61	$4 \times 10^{-}$			++++
IRF2BP2	1	rs514230	TC	LDL	T/A/0.48	−1.36	5×10^{-14}			+++?
APOB	2	rs1367117	LDL	TC	G/A/0.30	+4.05	4×10^{-114}			++++
		rs1042034	TG	HDL	T/C/0.22	−5.99	1×10^{-45}			+−++
GCKR	2	rs1260326	TG	TC	C/T/0.41	+8.76	6×10^{-133}	Y		++++
ABCG5/8	2	rs4299376	LDL	TC	T/G/0.30	+2.75	2×10^{-47}			++++
RAB3GAP1	2				C/A/0.34	+1.25	2×10^{-8}			+−??
COBLL1	2				T/C/0.40	−2.01	2×10^{-10}	Y		++++
		rs12328675	HDL		T/C/0.13	+0.68	3×10^{-10}			++?+
IRS1	2					+0.46	3×10^{-9}	Y	Y	++++
RAF1	3					−1.42	4×10^{-9}			+++?
MSL2L1	3	rs645040	TG		T/G/0.22	−2.22	3×10^{-8}			++−+
KLHL8	4	rs4421			T/G/0.41	−2.25	9×10^{-12}			++++
SLC39A8	4	rs1310			C/T/0.07	−0.84	7×10^{-11}	Y		+−?−
ARL15	5	rs6450176	HDL		G/A/0.26	−0.49	5×10^{-8}			−??+
MAP3K1	5	rs9686661	TG		C/T/0.20	+2.57	1×10^{-10}			++++
HMGCR	5	rs12916	TC	LDL	T/C/0.39	+2.84	9×10^{-47}			+++?
TIMD4	5	rs6882076	TC	LDL, TG	C/T/0.35	−1.98	7×10^{-28}			+++?
MYLIP	6	rs3757354	LDL	TC	C/T/0.22	−1.43	1×10^{-11}			+−−+
HFE	6	rs1800562	LDL	TC	G/A/0.06	−2.22	6×10^{-10}			++?+
HLA	6	rs3177928	TC	LDL	G/A/0.16	+2.31	4×10^{-19}	Y		+++?
		rs2247056	TG		C/T/0.25	−2.99	2×10^{-15}			+++−

HMG-CoA → Mevalonate → Cholesterol

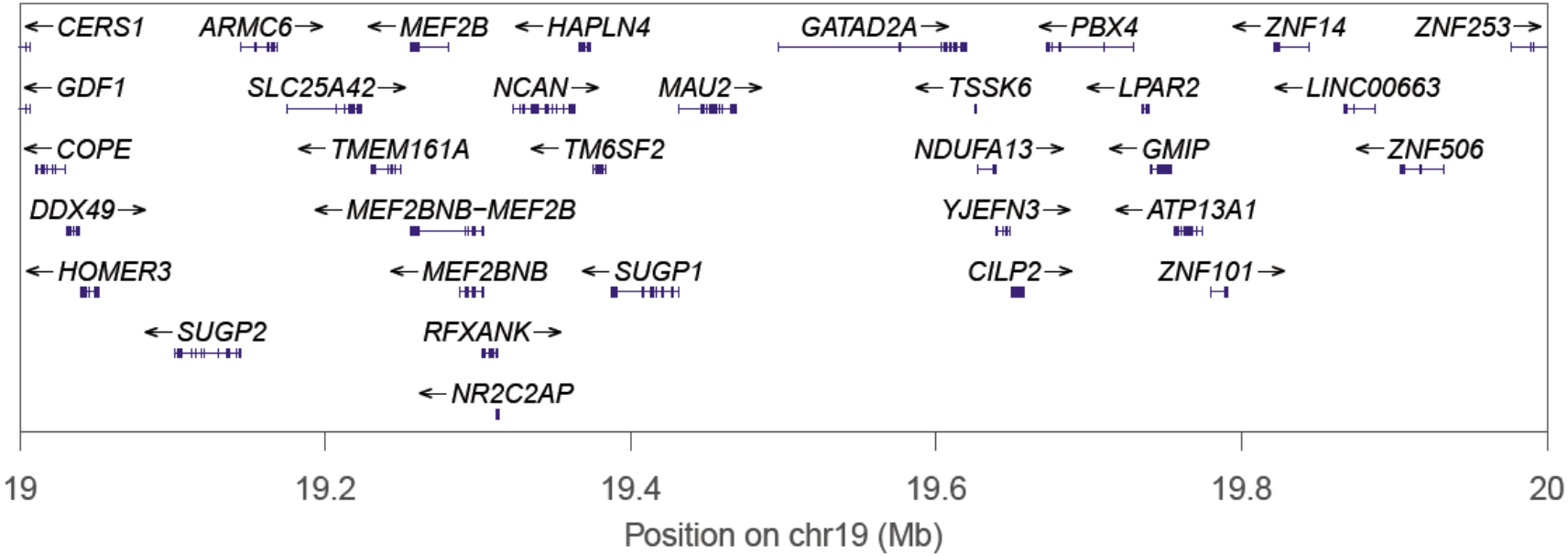
VIRKESTED FOR KOLESTEROLSENKENDE MEDISIN

Nå kjenner vi mange genområder som viser stabil assosiasjon til sykdom



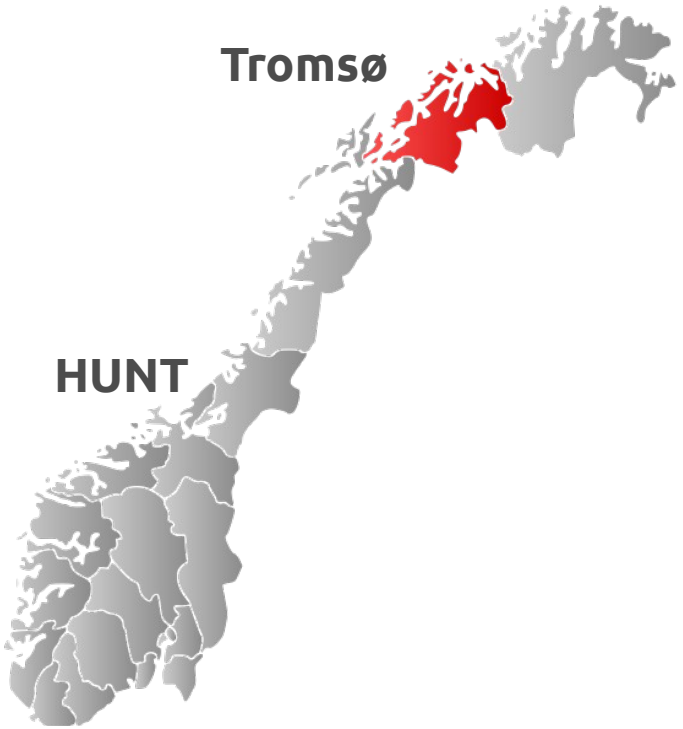
Willer et al. 2013

Men det har vist seg utfordrende å påvise genene som er involvert

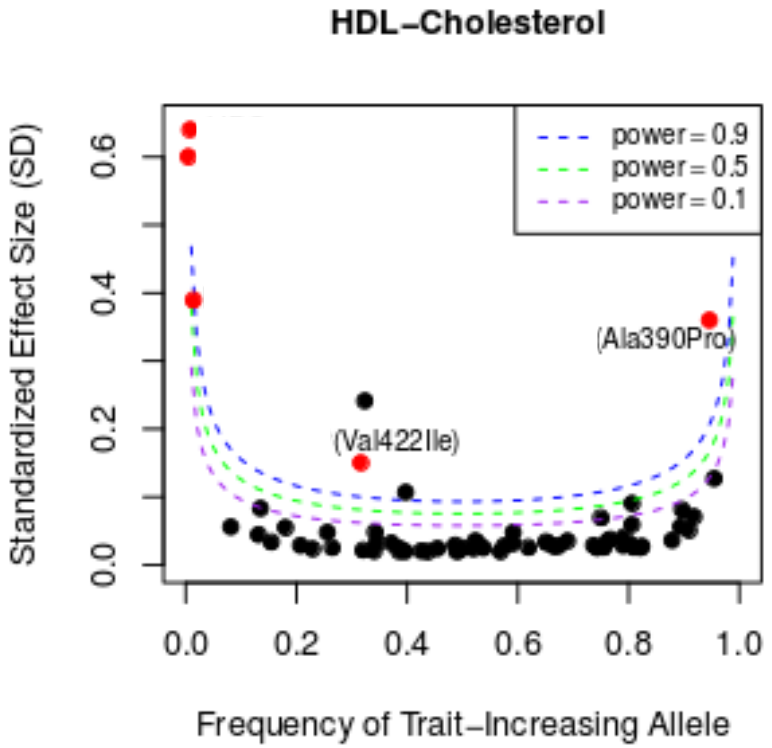


Steg 1: “Exome chip” i HUNT (N=5,771)

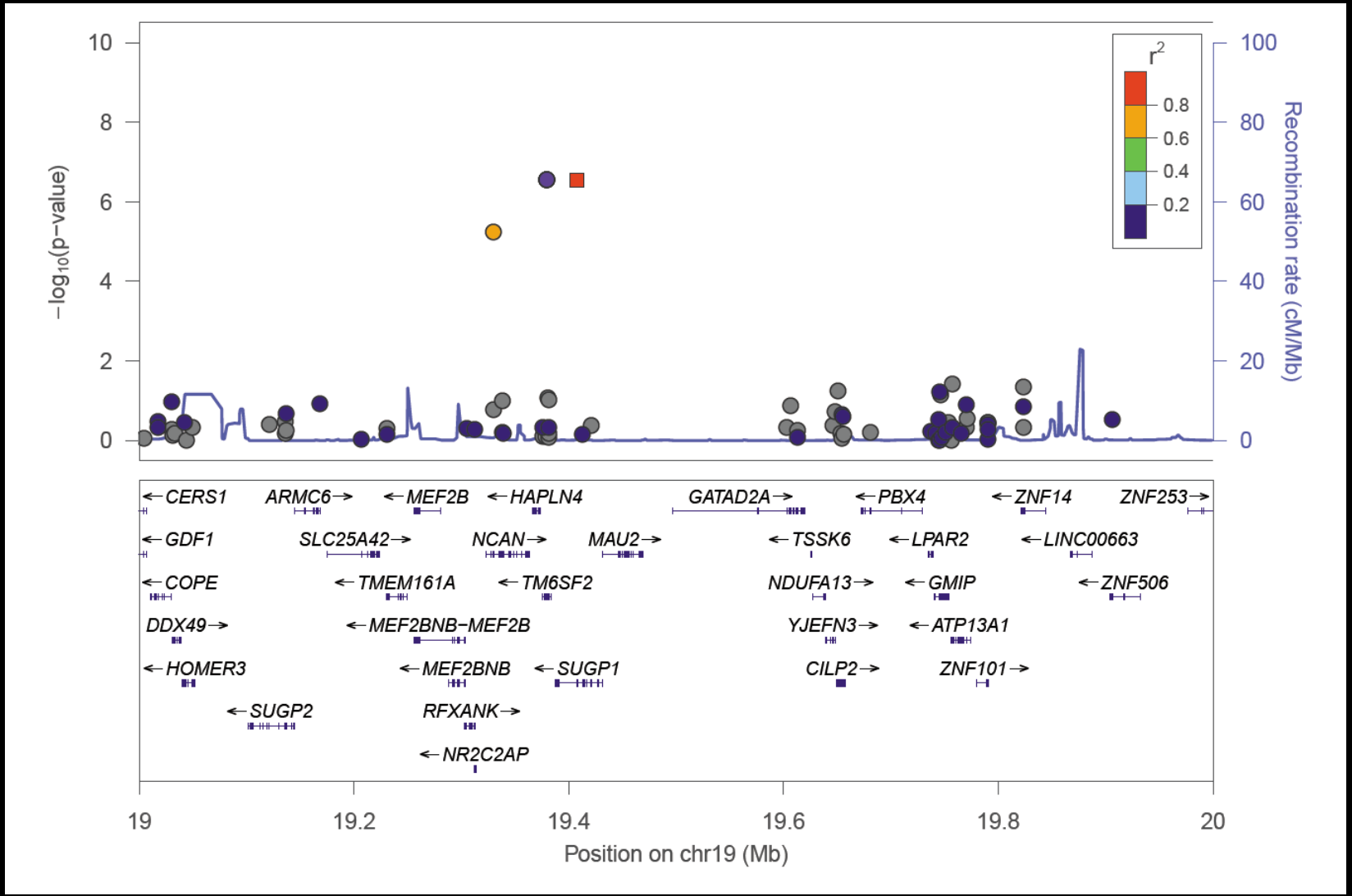
Steg 2: SNP basert oppfølging i Tromsø (N=4,666)



Det finnes sjelden genvariasjon med 'høy' effekt

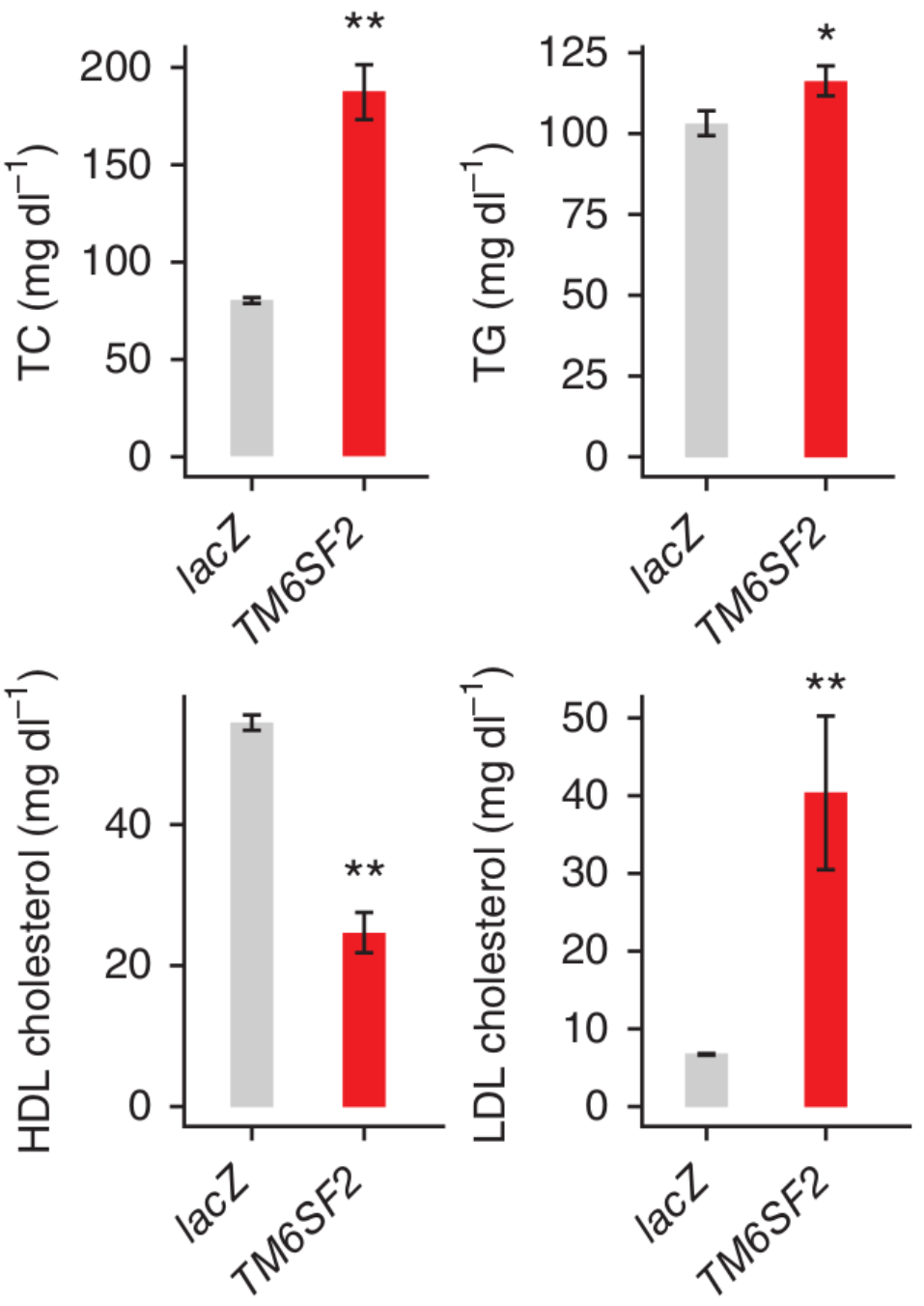


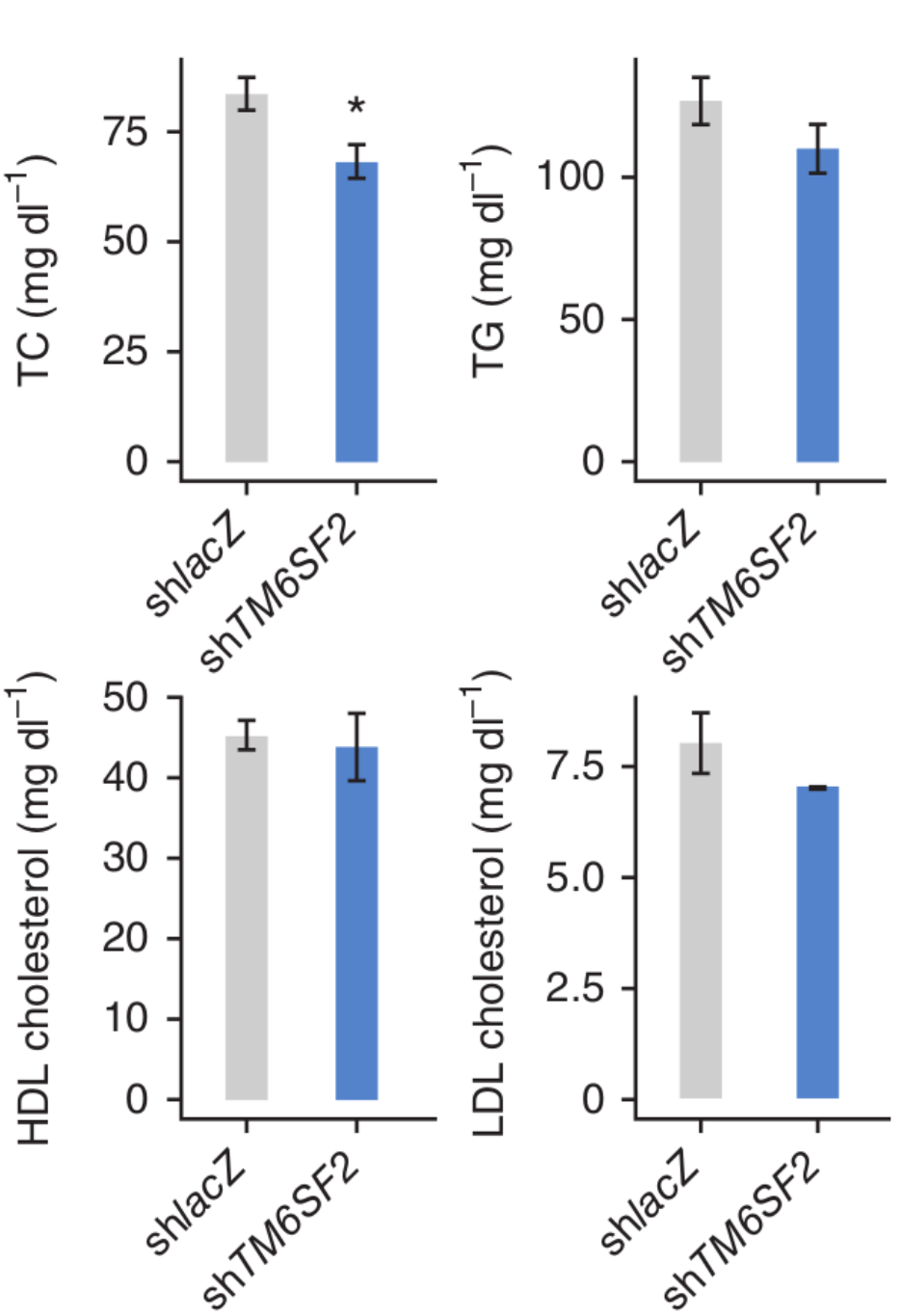
En variant i ***TM6SF2***-genet nådde statistisk signifikans for totalkolesterol



Overekspresjon

Knock-down





Systematisk vurdering av genvariasjon som koder for proteiner kan raskt lede til potensielle kausale gener

assosiasjon på innsiden av et gen..

↓

...kan fine-mappe et område...

↓

...som har klinisk relevans...

↓

og stemmer med funksjonell oppfølging

↓

= identifkasjon av et potensielt medikament mål for å endre lipidprofil og forebygge hjerteinfarkt

nature genetics

Systematic evaluation of coding variation identifies a candidate causal variant in *TM6SF2* influencing total cholesterol and myocardial infarction risk

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Blood lipid levels are heritable, treatable risk factors for cardiovascular disease. We systematically assessed genome-wide coding variation to identify new genes influencing lipid traits, fine map known lipid loci and evaluate whether low-frequency variants with large effects exist for these traits. Using an exome array, we genotyped 80,137 coding variants in 5,643 Norwegians. We followed up 18 variants in 4,666 Norwegians and identified ten loci with coding variants associated with a lipid trait ($P < 5 \times 10^{-8}$). One variant in *TM6SF2* (encoding p.Glu167Lys), residing in a known genome-wide association study locus for lipid traits, influences total cholesterol levels and is associated with myocardial infarction. Transient *TM6SF2* overexpression or knockdown of *Tm6sf2* in mice alters serum lipid profiles, consistent with the association observed in humans, identifying *TM6SF2* as a functional gene within a locus previously known as *NCAN-CILP2-PBX4* or 19p13. This study demonstrates that systematic assessment of coding variation can quickly point to a candidate causal gene.

Circulating blood lipid levels are heritable, treatable, risk factors for cardiovascular disease, a leading cause of death globally[1,2]. Understanding the genetic basis of lipid levels in humans can identify targets for new, improved therapies for cholesterol management and prevention of heart disease[3]. Genome-wide association studies (GWAS) for plasma lipid levels have so far identified association with 157 loci[4,5], represented primarily by one or more common variants (minor allele frequency (MAF) >5%) with small effect sizes. These GWAS variants together explain ~12–14% of the trait variation in lipid levels, corresponding to 20–30% of the total genetic contribution to these traits[6]. Some of the missing heritability may be due to low-frequency (MAF = 1–5%) and rare (MAF < 1%) variants that are not well tested by GWAS[7–9]. These low-frequency and rare variants are plentiful in the genome[10,11] but are difficult to capture on GWAS chips, either directly or through imputation[12–14].

Systematic assessment of association between blood lipid levels and coding variants has several potential benefits. First, it could implicate new loci in the regulation of blood lipids. Second, it could lead to the discovery of new lipid-modifying alleles at known loci that point to candidate causal genes. In some cases in which GWAS signals are shadows of a nearby rare variant with much larger effects, these alleles could be critical in directing follow-up functional experiments. For example, in *PCSK9*, a low-frequency functional variant explains the nearby common variant GWAS signal[15], suggesting that the GWAS variant has no relevant functional consequence and would not be a productive target for functional experiments. Even when they do not account for the GWAS signal, rare coding variants in known loci can pinpoint specific genes as candidates for follow-up and functional analyses and clarify the biology. A good example of the latter situation is *IFIH1*, for which multiple independently associated loss-of-function

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nature genetics

Loss-of-function mutations in *SLC30A8* protect against type 2 diabetes

Jason Flannick[1–3], Gudmar Thorleifsson[4], Nicola L Beer[1,5], Suzanne B R Jacobs[1], Niels Grarup[6], Noël P Burtt[1], Anubha Mahajan[7], Christian Fuchsberger[8], Gil Atzmon[9,10], Rafn Benediktsson[11], John Blangero[12], Don W Bowden[13–16], Ivan Brandslund[17,18], Julia Brosnan[19], Frank Burslem[20], John Chambers[21–23], Yoon Shin Cho[24], Cramer Christensen[25], Desirée A Douglas[26], Ravindranath Duggirala[12], Zachary Dymek[1], Yossi Farjoun[1], Timothy Fennell[1], Pierre Fontanillas[1], Tom Forsén[27,28], Stacey Gabriel[1], Benjamin Glaser[29,30], Daniel F Gudbjartsson[4], Craig Hanis[31], Torben Hansen[6,32], Astradur B Hreidarsson[11], Kristian Hveem[33], Erik Ingelsson[7,34], Bo Isomaa[35,36], Stefan Johansson[37–39], Torben Jørgensen[40–42], Marit Eika Jørgensen[43], Sekar Kathiresan[1,44–46], Augustine Kong[4], Jaspal Kooner[22,23,47], Jasmina Kravic[48], Markku Laakso[49], Jong-Young Lee[50], Lars Lind[51], Cecilia M Lindgren[1,7], Allan Linneberg[40,41,52], Gisli Masson[4], Thomas Meitinger[53], Karen L Mohlke[54], Anders Molven[37,55,56], Andrew P Morris[7,57], Shobha Potluri[58], Rainer Rauramaa[59,60], Rasmus Ribel-Madsen[6], Ann-Marie Richard[19], Tim Rolph[19], Veikko Salomaa[61], Ayellet V Segrè[1,2], Hanna Skärstrand[26], Valgerdur Steinthorsdottir[4], Heather M Stringham[8], Patrick Sulem[4], E Shyong Tai[62–64], Yik Ying Teo[62,65–68], Tanya Teslovich[8], Unnur Thorsteinsdottir[4,69], Jeff K Trimmer[19], Tiinamaija Tuomi[27,35], Jaakko Tuomilehto[70–72], Fariba Vaziri-Sani[26], Benjamin F Voight[1,73,74], James G Wilson[75], Michael Boehnke[8], Mark I McCarthy[5,7,76], Pål R Njølstad[1,37,77], Oluf Pedersen[6], Go-T2D Consortium[78], T2D-GENES Consortium[78], Leif Groop[48,79], David R Cox[58], Kari Stefansson[4,69] & David Altshuler[1–3,44,45,80,81]

Loss-of-function mutations protective against human disease provide *in vivo* validation of therapeutic targets[1–3], but none have yet been described for type 2 diabetes (T2D). Through sequencing or genotyping of ~150,000 individuals across 5 ancestry groups, we identified 12 rare protein-truncating variants in *SLC30A8*, which encodes an islet zinc transporter (ZnT8)[4] and harbors a common variant (p.Trp325Arg) associated with T2D risk and glucose and proinsulin levels[5–7]. Collectively, carriers of protein-truncating variants had 65% reduced T2D risk ($P = 1.7 \times 10^{-6}$), and non-diabetic Icelandic carriers of a frameshift variant (p.Lys34Serfs*50) demonstrated reduced glucose levels (−0.17 s.d., $P = 4.6 \times 10^{-4}$). The two most common protein-truncating variants (p.Arg138* and p.lys34Serfs*50) individually associate with T2D protection and encode unstable ZnT8 proteins. Previous functional study of *SLC30A8* suggested that reduced zinc transport increases T2D risk[8,9], and phenotypic heterogeneity was observed in mouse *Slc30a8* knockouts[10–15]. In contrast, loss-of-function mutations in humans provide strong evidence that *SLC30A8* haploinsufficiency protects against T2D, suggesting ZnT8 inhibition as a therapeutic strategy in T2D prevention.

Genome-wide association studies (GWAS) have identified 65 genomic loci associated with T2D risk[7], highlighting previously unidentified pathological pathways. Translation of these loci into novel therapeutic targets[16] requires the identification of causal mutations and genes, as well as information on the directional relationship between protein activity and disease risk[17]. Toward this end, loss-of-function mutations that protect against disease (without adverse phenotypes) are among the most useful findings from human genetics, suggesting targets that, upon inhibition, might prevent disease in the general population.

To identify loss-of-function variants protective against T2D, in 2009, a collaboration of Pfizer, Inc., Massachusetts General Hospital, the Broad Institute and Lund University sequenced the exons of 115 genes near T2D association signals identified by GWAS (**Supplementary Fig. 1** and **Supplementary Tables 1** and **2**) in 758 individuals from Finland or Sweden (modeling previous studies[18]). To increase power, we selected individuals at the extremes of T2D risk, including 352 young and lean T2D cases and 406 elderly and obese euglycemic controls[19] (**Supplementary Table 3**). In total, we identified 1,768 nonsynonymous variants (1,683 single-nucleotide variants (SNVs) and 85 indels), 1,474 (83%) with minor allele frequency (MAF) of <1% and 1,108 (63%) observed in only one individual. We found no evidence of association with T2D when testing individual variants or a burden of rare variants within genes (**Supplementary Fig. 2**). Genotyping of 71 select SNVs (showing nominally significant association ($P < 0.05$) or predicted to affect

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Table 1 Association of *SLC30A8* variants with T2D

Variant	Ancestry	Country	Cohort	*N*		Carriers		Allele frequency		OR (95% CI)	*P*
				Cases	Controls	Cases	Controls	Cases (%)	Controls (%)		
p.Arg138*	European	Finland	Botnia	3,727	5,440	9	39	0.12	0.36	0.47 (0.27–0.81)	0.0067
	European	Sweden	Malmo	6,960	5,480	2	3	0.014	0.027		
	European	Sweden	PIVUS/ULSAM	270	1,734	1	3	0.19	0.087		
	European	Denmark	Danish	3,889	7,869	0	9	0.0	0.057		
	European	Finland	Finnish	4,050	8,696	1	2	0.012	0.011		
	South Asian	Singapore	Singapore Indians	562	585	1	1	0.089	0.085		
	European	UK	UKT2D	321	319	0	1	0.0	0.16		
p.Lys34Serfs*50	European	Iceland	deCODE	2,953	67,919	2	248	0.034	0.18	0.17 (0.05–0.52)	0.0019
	European	Norway	HUNT2	1,645	4,069	0	3	0.0	0.037		
c.71+2T>A	African American	United States	WFS	501	527	1	0	0.1	0.0	0.30 (0.14–0.64)	0.0021
	African American	United States	JHS	530	533	0	1	0.0	0.094		
p.Met50Ile	European	Germany	KORA	97	91	0	1	0.0	0.55		
c.271+G>A	East Asian	Korea	KARE	520	551	0	1	0.0	0.091		
	South Asian	Singapore	Singapore Indians	562	585	0	1	0.0	0.085		
c.419–1G>C	South Asian	UK	LOLIPOP	530	537	1	0	0.094	0.0		
p.Trp152*	European	Finland	Botnia	134	180	0	1	0.0	0.28		
p.Gln174*	South Asian	UK	LOLIPOP	530	537	1	5	0.094	0.47		
c.572+1G>A	African American	United States	JHS	530	533	0	1	0.0	0.094		
p.Tyr284*	South Asian	UK	LOLIPOP	530	537	0	2	0.0	0.19		
	South Asian	Singapore	Singapore Indians	562	585	0	1	0.0	0.085		
p.Ile291Phefs*2	African American	United States	JHS	530	533	0	1	0.0	0.094		
p.Ser327Thrs*55	African American	United States	WFS	501	527	0	2	0.0	0.19		
Combined	–	–	–	30,433	118,701	19	326	–	–	0.34 (0.21–0.53)	1.7×10^{-6}

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	European	Norway	HUNT2	1,645	4,069	0	3	0.0	0.037		
c.71+2T>A	African American	United States	WFS	501	527	1	0	0.1	0.0	0.30 (0.14–0.64)	0.0021
	African American	United States	JHS	530	533	0	1	0.0	0.094		
p.Met50Ile	European	Germany	KORA	97	91	0	1	0.0	0.55		
c.271+G>A	East Asian	Korea	KARE	520	551	0	1	0.0	0.091		
	South Asian	Singapore	Singapore Indians	562	585	0	1	0.0	0.085		
c.419–1G>C	South Asian	UK	LOLIPOP	530	537	1	0	0.094	0.0		
p.Trp152*	European	Finland	Botnia	134	180	0	1	0.0	0.28		
p.Gln174*	South Asian	UK	LOLIPOP	530	537	1	5	0.094	0.47		
c.572+1G>A	African American	United States	JHS	530	533	0	1	0.0	0.094		
p.Tyr284*	South Asian	UK	LOLIPOP	530	537	0	2	0.0	0.19		
	South Asian	Singapore	Singapore Indians	562	585	0	1	0.0	0.085		
p.Ile291Phefs*2	African American	United States	JHS	530	533	0	1	0.0	0.094		
p.Ser327Thrs*55	African American	United States	WFS	501	527	0	2	0.0	0.19		
Combined	–	–	–	30,433	118,701	19	326	–	–	0.34 (0.21–0.53)	1.7×10^{-6}

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HUNT-MI: Studiedel på supraventrikulære takykardier

Dette dokumentet beskriver bakgrunnen og de spesifikke problemstillingene knyttet til HUNT-MIs studiedel på supraventrikulære takykardier. Generell informasjonen om prosjektet finnes i hoveddokumentet "HUNT-MI - økt forståelse av helse og sykdom gjennom studier av genetiske fatorer på befolkningsnivå" (REK#2014/144).

Medarbeidere

I tillegg til personer listet i hovedsøknaden, vil følgende forskere ha tilgang til data beskrevet i denne studiedelen:

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Delprosjektledere analyse	**Vegard Malmo**, MD, St Olavs Hospital og NTNU **Oddgeir Lingaas Holmen**, MD, ISM/NTNU

Generelt om supraventrikulære takykardier

Generelt om takykardier. Takykardier (episoder med anfallsvis rask hjertefrekvens) deles i hovedsak i ventrikulære og supraventrikulære. Ventrikulære takykardier sitter i hjertets hovedkamre (høyre og/eller venstre hovedkammer) og kan potensielt være dødelige for pasienten. De supraventrikulære takykardiene kommer fra forkamrene eller deler av ledningssystemet i hjertet som sitter over hovedkamrene. Disse takykardiene er mye vanligere enn ventrikulære takykardier og er i all hovedsak mindre alvorlige for pasienten.

Generell forekomst. Atrieflimmer er den vanligste hjerterytmeforstyrrelsen, med en forekomst på 2-3% i den voksne befolkningen, og forekomsten er økende.[1,2] Tilstanden er assosiert med økt sykelighet og dødelighet, i hovedsak pga. en økt risiko for hjerneslag (atrieflimmer er årsak til ca 20% av alle hjerneslag), samt komorbiditeter som hypertensjon, kransåresykdom, overvekt, diabetes og hjertesvikt.[3,4] Atrieflimmer medfører derfor en betydningsfull belastning både kostnadsmessig og ressursmessig for helsevesenet. Atrieflimmer skyldes kaotiske signal i venstre forkammer. Atrieflutter skyldes derimot signal som går mer regelmessig i større sløyfer. De to tilstandene henger imidlertid på mange vis sammen, med lignende risikofaktorer og behandling, og man ser ofte begge tilstandene hos mange pasienter. Det er derfor naturlig å se på disse tilstandene samlet når man skal se på bakenforliggende årsaker og genetikk. I tillegg har man atrietakykardi som også skyldes endringer i forkammeret, men disse signalene går saktere enn ved atrieflimmer og atrieflutter. Det finnes også andre typer supraventrikulære takykadier som skyldes endringeri hjertets ledningssytem og kommer av mer rene utviklingsforstyrrelser og har ikke de samme risikofaktorene. Dette er AV-nodal reentrytakykardi, WPW-syndrom, samt asymptomatisk preeksitasjonssyndrom.

Symptomer og behandling. Det er stor forskjell mellom hvordan belastningen av supraventrikulære takykardier forløper seg hos den enkelte. Noen har stabil sykdom med få og korte anfall, mens andre har økende forekomst med store subjektive plager. Medikamenter har varierende effekt og kan i mange tilfeller gi plagsomme bivirkninger. Et alternativ til medikamentell behandling er et inngrep (ablasjon) der man lager arrvev i hjerteområder for å fjerne anfallene. Ablasjon er imidlertid et ressurskrevende inngrep hvor mange pasienter må gjennom flere inngrep før de blir symptomfrie. Langtidseffektene ved atrieflimmer er usikre, mens de er bedre ved de øvrige supraventrikulære takykardiene.

Arvelig tilstand. Arv er kjent å ha en innvirkning på atrieflimmer og atrieflutter, særlig hos dem som får det i yngre alder.[5-7] Dyrestudier har vist at endring av ulike gener medfører økt sårbarhet for atrieflimmer.[8,9] De øvrige takykardiene skyldes i større grad utviklingsforstyrrelser i ledningssystemet og man forventer at genetiske årsaker har enda større innvirkning. Økt kunnskap om genetiske mekanismer til sykdommene vil kunne gi bedre innsikt i de grunnleggende mekanismene, som igjen vil kunne gjøre det mulig å finne nye risikofaktorer og risikomarkører med håp om å påvise nye angrepspunkt for medikamenter.

Spesielt om supraventrikulære takykardier i HUNT

Ut fra en valideringsstudie som vi (Loennechen, Ellekjær og Malmo) har gjort i tre kommuner (Steinkjer, Verdal og Inderøy) **forventer vi å finne ca. 3,600 personer med atrieflimmer og atrieiflutter** i HUNT (både HUNT 2 og HUNT 3). Vi har så langt validert 849 atrieflimmerdiagnoser for deltakere i HUNT 3 ved å koble data fra HUNT med elektroniske sykehusdiagnoser (ICD-9 og ICD-10) og manuell verifisering i sykehusjournaler. Vi planlegger å utvide denne valideringen til hele HUNT-materialet. Når det gjelder de øvrige supraventrikulære takykardiene er disse mindre vanlige. Det finnes ikke informasjon om disse i HUNT databank, så denne informasjonen må hentes fra sykehusregistre.

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CVD	Myocardioal infarction and lipids, anthropometric traits, blood pressure
CVD	Supraventricular tachycarrhythmia
CVD	Thoraic and abdominal aneurysms
CVD	Self-reported physical activity
CVD	Subarachnoid hemorrhage and unruptured intracranial aneurysms
CVD	Familiar hypercholesterolemia
CVD	Reduced heart function
CVD	Chronic kidney disease
CVD	Sosio economy and cognitive factors in cardiovascular risk
ENDO	Type 1 diabetes
ENDO	Type 2 diabetes
ENDO	Thyroid dysfunction
ENDO	Osteoporosis
NEURO	Headache
NEURO	Depression, bipolar, anxiety, addiction, schizofrenia
NEURO	Muscular and skeletal pain, chronic generalized pain
NEURO	Stroke (ischemic and hemorrhagic)
NEURO	Sleep and sleep disorders
GASTRO	Inflammatory bowel disease (Chron's disease and ulcerative colitis)
GASTRO	Irritable bowel syndrome
GASTRO	Gastroesophageal reflux disease (GERD)
GASTRO	Non-familiar colorectal cancer
SKIN	Psoriasis
SKIN	Skin cancers (malanoma, squamous-cell cancer)
LUNG	Common diseases (Asthma, COPD, Thinitis, Sarcoidosis, Sinusitis)
RHEUMA	Common diseases
INFECTION	Common diseases
CANCER	Breast cancer
CANCER	Inherited colorectal cancer


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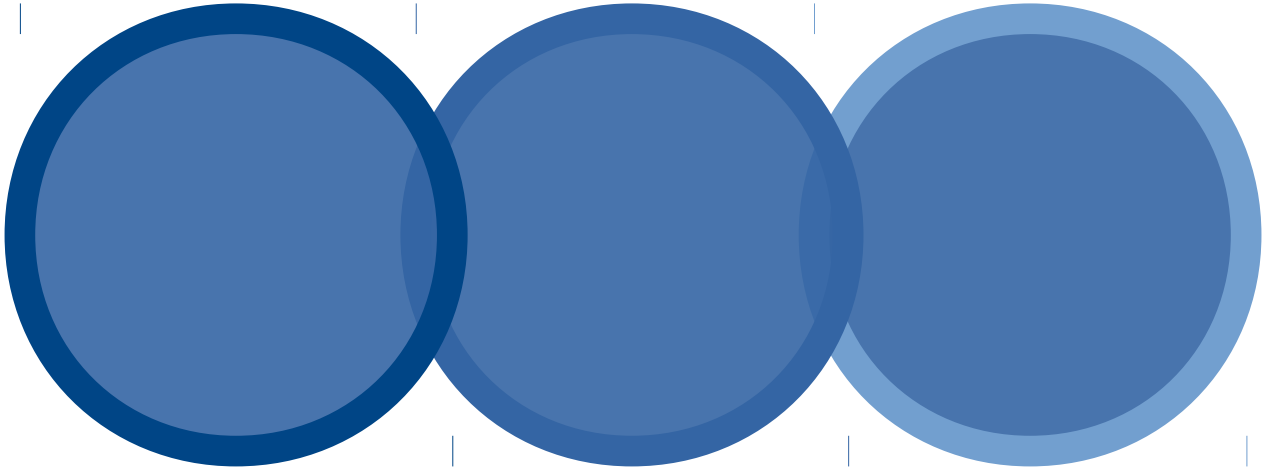


Ny genvariasjon knyttet til sykdom

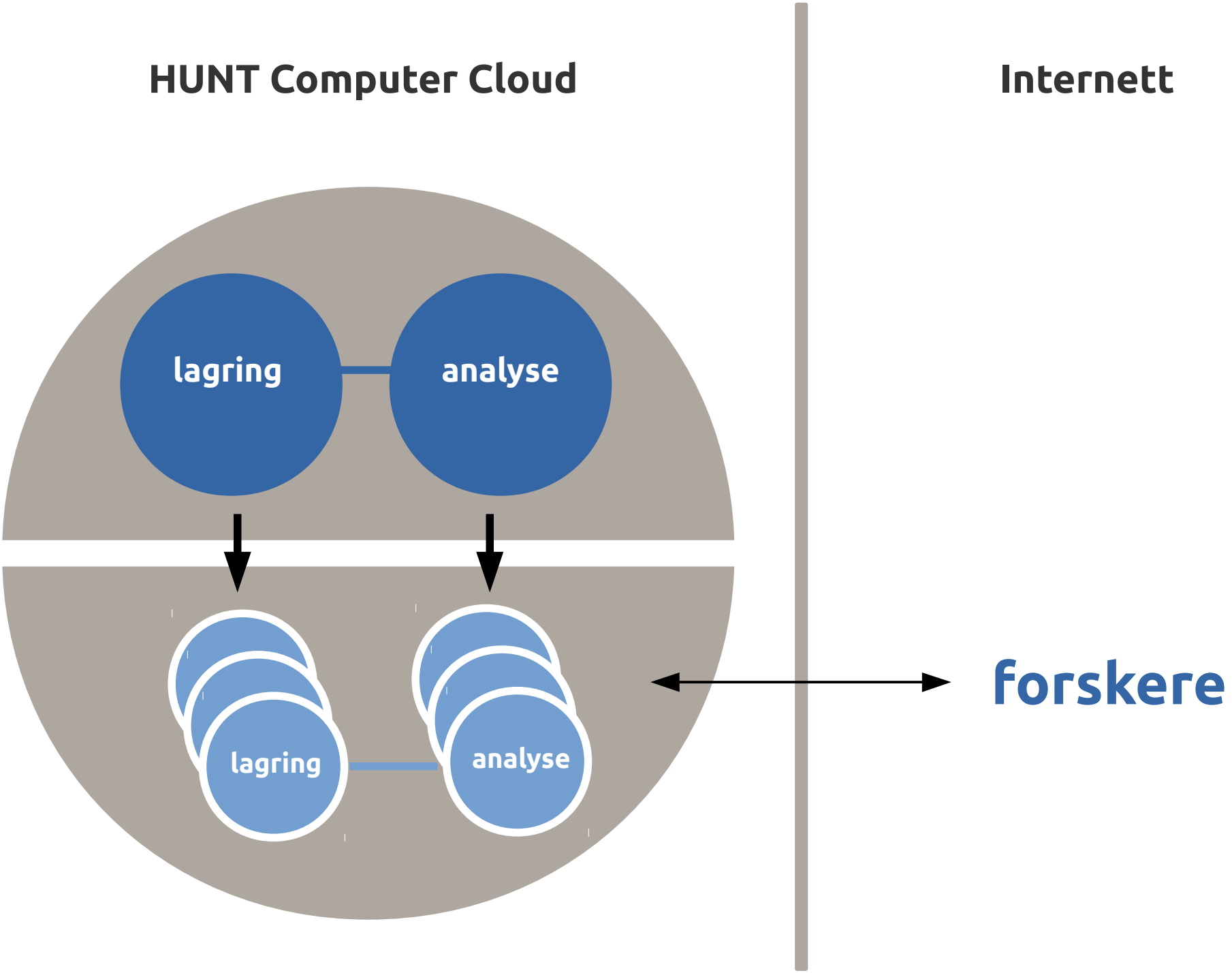
knock-out alleler

Utforske årsaks-sammenhenger

mendelisk-randomisering

Unike fenotyper og PhD utdanning

datakobling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