The panorama of ALS genomics

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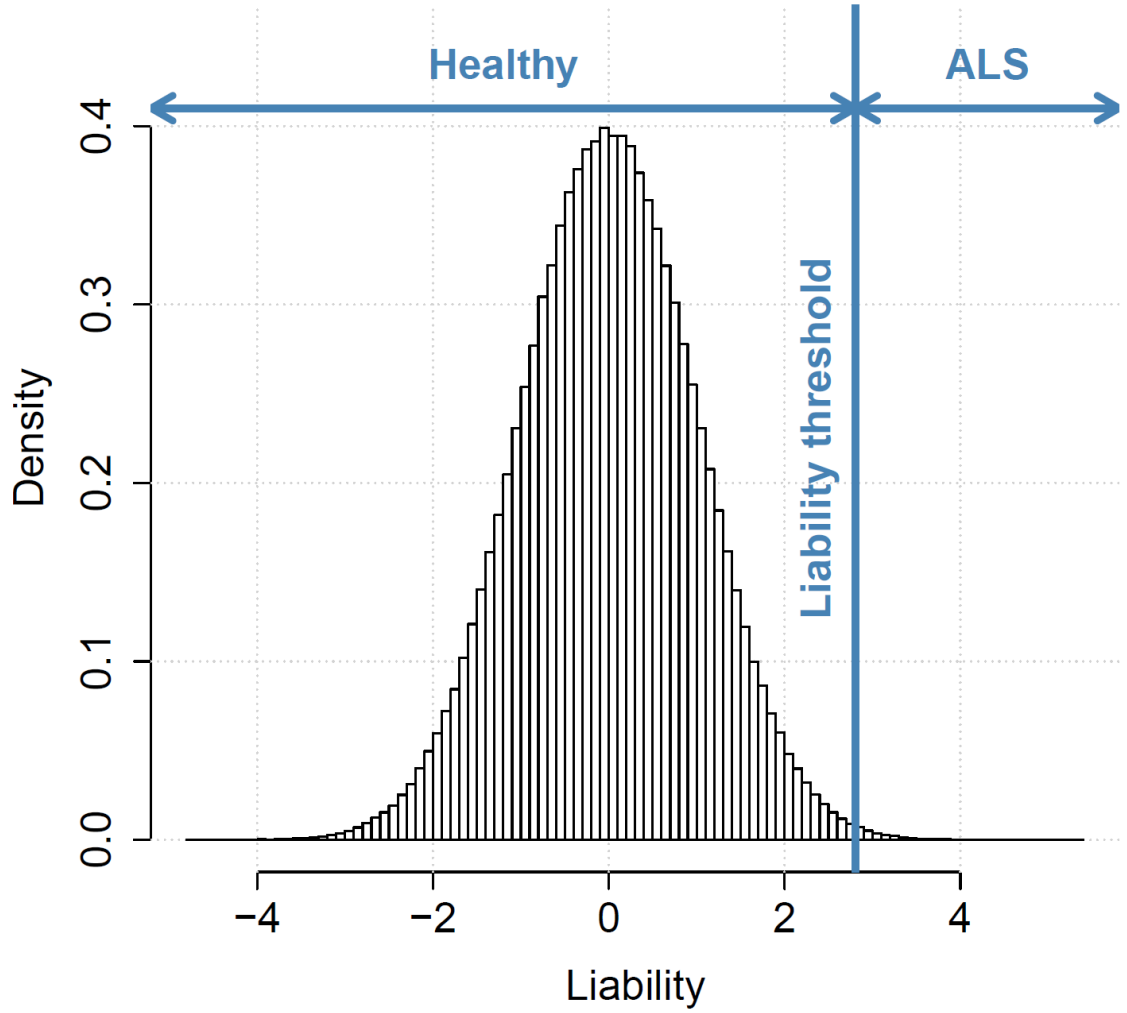
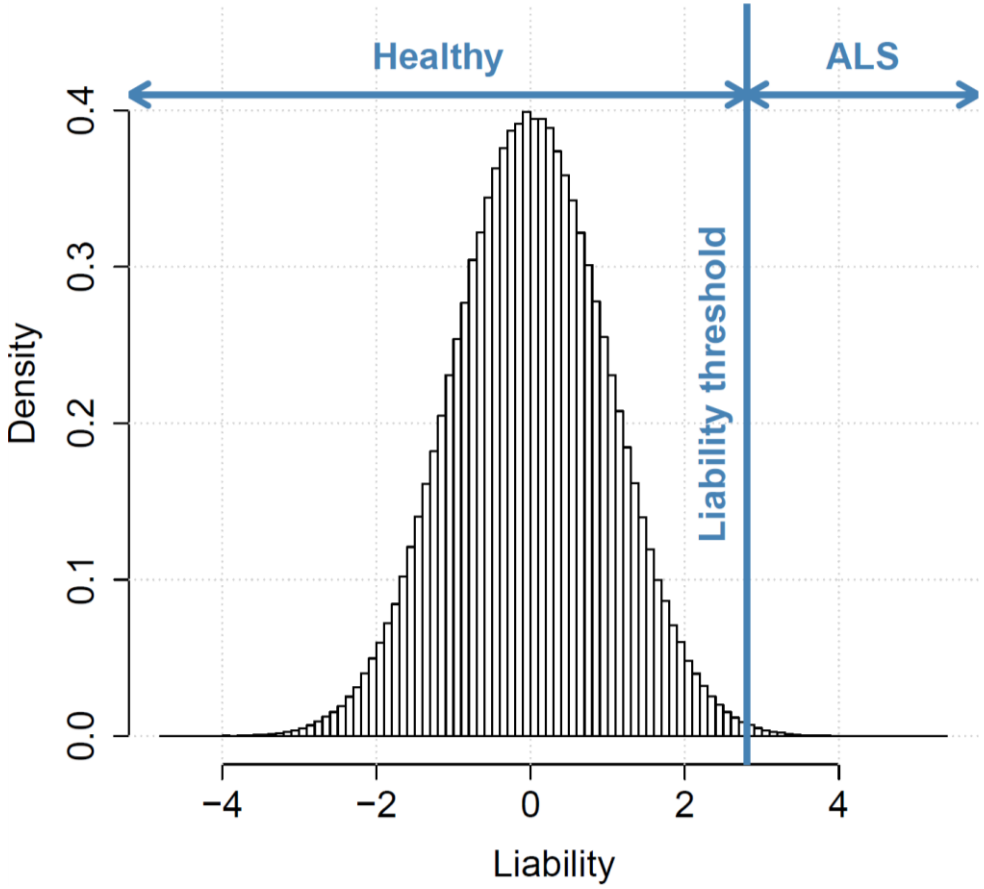
Is ALS genetic?

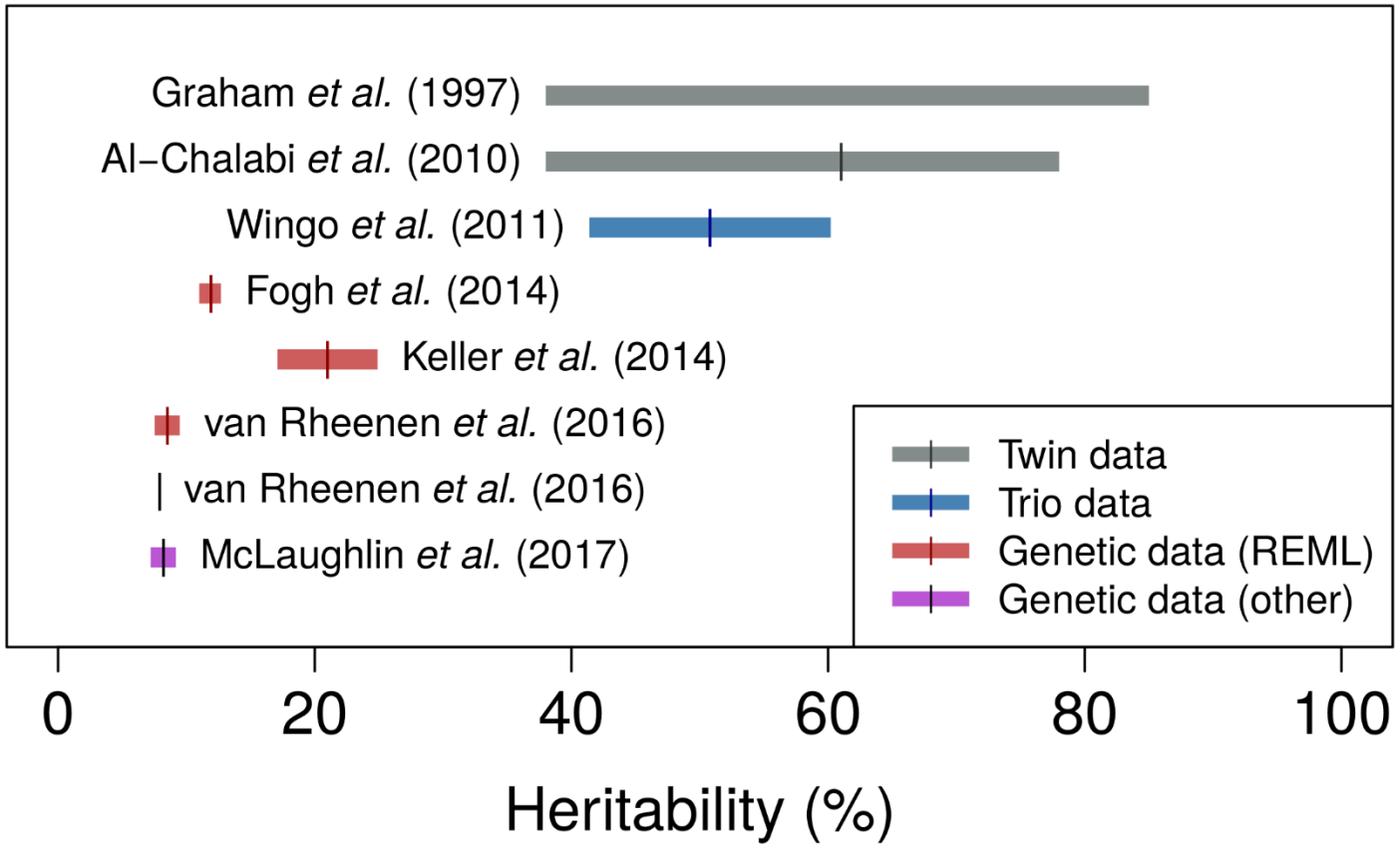
Liability to develop ALS - explain liability on this slide



Is ALS genetic?

Heritability: the proportion of variance in liability conferred by genetic variation



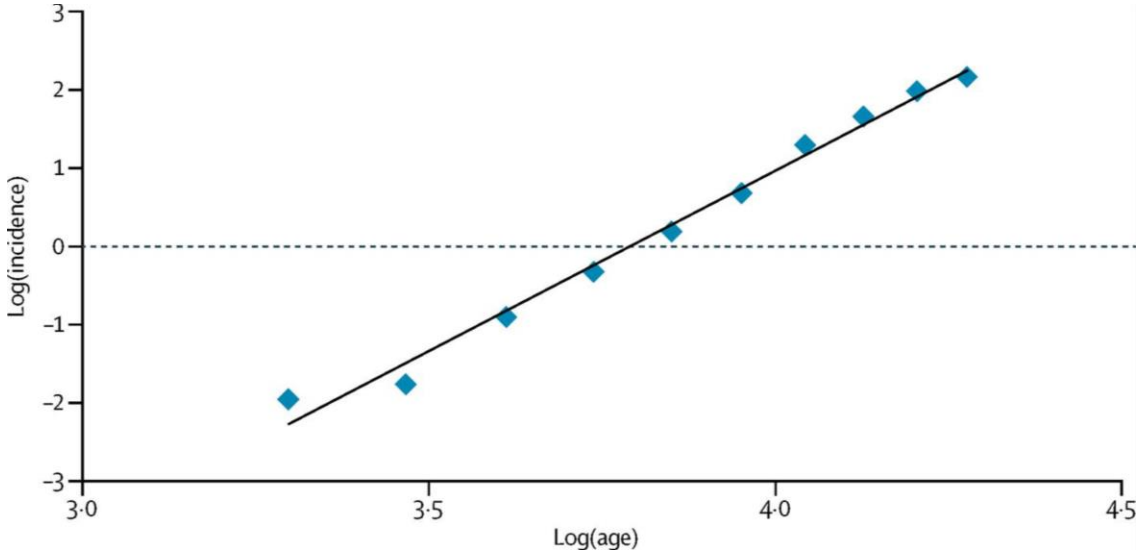


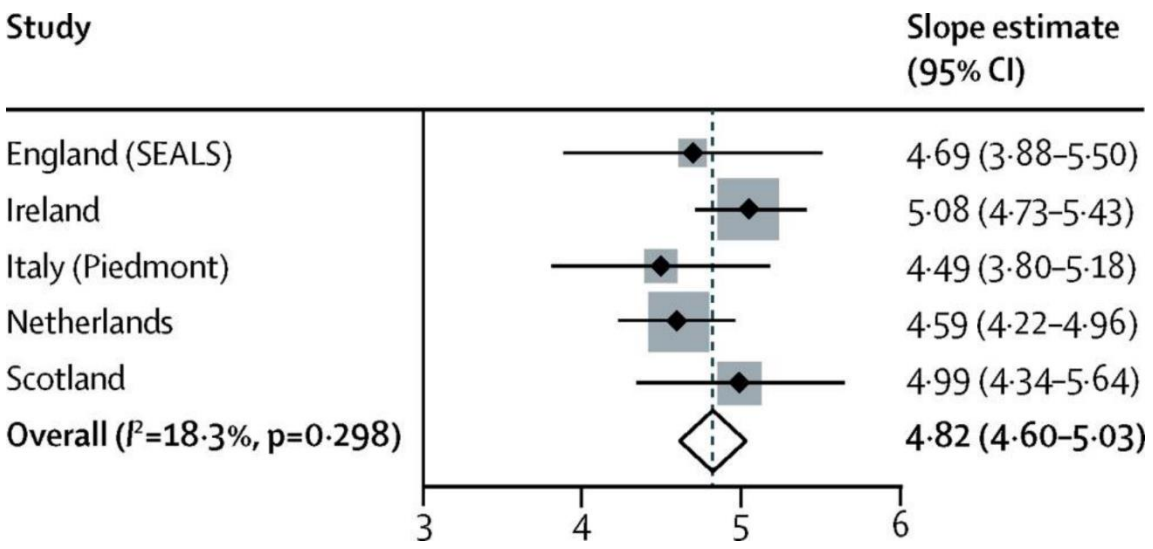
Non-genetic risk

Multiple lifetime steps/exposures are required to develop ALS

Age-specific incidence — Steps — Time (age)

$$\log i = (\boldsymbol{n} - 1)\log t + \log \prod_{i=1}^{n} u_n$$

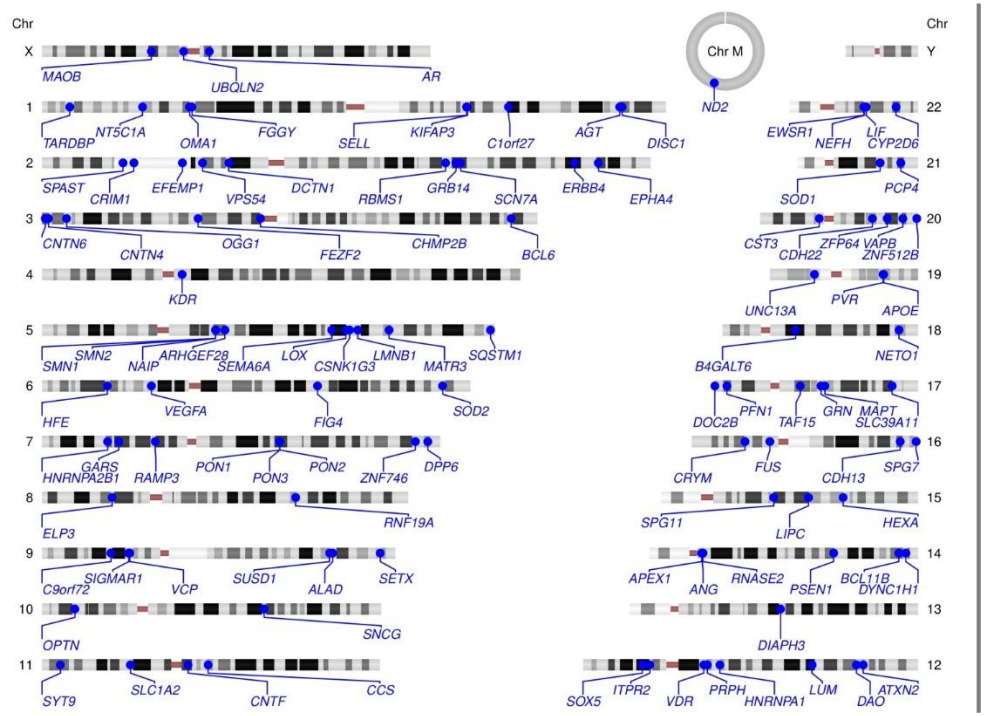




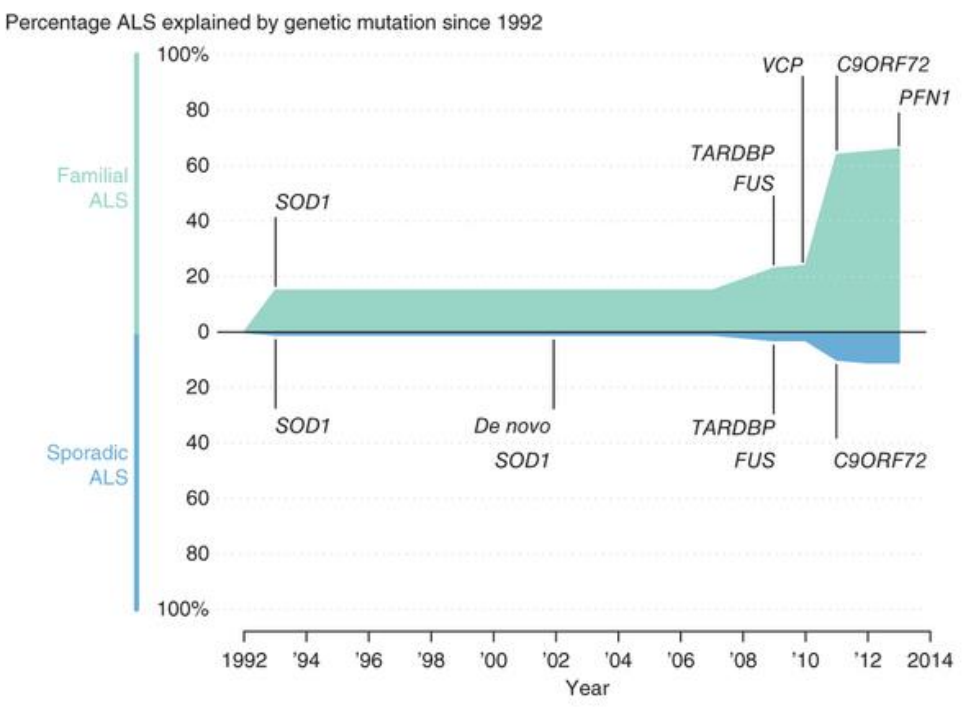
Al-Chalabi *et al.* (2014) *Lancet Neurol* 13(11):1108-1113

Genetics of ALS

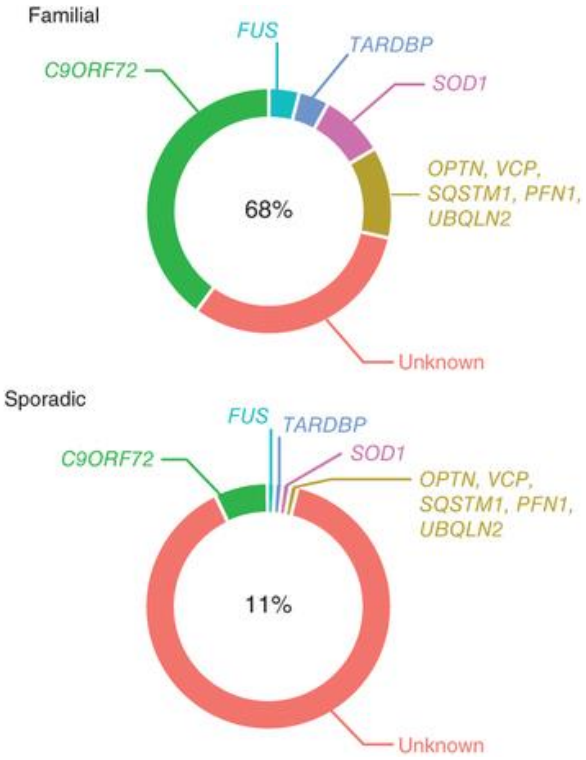
Genes that have been investigated in ALS



McLaughlin *et al.* (2015) In *Movement Disorder Genetics*, Springer



Renton *et al.* (2013) Nature Neuroscience 17:17-23



How do we discover new ALS genes?

Genome-wide association study (GWAS)

Person 1	... TCAGCCATGCTACT**C**GATCGACTAA**G**CG ...	(maternal)
	... TCAGCCATGCTACT**C**GATCGACTAATCG ...	(paternal)
Person 2	... TCAGCCATGCTACT**C**GATCGACTAA**G**CG ...	(maternal)
	... TCAGCCATGCTACT**T**GATCGACTAATCG ...	(paternal)
Person 3	... TCAGCCATGCTACT**T**GATCGACTAATCG ...	(maternal)
	... TCAGCCATGCTACT**T**GATCGACTAATCG ...	(paternal)

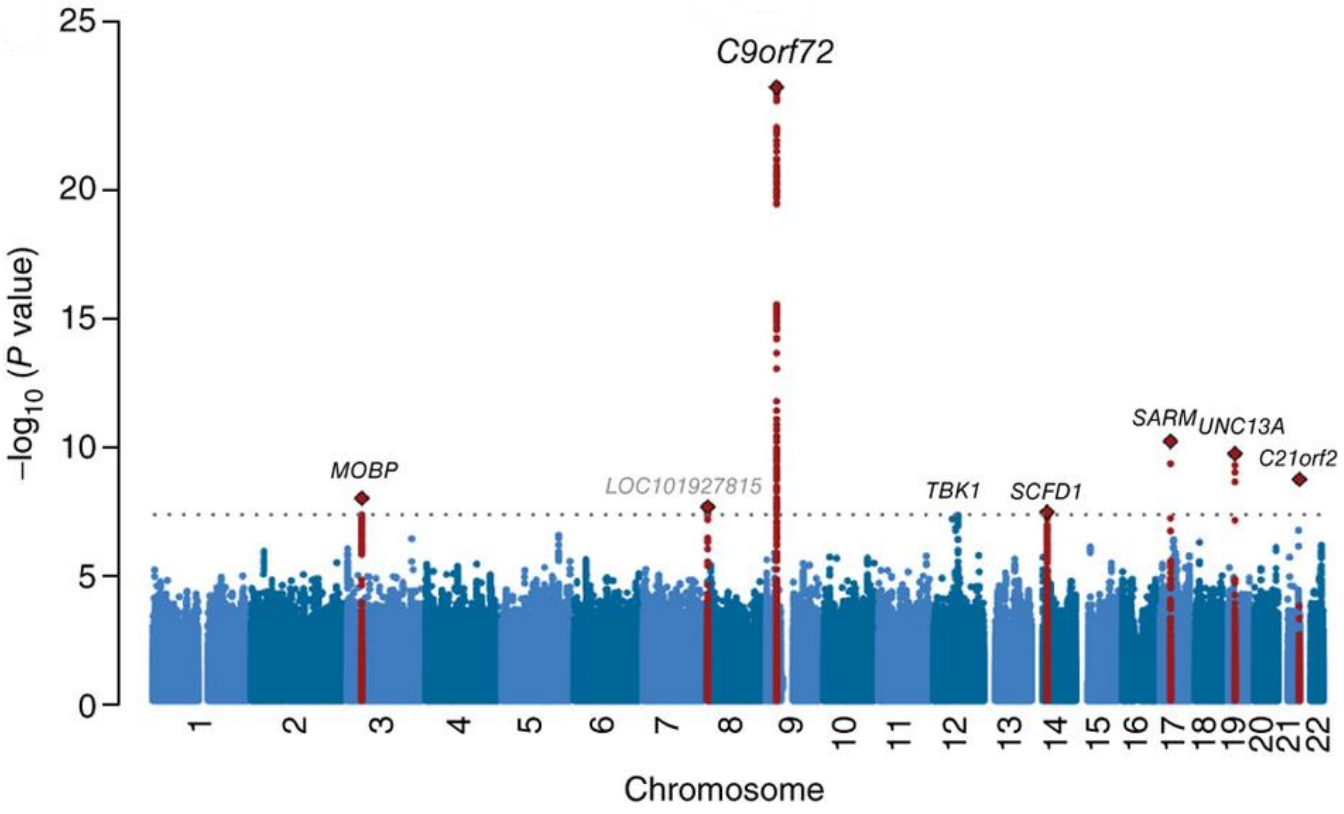
Single nucleotide polymorphism (SNP)

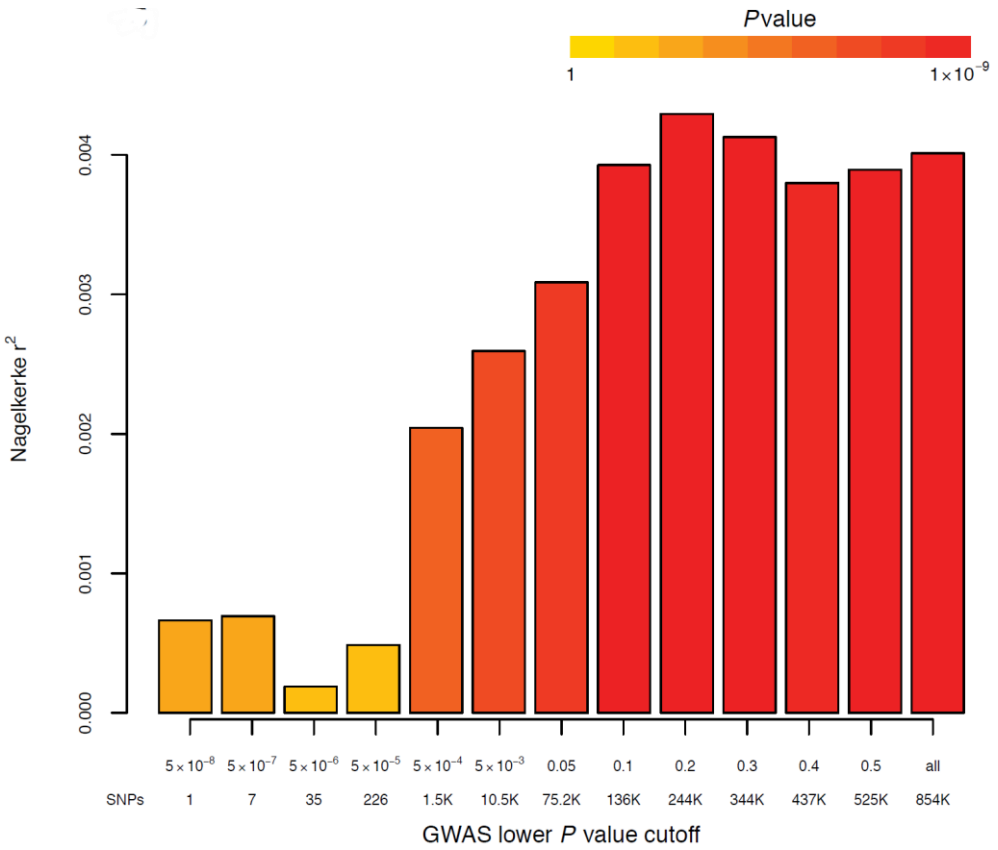
If only present in one individual, or if rare	If rare and observed in disease context	If common in the population
Variant or single nucleotide variant (SNV)	Mutation	Single nucleotide polymorphism (SNP)

SNP1	*SNP2*	*SNP…*
Cases Count of G: 2104 of 4000 Frequency of G: 52.6%	**Cases** Count of G: 1648 of 4000 Frequency of G: 41.2%	*Repeat for all SNPs*
Controls Count of G: 2676 of 6000 Frequency of G: 44.6%	**Controls** Count of G: 2532 of 6000 Frequency of G: 42.2%	
P-value: $5.0 \cdot 10^{-15}$	**P-value:** 0.33	

2016 ALS GWAS

13 countries; 12,577 ALS cases; 23,475 healthy controls





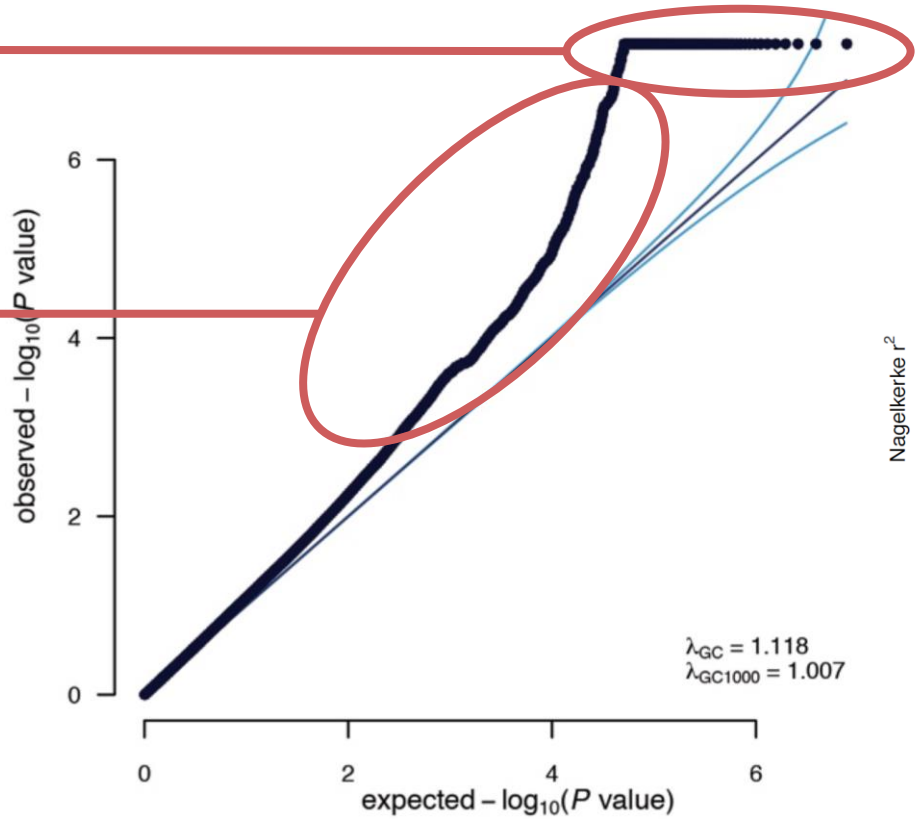
van Rheenen *et al.* (2016) *Nat Genet* 48(9):1043-8

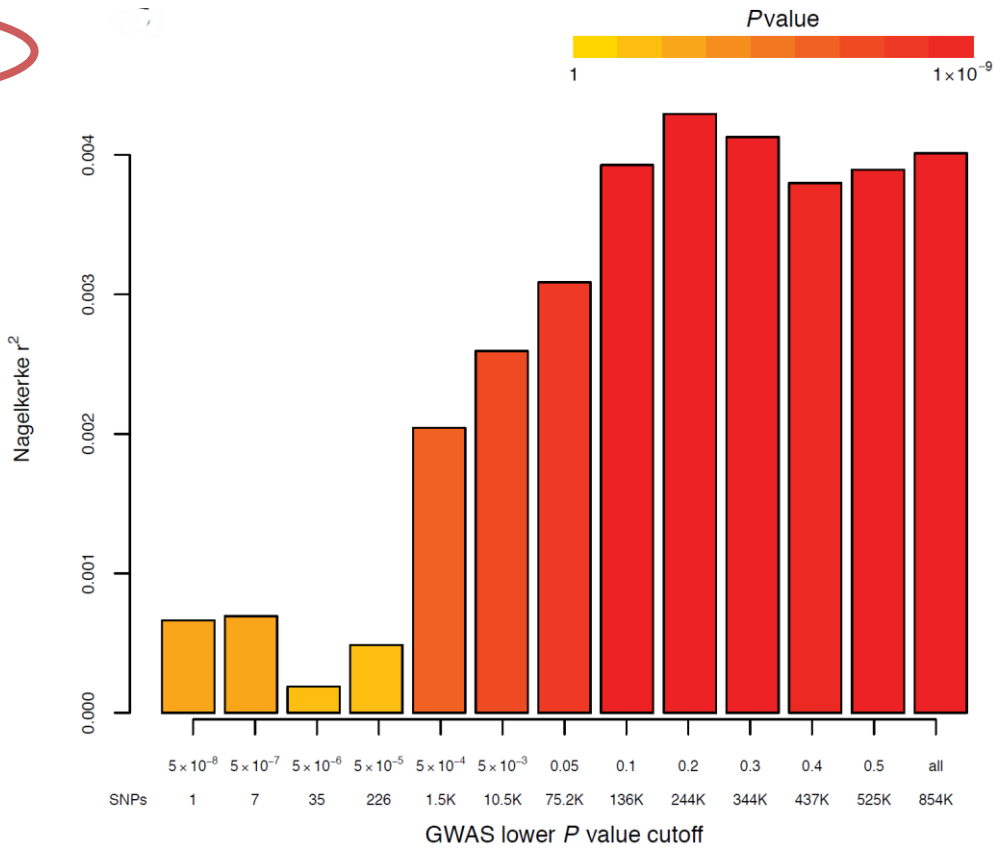
2016 ALS GWAS

13 countries; 12,577 ALS cases; 23,475 healthy controls

Significantly-associated SNPs
($p < 5 \times 10^{-8}$)

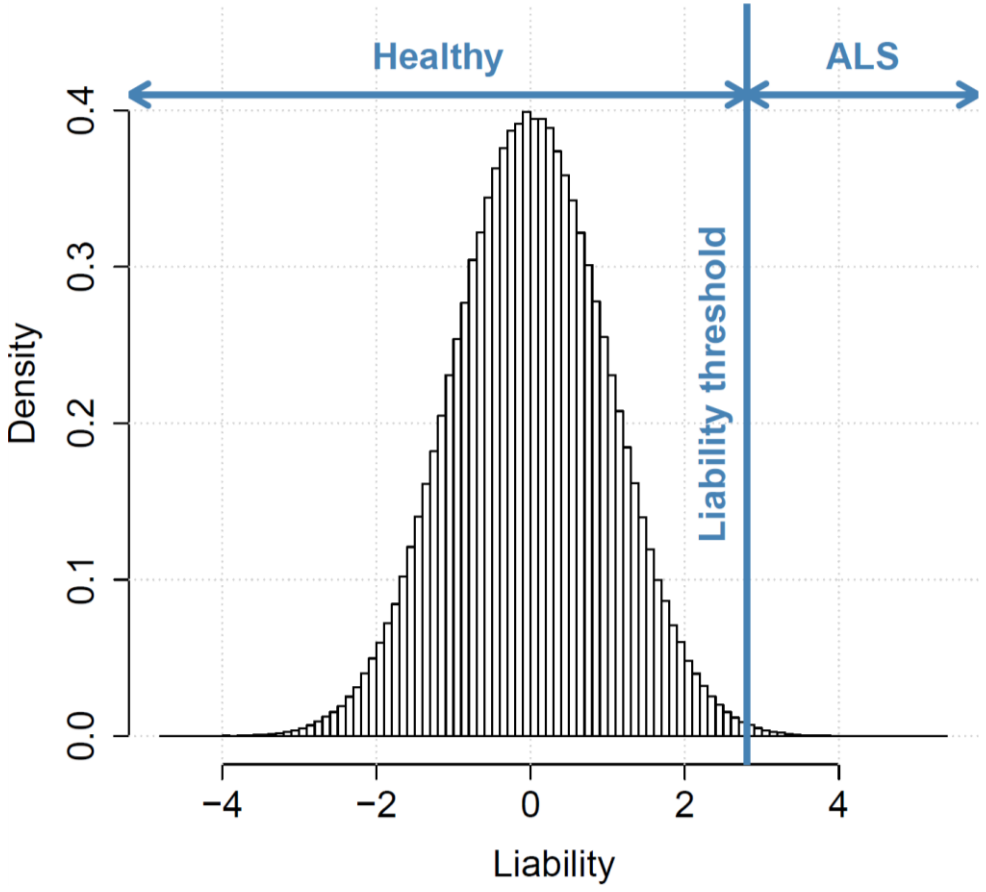
Sub-threshold SNPs
(more associated than they should be)

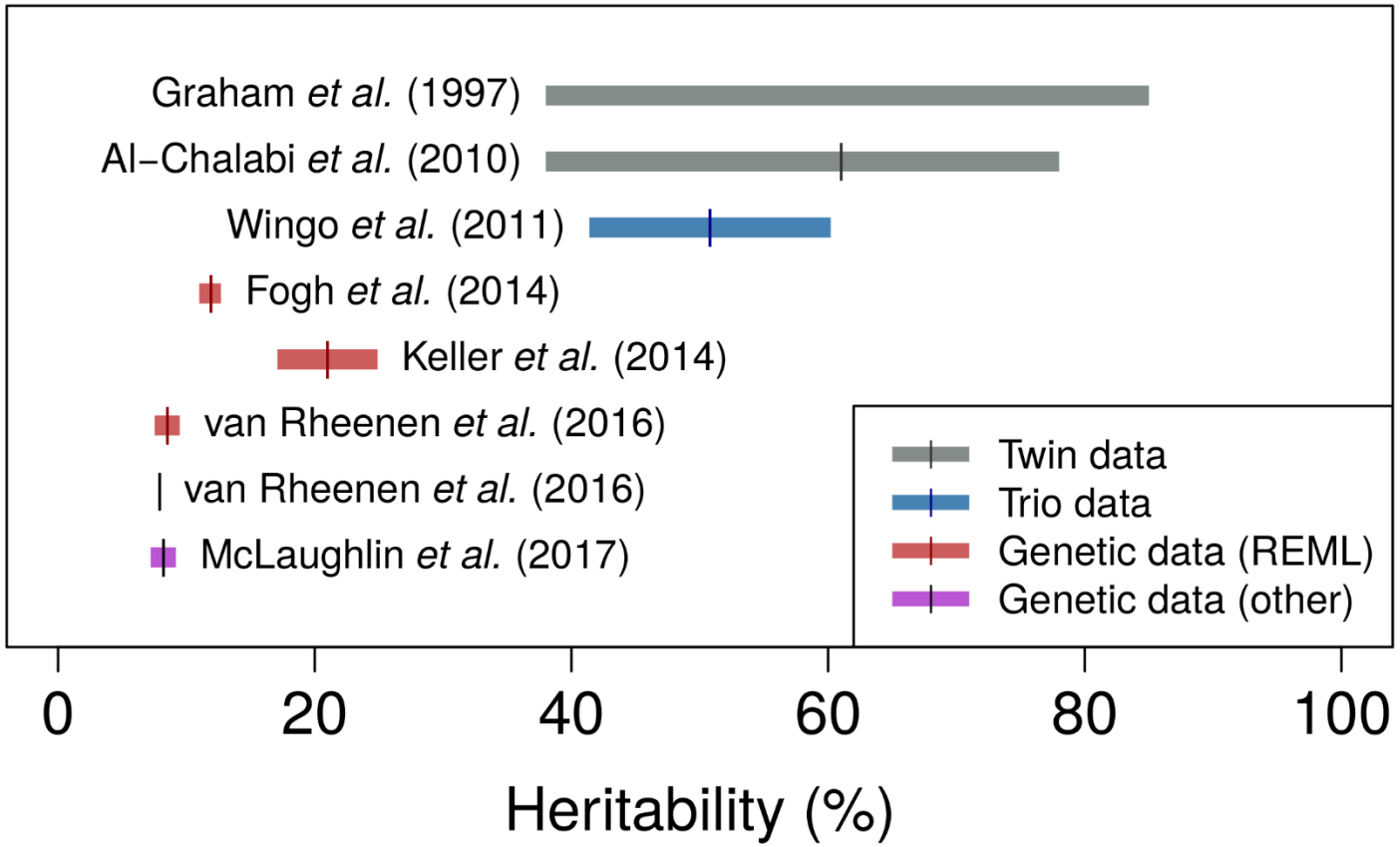




Heritability revisited

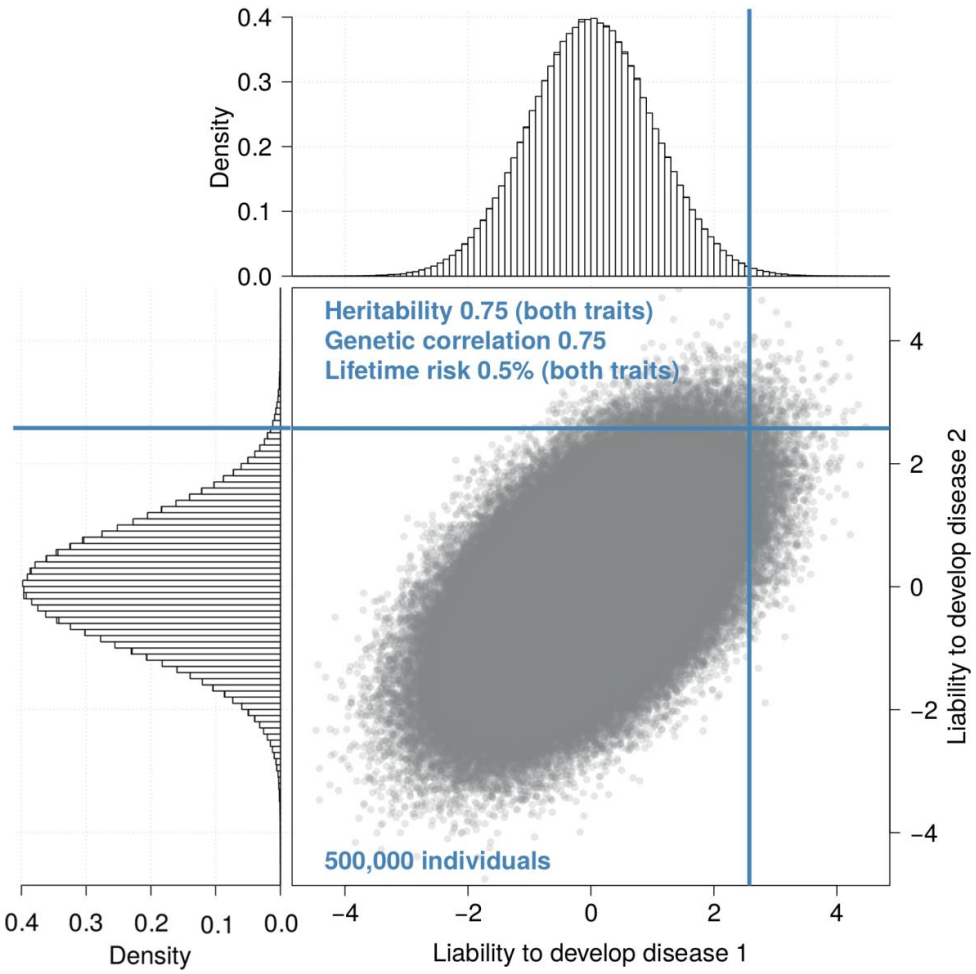
SNP-based heritability (polygenic risk)





Genetic correlation

Covariance between two traits due to shared genetic variation



ORIGINAL ARTICLE

Aggregation of Neurologic and Neuropsychiatric Disease in Amyotrophic Lateral Sclerosis Kindreds: A Population-Based Case–Control Cohort Study of Familial and Sporadic Amyotrophic Lateral Sclerosis

Susan Byrne, PhD,[1,2] Mark Heverin, MSc,[2] Marwa Elamin, PhD,[2] Peter Bede, MD,[1,2] Catherine Lynch, MSc,[1] Kevin Kenna, BSc,[3] Russell MacLaughlin, PhD,[1] Cathal Walsh, PhD,[4] Ammar Al Chalabi, PhD,[5] and Orla Hardiman, FRCPI[1,2]

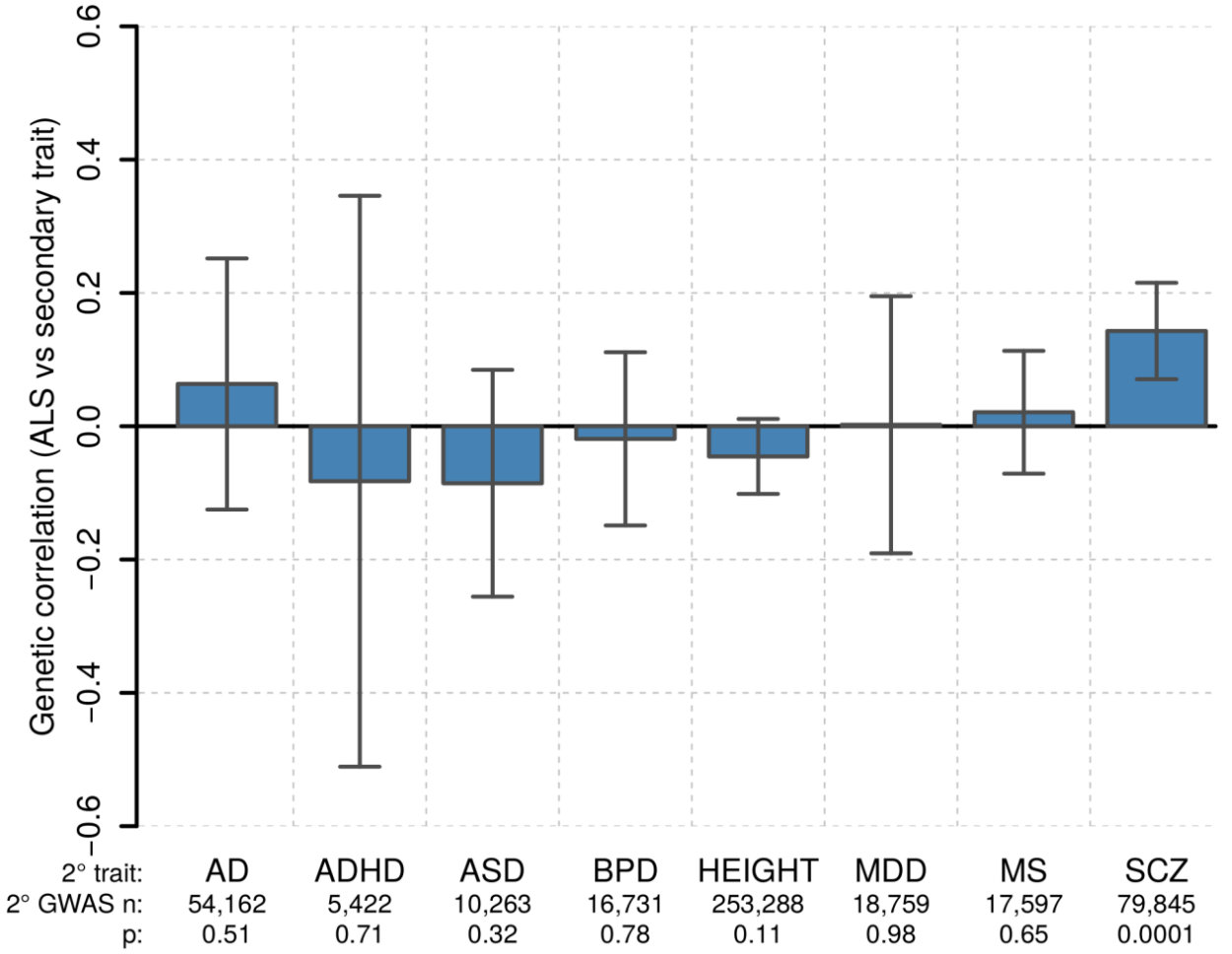
TABLE 5. Relatives of C9-Positive Cases and C9-Negative Cases Compared to Controls in a Cox Regression Proportional Model

Disease	Relatives	HR	95% CI	*p*
Parkinson disease	Relatives of C9-positive patients	1.3	0.5–3.7	0.570
	Relatives of C9-negative patients	0.7	0.4–1.1	0.126
Dementia	Relatives of C9-positive patients	1.6	1.1–2.4	0.017[a]
	Relatives of C9-negative patients	1.2	0.9–1.4	0.100
Depression	Relatives of C9-positive patients	3.3	1.6–7.0	0.002[a]
	Relatives of C9-negative patients	0.6	0.3–1.1	0.075
Schizophrenia/psychotic illness	Relatives of C9-positive patients	9.9	4.8–20.5	<0.0001[a]
	Relatives of C9-negative patients	3.9	2.4–6.5	<0.0001[a]
Suicide	Relatives of C9-positive patients	16.6	5.6–49.4	<0.0001[a]
	Relatives of C9-negative patients	5.1	2.2–12.1	<0.0001[a]

[a]Statistically significant.
CI = confidence interval; HR = hazard ratio.

ALS and schizophrenia are genetically correlated

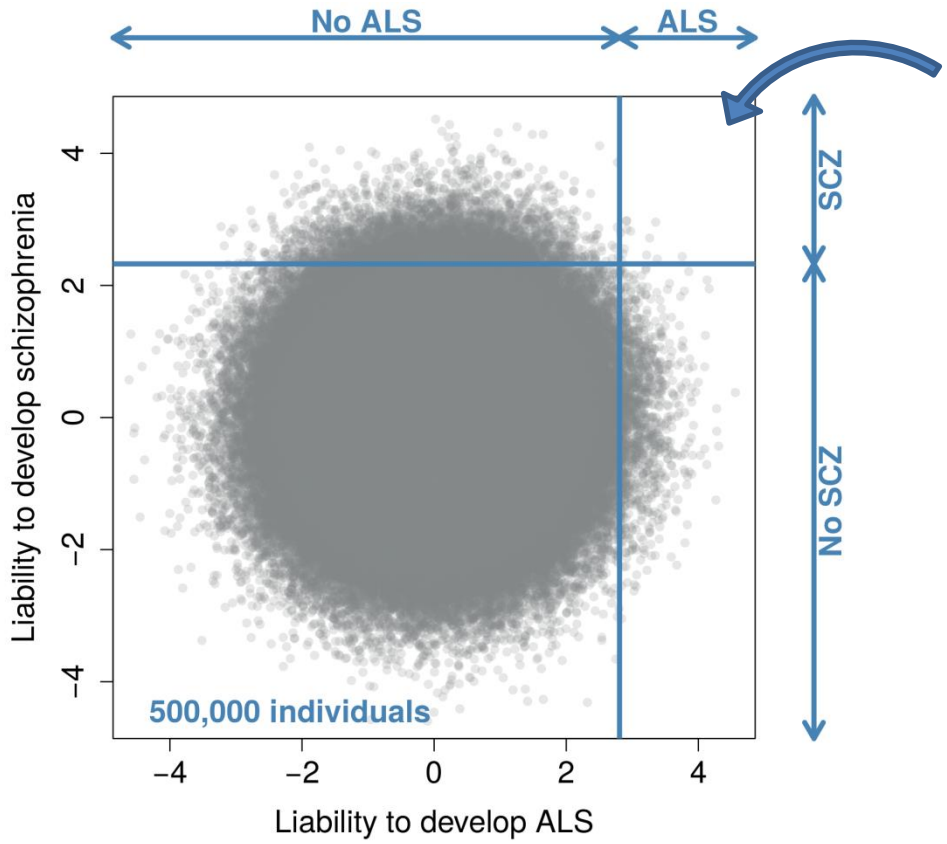
Genetic correlation of 14.3% refers to polygenic components of both diseases



McLaughlin, Schijven *et al.* (2017) *Nat Commun* 8:14774

ALS and schizophrenia are genetically correlated

Implications



Individuals who develop both ALS and schizophrenia

Null expectation
1 in 40,000

With observed genetic correlation
1 in 34,337

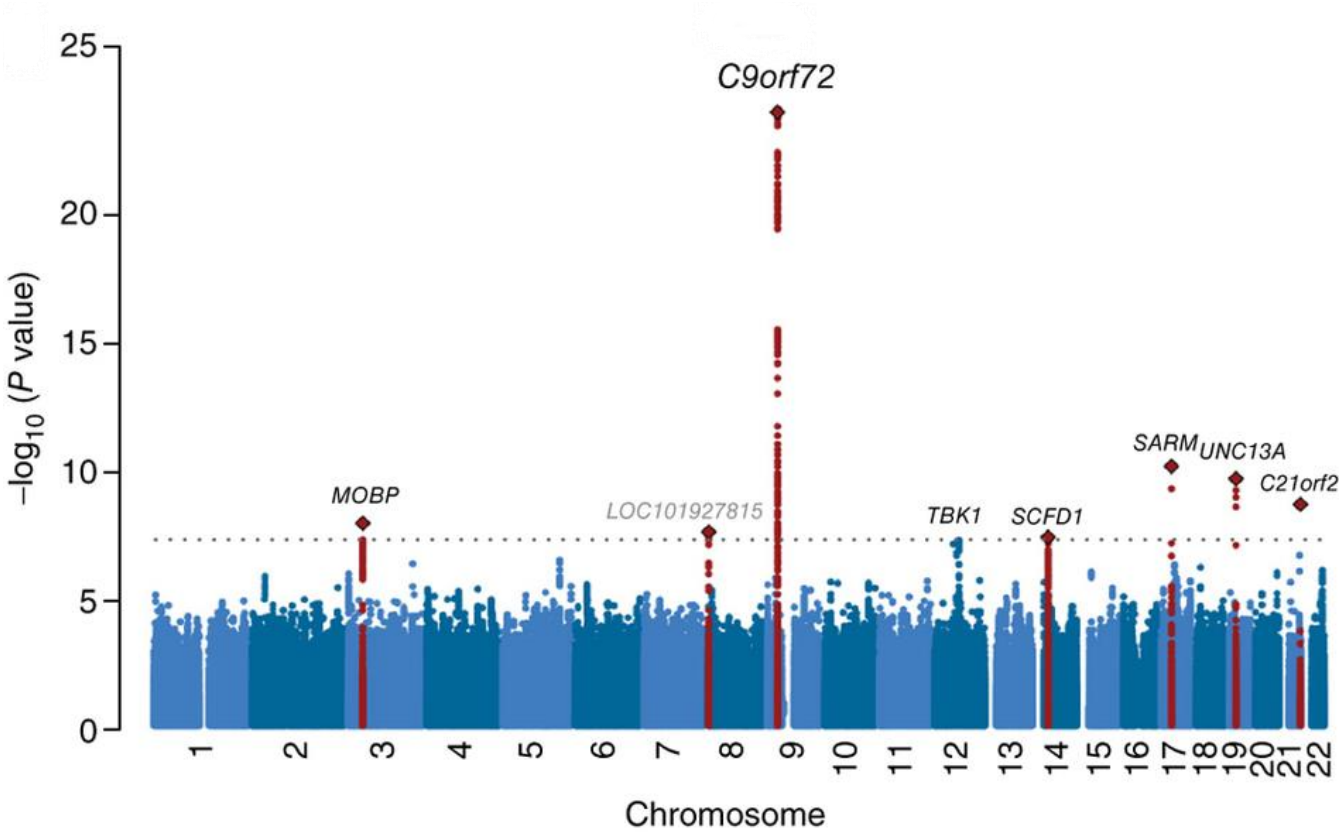
ALS register size required for 80% power to detect this difference: **16,448**

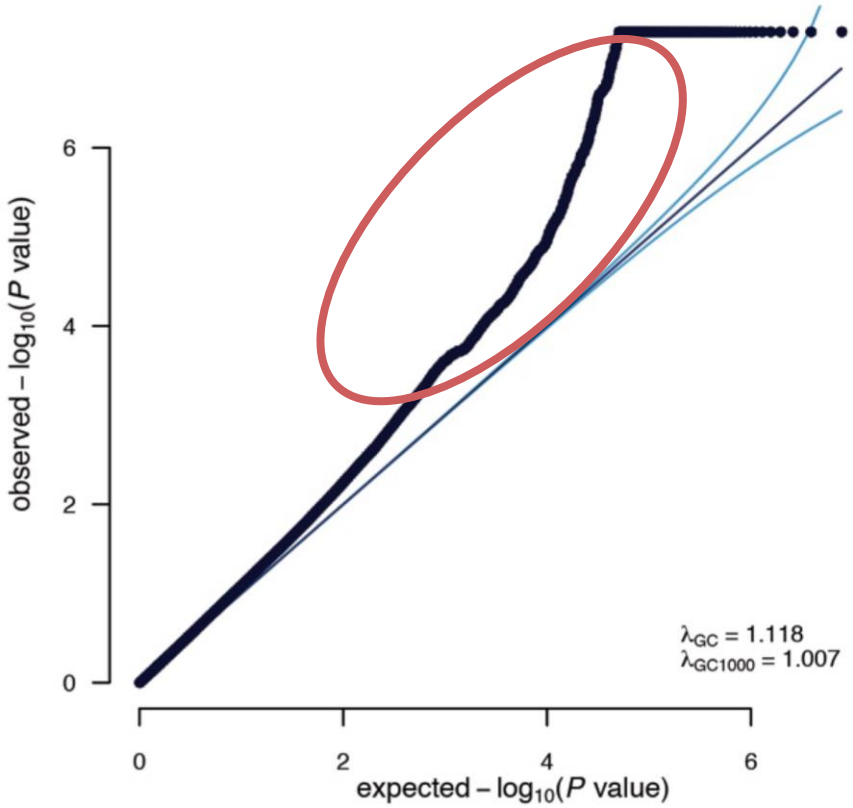
Odds ratio for developing ALS given schizophrenia (or *vice versa*): **1.17**

GWAS in ALS

General conclusions and further considerations

1. Bigger GWAS will discover more disease loci

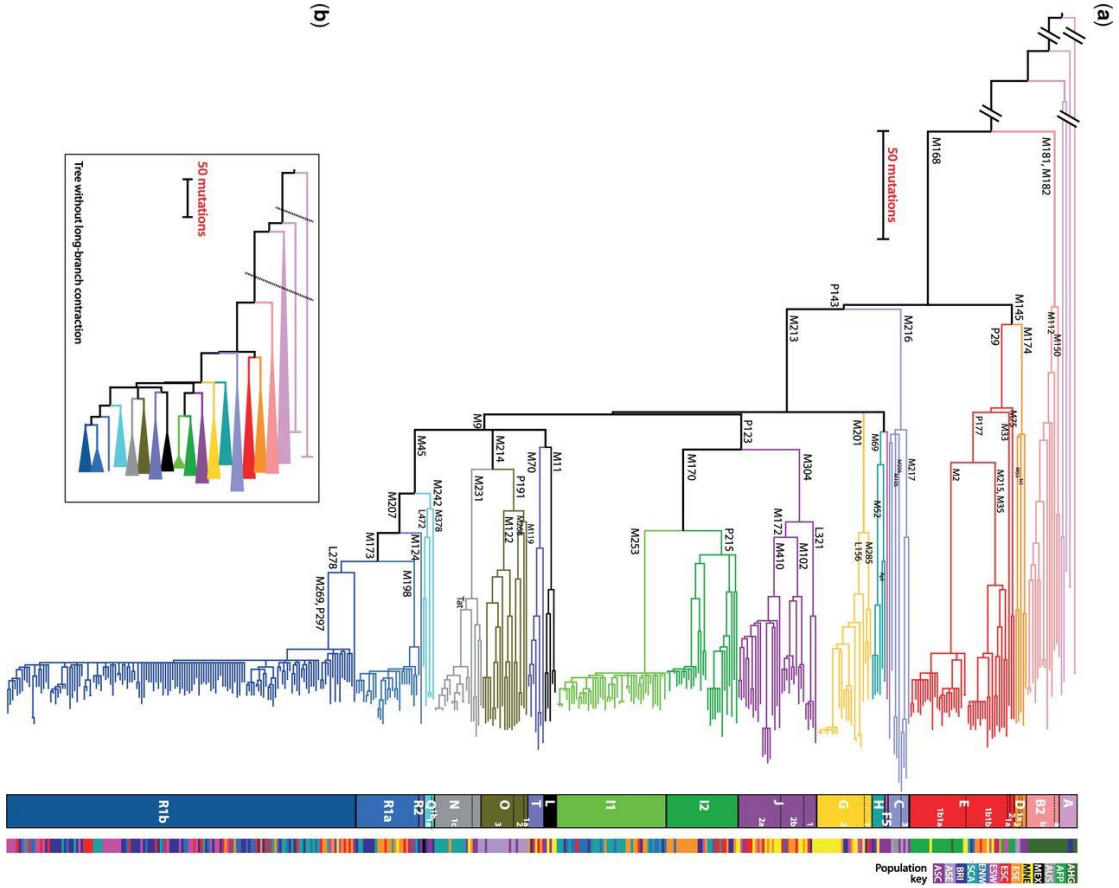




GWAS in ALS

General conclusions and further considerations

2. Involving more countries will answer deeper questions



GWAS in ALS

General conclusions and further considerations

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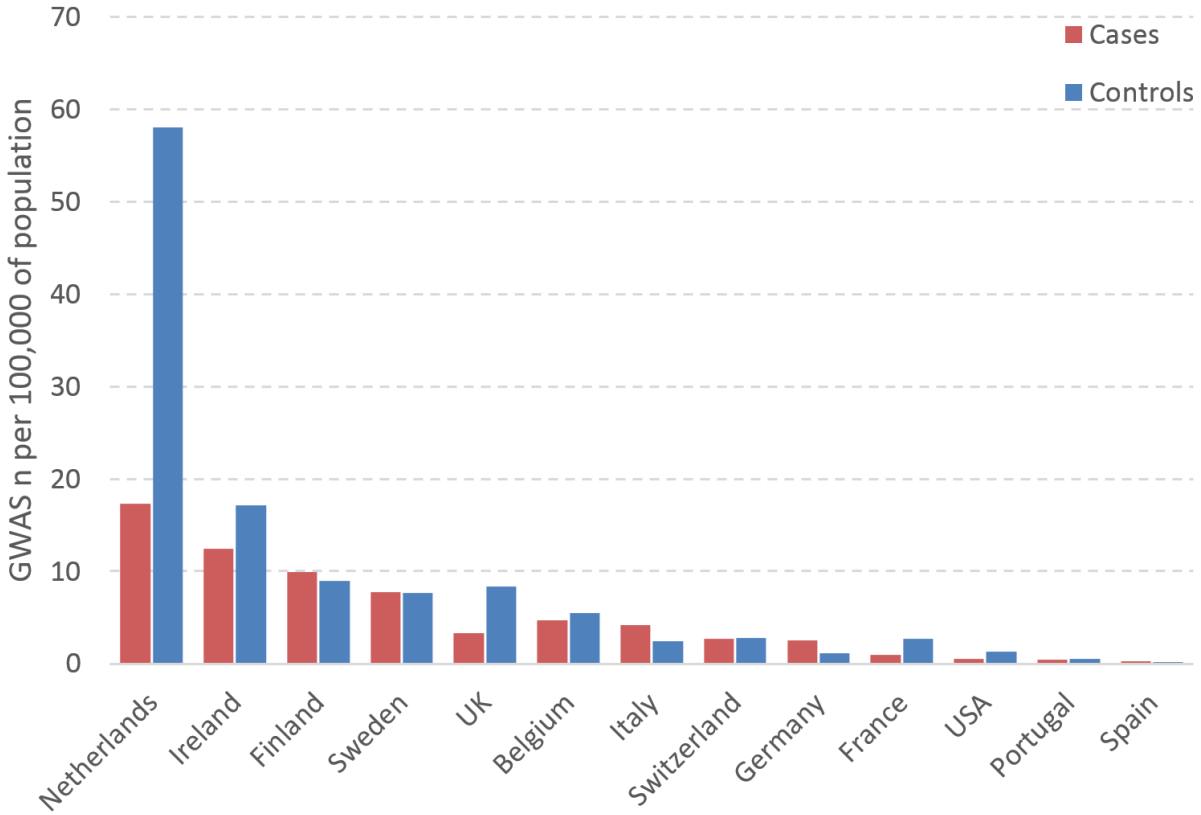
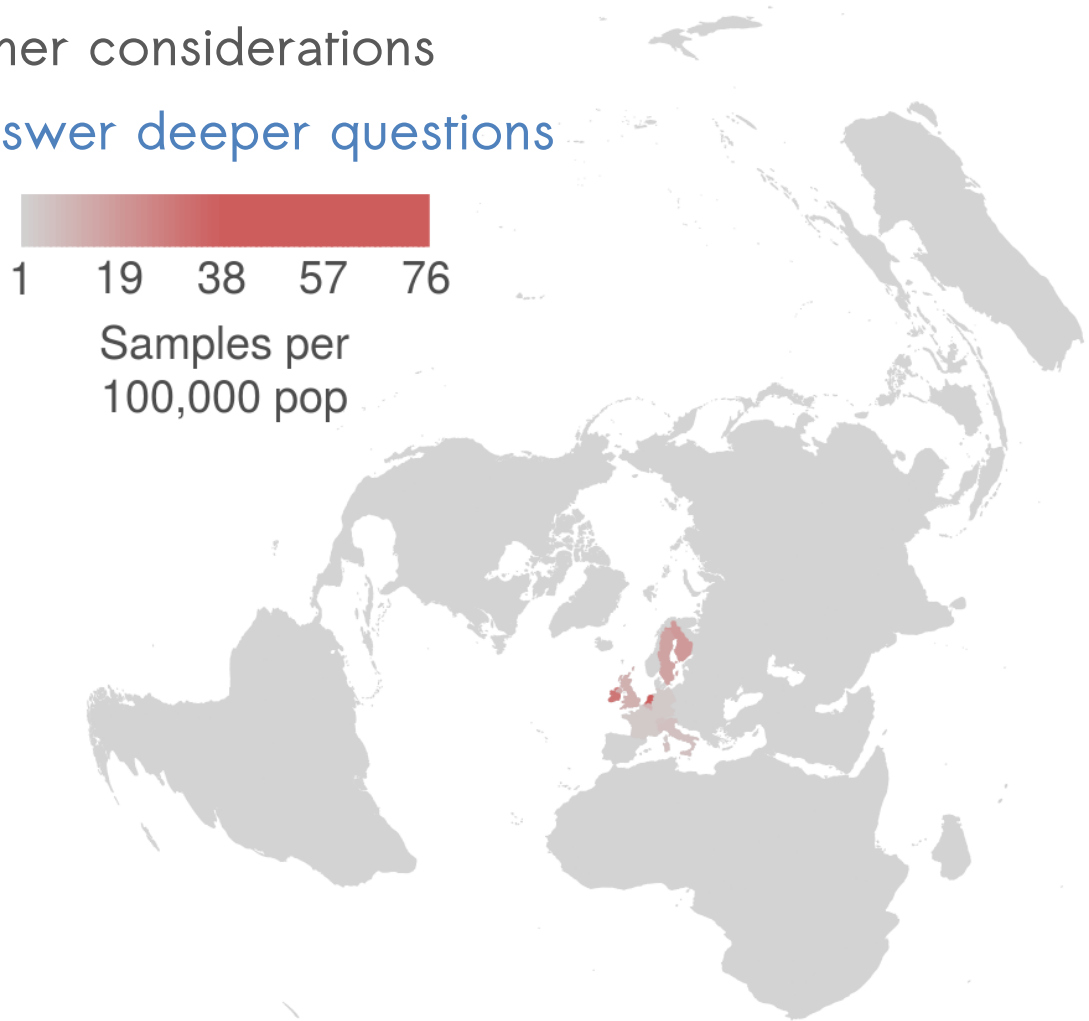
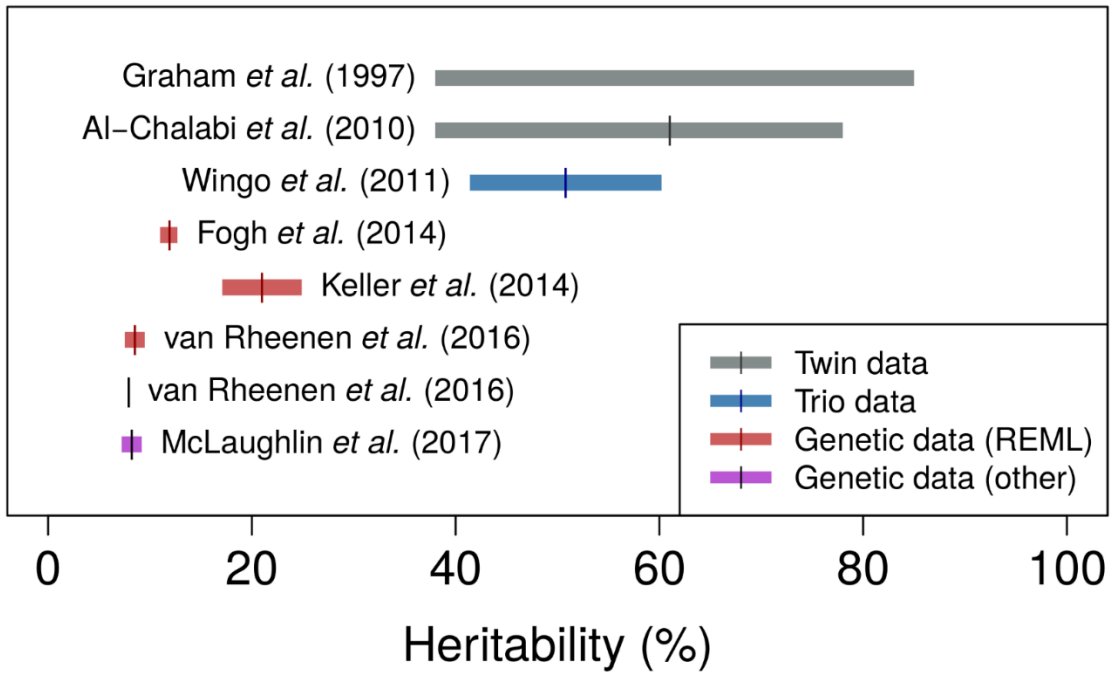


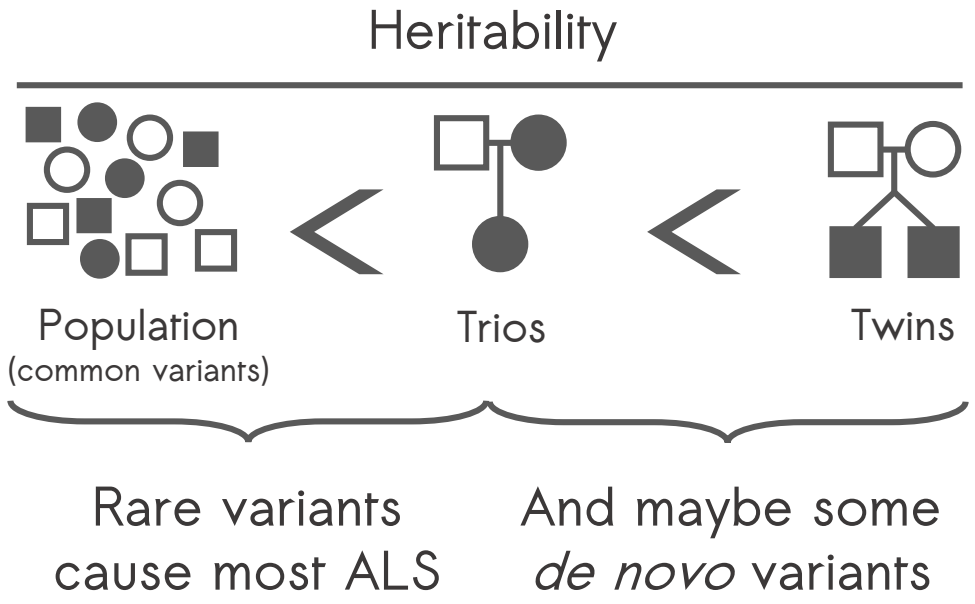


GWAS in ALS

General conclusions and further considerations

3. GWAS has helped us to better understand the genetic architecture of ALS





Finding rare variants

Exome sequencing

Previous approach: SNP chips (GWAS)

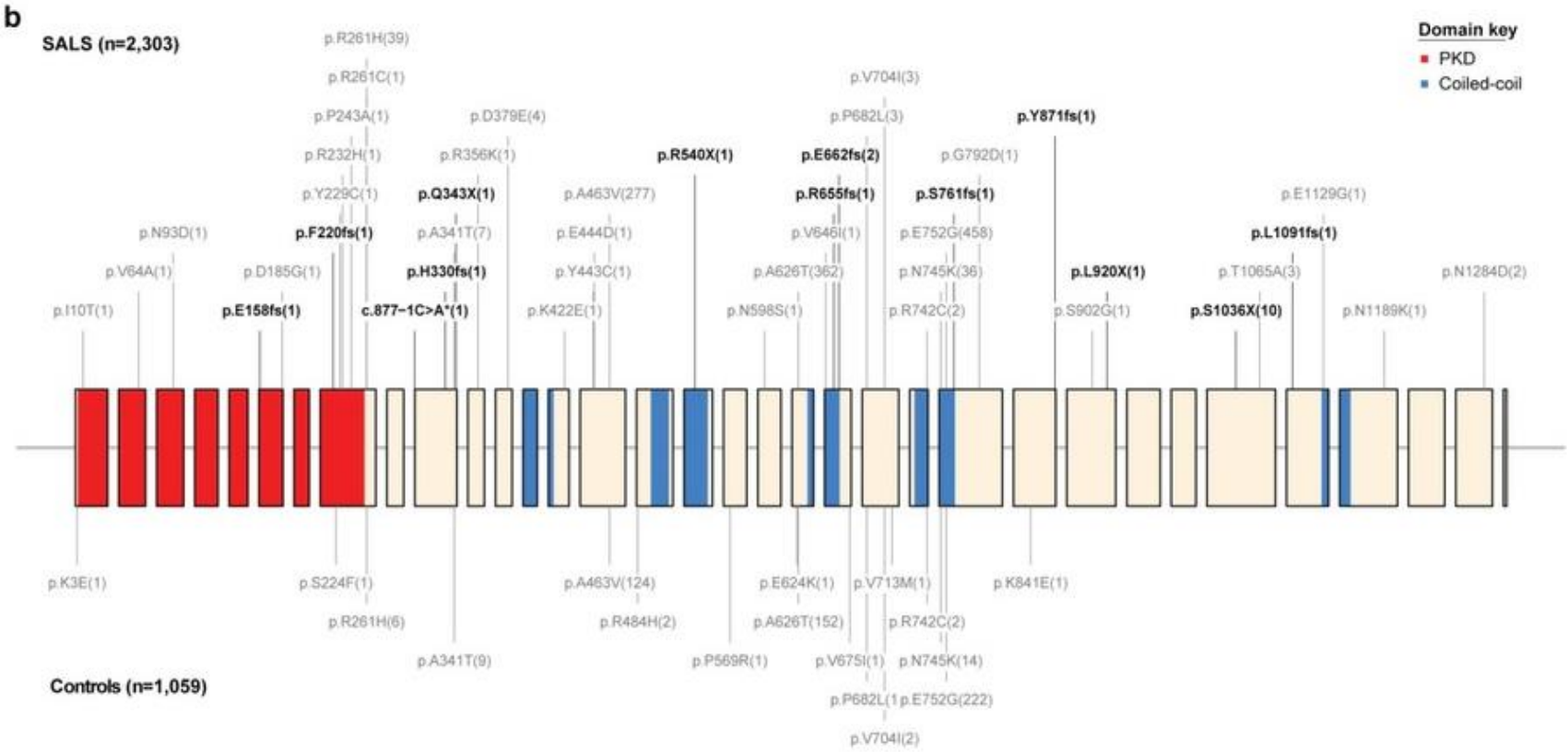
```
                    exon                      intron
-----------|||||||||||||||||||||||||||||||||-------------------- < gene exons/introns
CTGCTAGCTAGTCTATCGTGCTAGCTAGCTAGCTAGCTAGCGCGTATCGATGAGTCAGCCGTAG < reference genome
 ... ... ... C ... ... ... ... ... ... ... ... A ... ... ... ... < paternal chromosome
 ... ... ... T ... ... ... ... ... ... ... ... A ... ... ... ... < maternal chromosome
```

New approach: exome sequencing

```
-----------||||||||||||||||||||||||||||||||--------------------- < gene exons/introns
CTGCTAGCTAGTCTATCGTGCTAGCTAGCTAGCTAGCTAGCGCGTATCGATGAGTCAGCCGTAG < reference genome
 ... ... ..TCCATCGTGCTAGCTAGCTAGCTAGCTAGCGC. ... ... ... ... ... < paternal chromosome
 ... ... ..TCTATCGTGCTAGCTAGTTAGCTAGCTAGCGC. ... ... ... ... ... < maternal chromosome
```

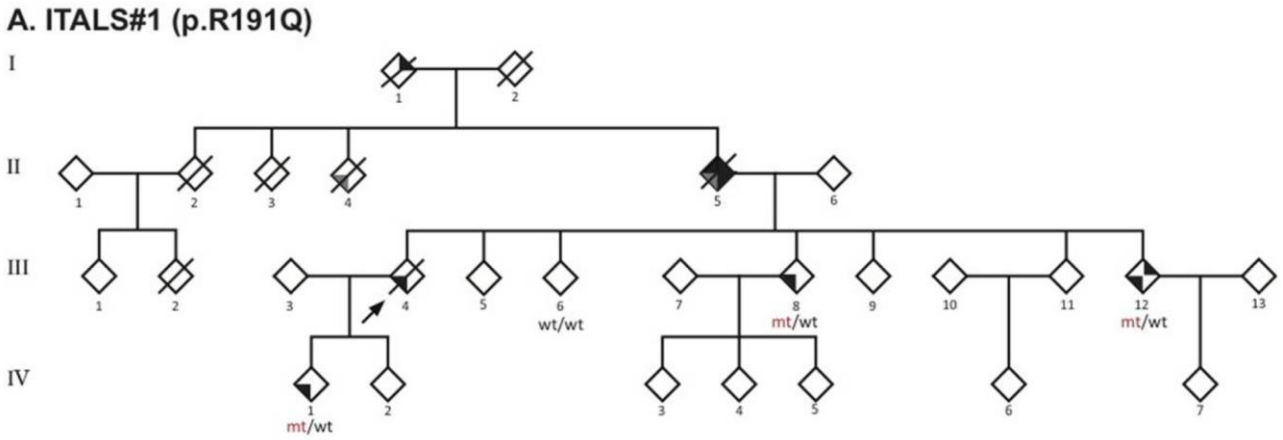
Implicating rare variants

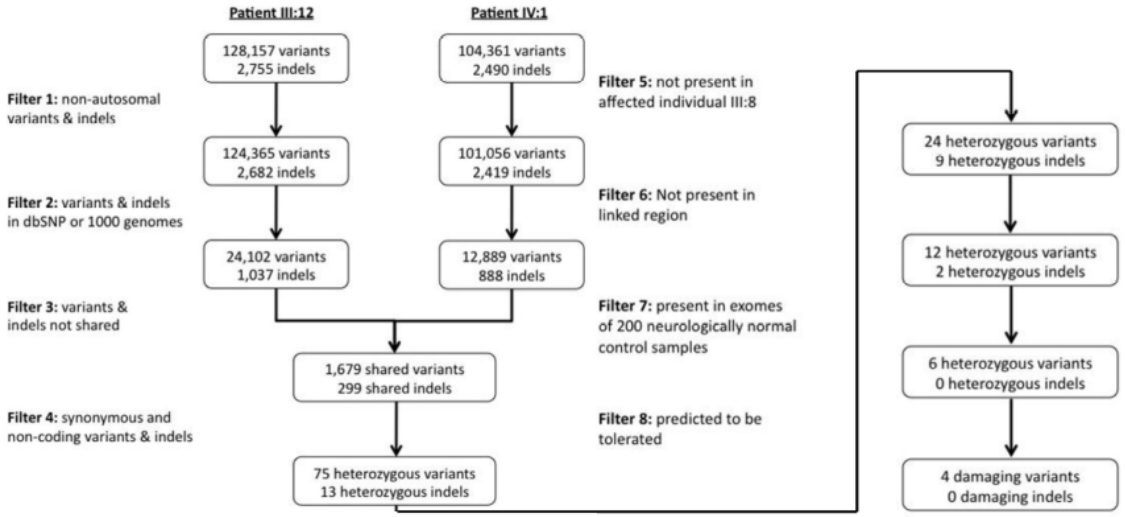
Assessing significance by burden testing



Implicating rare variants

Exome sequencing with pedigrees

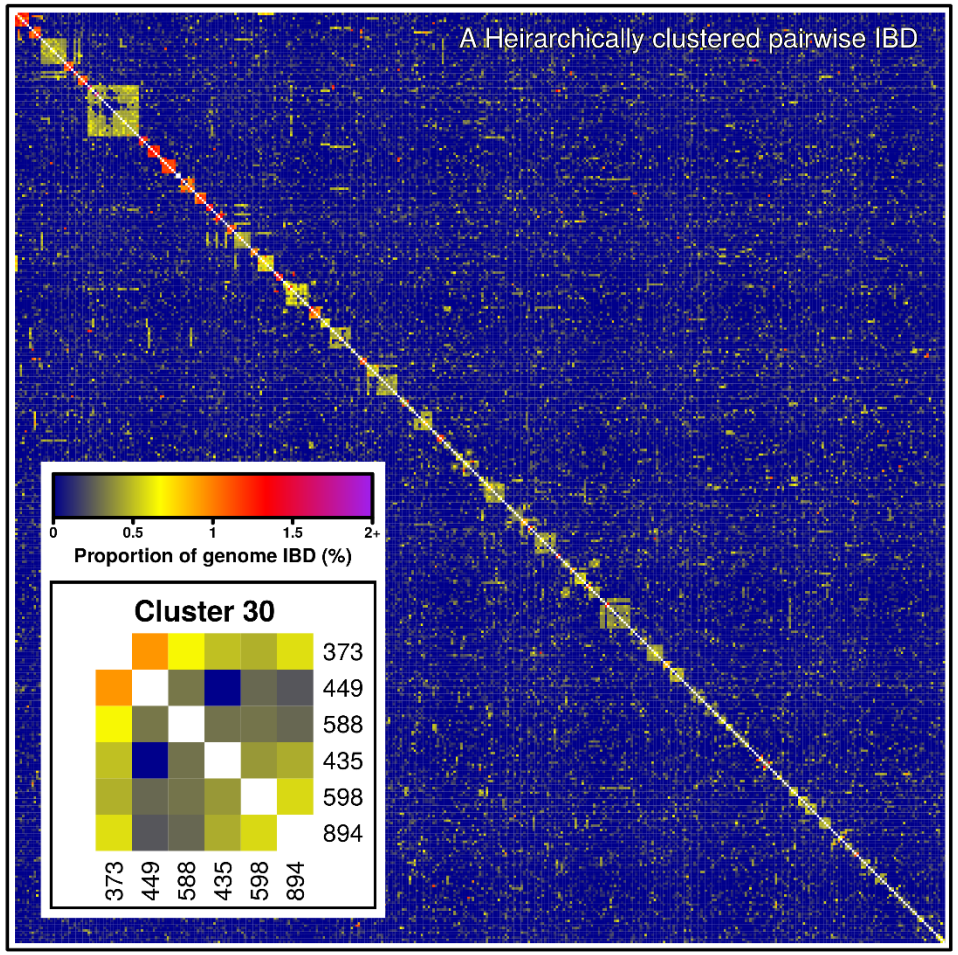


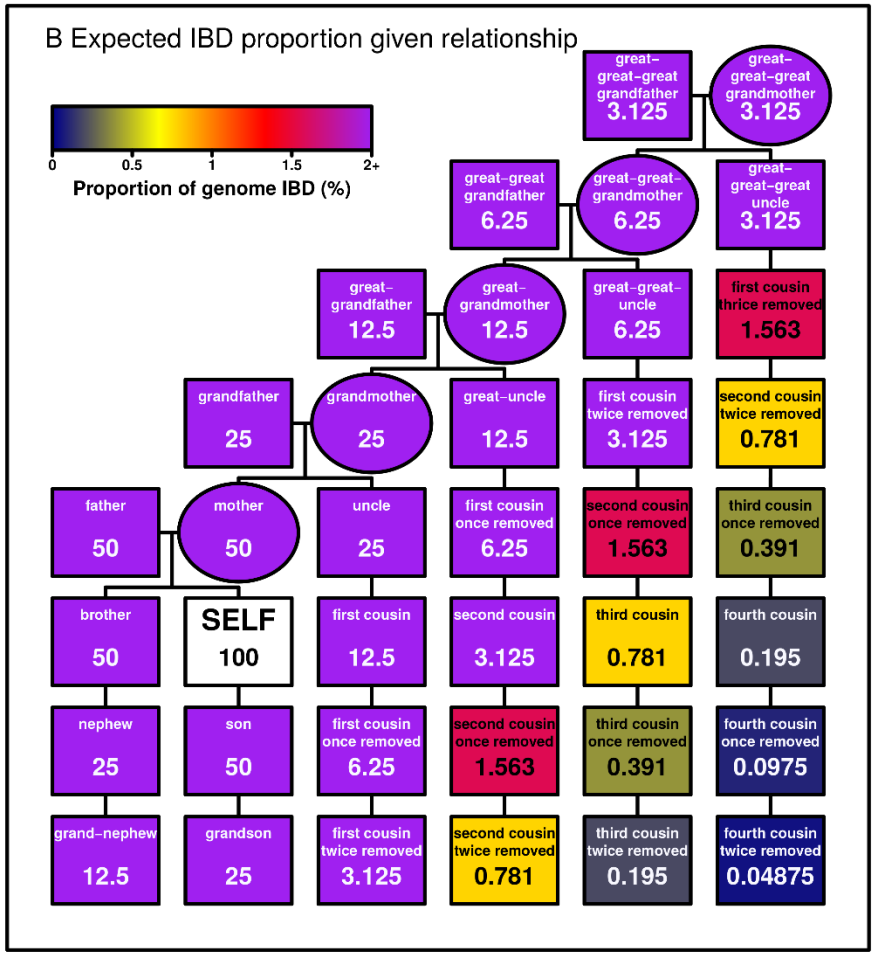


Johnson *et al.* (2010) Neuron 68(5):857-64

Implicating rare variants

Pseudofamily analysis (IBD = *identity by descent*, ie relatedness)





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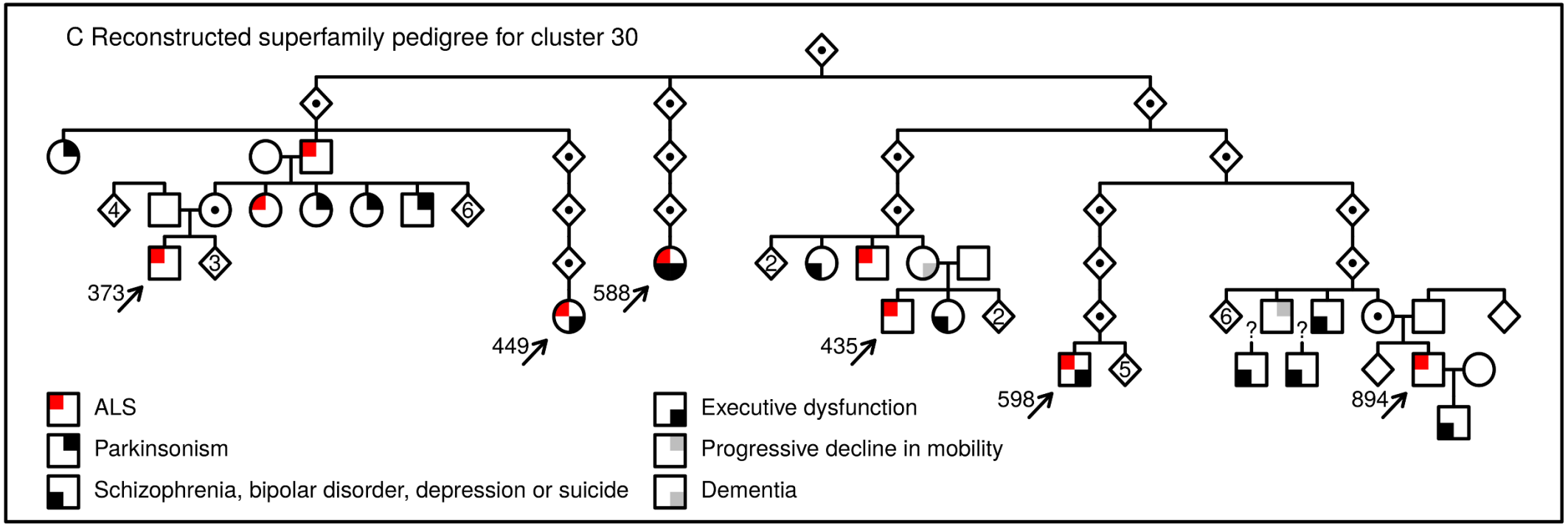


Exome sequencing in ALS

Genes discovered using exome sequencing

NEK1 variants confer susceptibility t
lateral sclerosis

Exome-wide Rare Variant Anal
TUBA4A Mutations Associated

LETTER

Mutations in the profilin 1
amyotrophic lateral scleros

Neuron
Report

Exome Sequencing Reveals *VCP* M
as a Cause of Familial ALS

RESEARCH ARTICLE | AMYOTROPHIC LATERAL SCLEROSIS

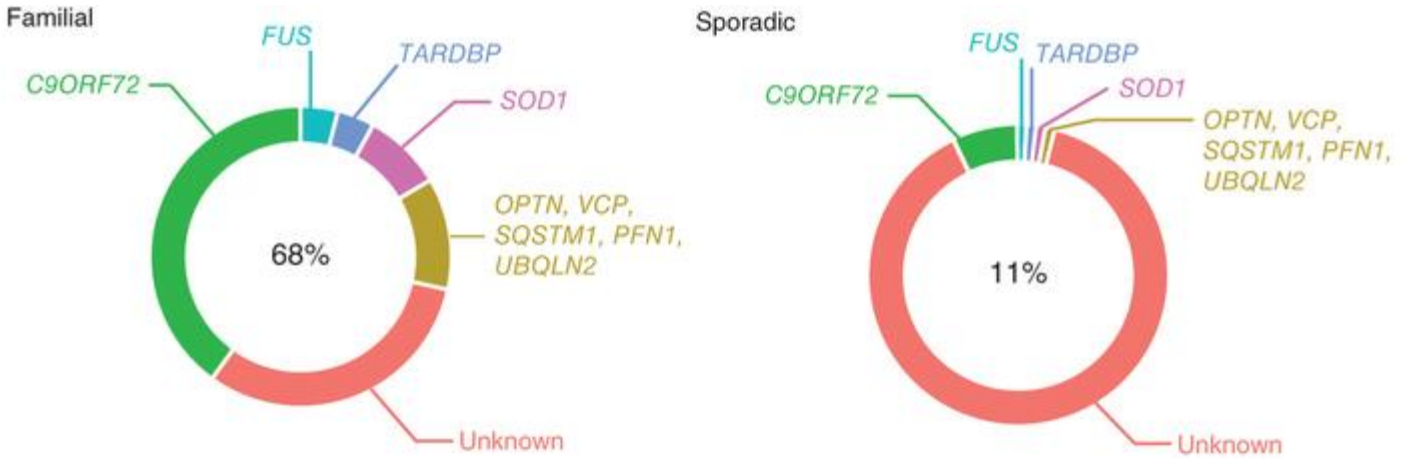
Mutations in the vesicular trafficking protein annexin A11 are associated with amyotrophic lateral sclerosis

Annexing another protein in ALS pathogenesis

Abstract

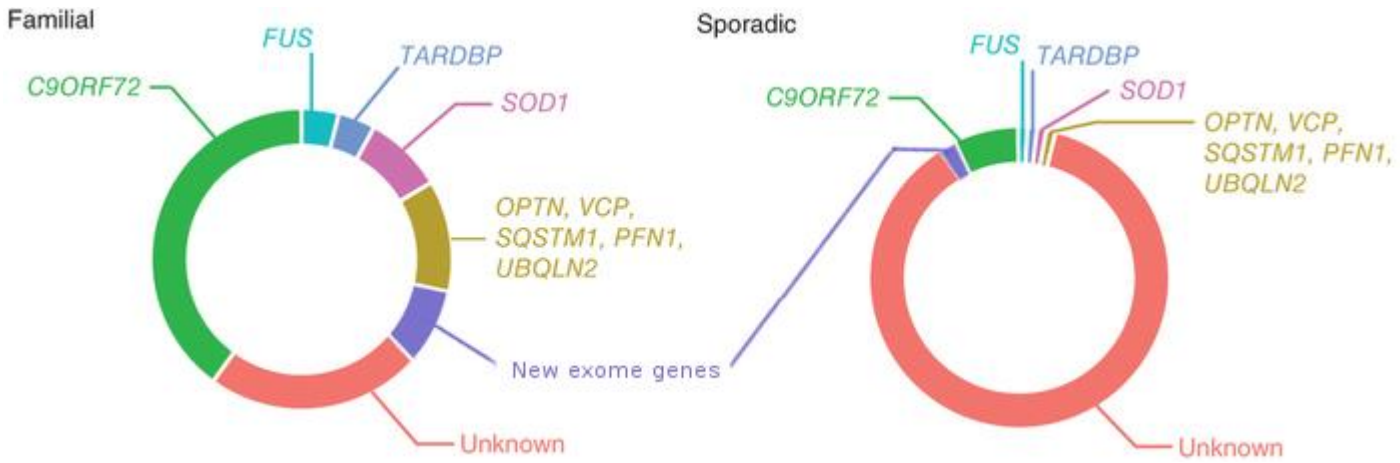
Updating ALS genomics

One gene at a time



Updating ALS genomics

One gene at a time



From exome to whole-genome sequencing

Original approach: SNP chips (GWAS)

```
----------||||||||||||||||||||||||||||||||||||----------  < gene exons/introns
CTGCTAGCTAGTCTATCGTGCTAGCTAGCTAGCTAGCTAGCGCGTATCGATGAGTCAGCCGTAG  < reference genome
 ... ... ... C ... ... ... ... ... ... ... ... A ... ... ... ...  < paternal chromosome
 ... ... ... T ... ... ... ... ... ... ... ... A ... ... ... ...  < maternal chromosome
```

New approach: exome sequencing

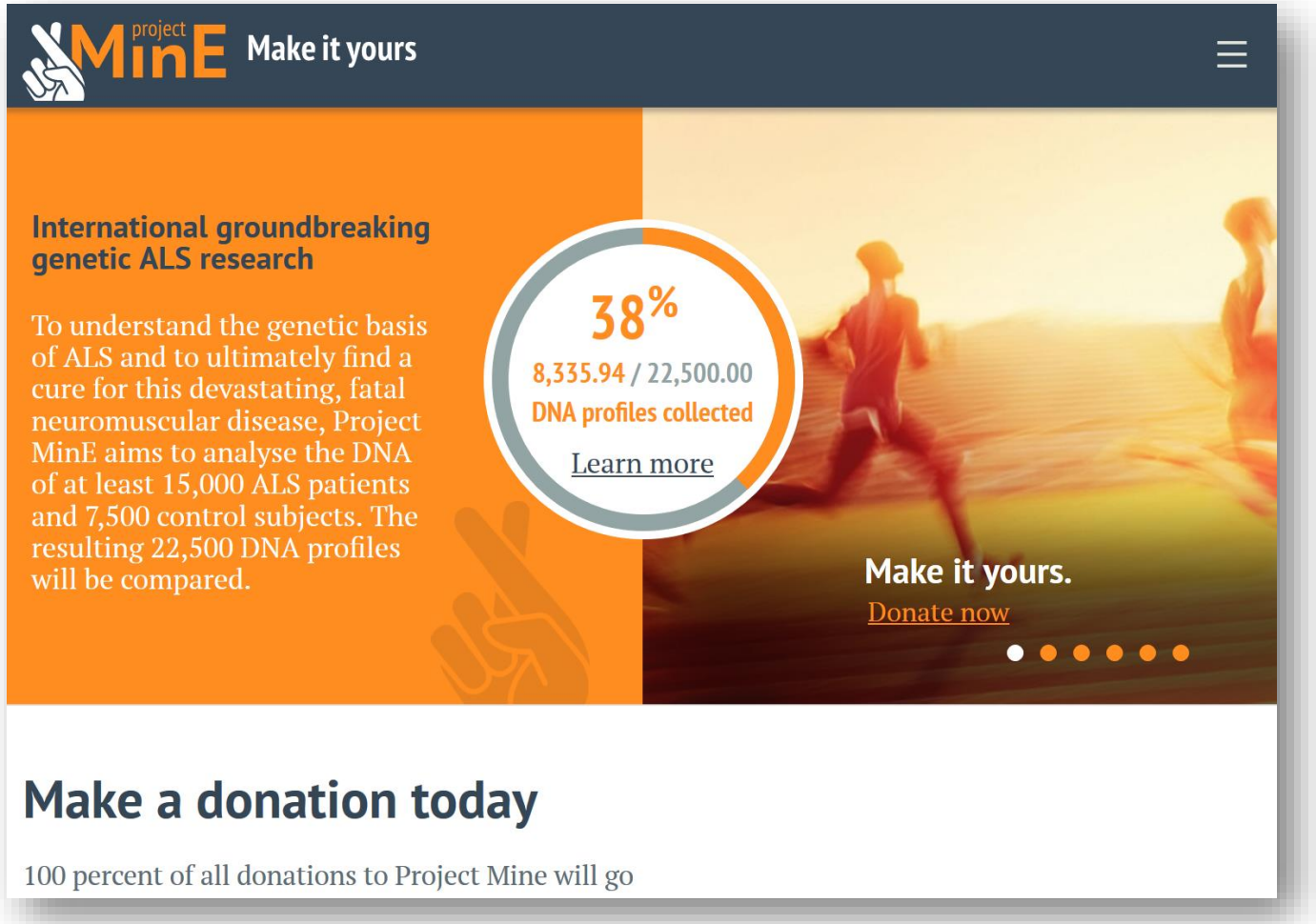
```
----------||||||||||||||||||||||||||||||||||||----------  < gene exons/introns
CTGCTAGCTAGTCTATCGTGCTAGCTAGCTAGCTAGCTAGCGCGTATCGATGAGTCAGCCGTAG  < reference genome
 ... ... ..TCCATCGTGCTAGCTAGCTAGCTAGCTAGCGC. ... ... ... ... ...  < paternal chromosome
 ... ... ..TCTATCGTGCTAGCTAGTTAGCTAGCTAGCGC. ... ... ... ... ...  < maternal chromosome
```

Newer approach: whole-genome sequencing

```
----------||||||||||||||||||||||||||||||||||||----------  < gene exons/introns
CTGCTAGCTAGTCTATCGTGCTAGCTAGCTAGCTAGCTAGCGCGTATCGATGAGTCAGCCGTAG  < reference genome
CTGCTAGCTAGTCCATCGTGCTAGCTAGCTAGCTAGCTAGCGCGTATAGATGACTCAGCCGTAG  < paternal chromosome
CTGCTAGCTAGTCTATCGTGCTAGCTAGTTAGCTAGCTAGCGCGTATAGATGAGTCAGCCGTAG  < maternal chromosome
```

Whole-genome sequencing in large populations

Project MinE



A hypothesis

(to explain why so much is still unexplained in ALS genetics)

A multitude of rare repeat expansions cause a substantial proportion of ALS

A multitude of rare repeat expansions cause a substantial proportion of ALS

C9orf72 repeat expansion

Human reference genome (chr9:27,573,516-27,573,556)
…GACCACGCCCCGGCCCCGGCCCCGGCCCCTAGCGCGCGACT…

Healthy individual (typical)
…GACCACGCCCCGGCCCC------GGCCCCTAGCGCGCGACT…

C9orf72-positive ALS
…GACCACGCCCCGGCCCC$(G_2C_4)_n$GGCCCCTAGCGCGCGACT…

(where n = potentially >1,000)

Table 1 Repeat expansions that cause neurodegeneration

Gene	Disease	Repeat motif	(Non)coding	Pathogenic range
AFF2/FMR3	FRAXE mental retardation syndrome	CCG	Noncoding	>200
AR	Spinal and bulbar muscular atrophy	CAG	Coding	40-62
ARX	X-linked mental retardation	GCG	Coding	17-23
ATN1	Dentatorubral-pallidoluysian atrophy	CAG	Coding	49-88
ATXN1	Spinocerebellar ataxia type 1	CAG	Coding	39-83
ATXN10	Spinocerebellar ataxia type 10	ATTCT	Noncoding	280-4500
ATXN2	Spinocerebellar ataxia type 2	CAG	Coding	34-59
	Amyotrophic lateral sclerosis	CAG	Coding	27-33
ATXN3	Spinocerebellar ataxia type 3	CAG	Coding	55-84
ATXN7	Spinocerebellar ataxia type 7	CAG	Coding	34->300
ATXN8	Spinocerebellar ataxia type 8	CAG/CTG	Both	80-1300
C9orf72	ALS/FTD	GGGGCC	Noncoding	>30
CACNA1A	Spinocerebellar ataxia type 6	CAG	Coding	21-30
CNBP	Myotonic dystrophy type 2	CCTG	Noncoding	75-11000
CSTB	Epilepsy progressive myoclonia	$(C)_4G(C)_4GCG$	Noncoding	30-75
DIP2B	FRA12A mental retardation syndrome	CGG	Noncoding	>23
DMPK	Myotonic dystrophy type 1	CTG	Noncoding	50-6500
FMR1	Fragile X mental retardation type 1	CGG	Noncoding	>200
	Fragile X-associated tremor ataxia syndrome	CGG	Noncoding	55-200
	Fragile X mental retardation type 2	CGG	Noncoding	200-900
FXN	Friedreich's ataxia	GAA	Noncoding	66-1700
HTT	Huntington's disease	CAG	Coding	>35
JPH3	Huntington's disease-like 2	CAG/CTG	Noncoding	>41
NOP56	Spinocerebellar ataxia type 36	GGCCTG	Noncoding	1500-2500
PABPN1	Oculopharyngeal muscular dystrophy	GCG	Coding	11-17
PPP2R2B	Spinocerebellar ataxia type 12	CAG/CTG	Noncoding	55-78
TBP	Spinocerebellar ataxia type 17	CAG	Coding	49-66
TK2-BEAN	Spinocerebellar ataxia type 31	TGGAA	Noncoding	500-760

Pathogenic range is the number of repeats required to manifest disease

Some questions in ALS genomics

(and some possible answers)

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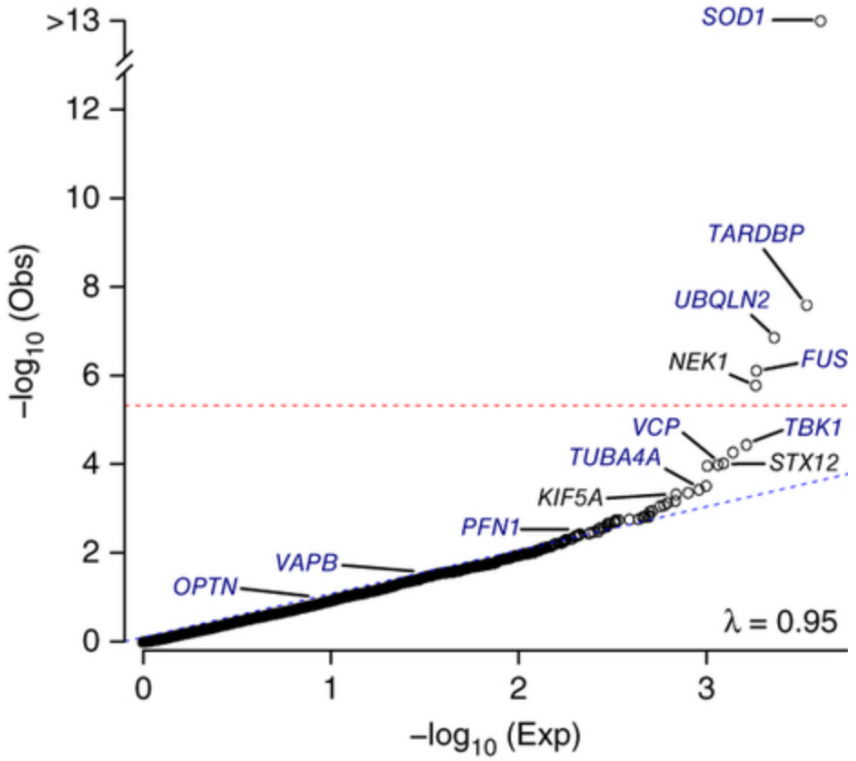
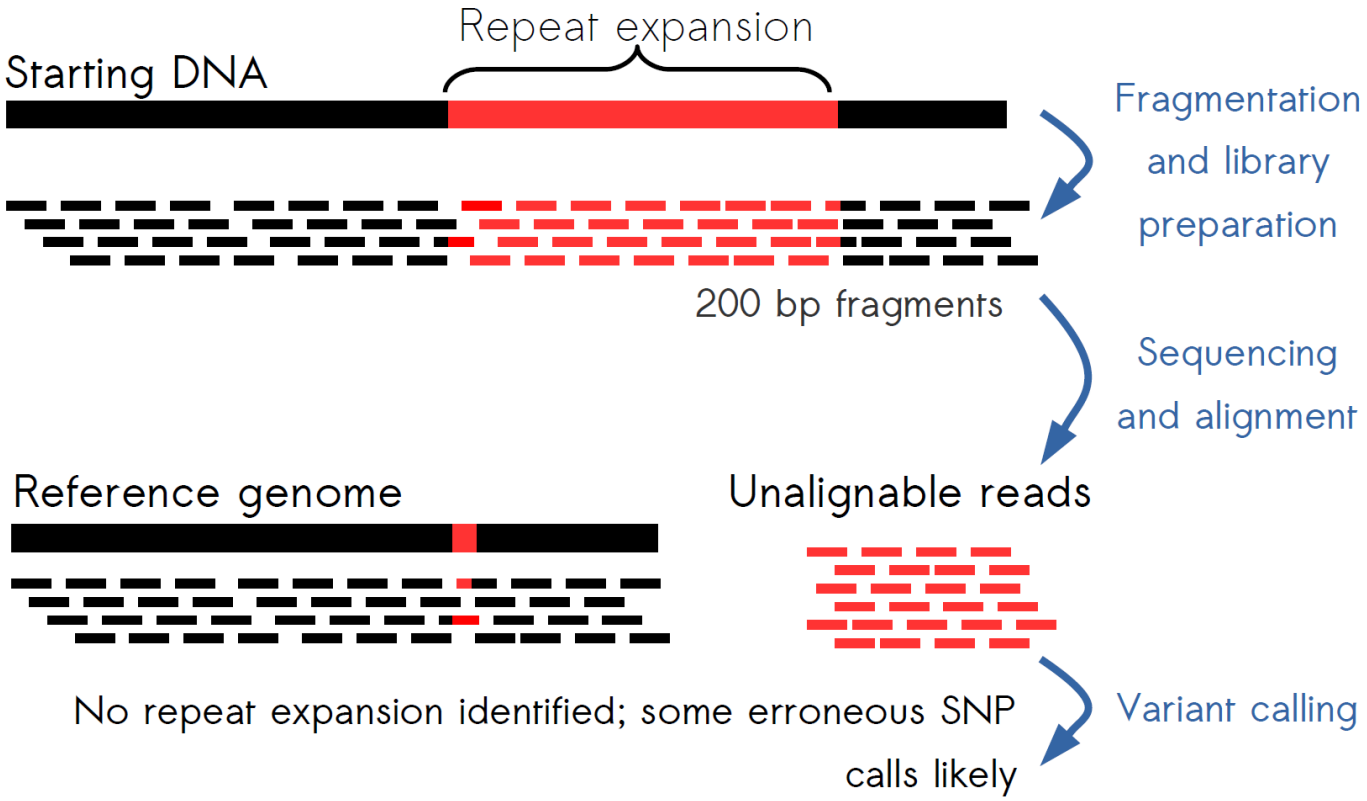


Repeat expansions are hard to sequence

Next-generation sequencing: a simplified overview



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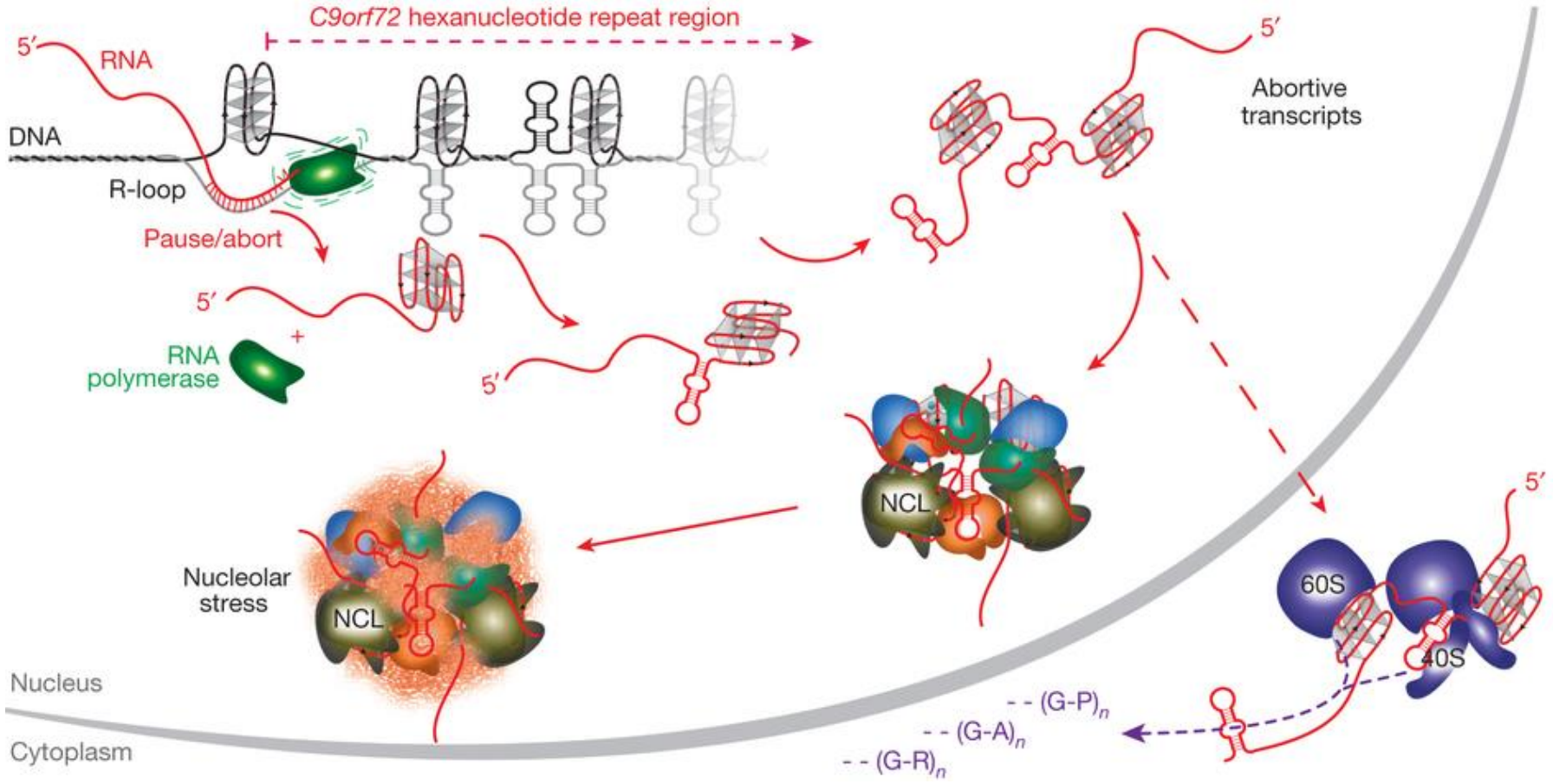
C9orf72 repeat expansion

Mechanisms of disease



Haeusler *et al.* (2014) Nature 507:195-200

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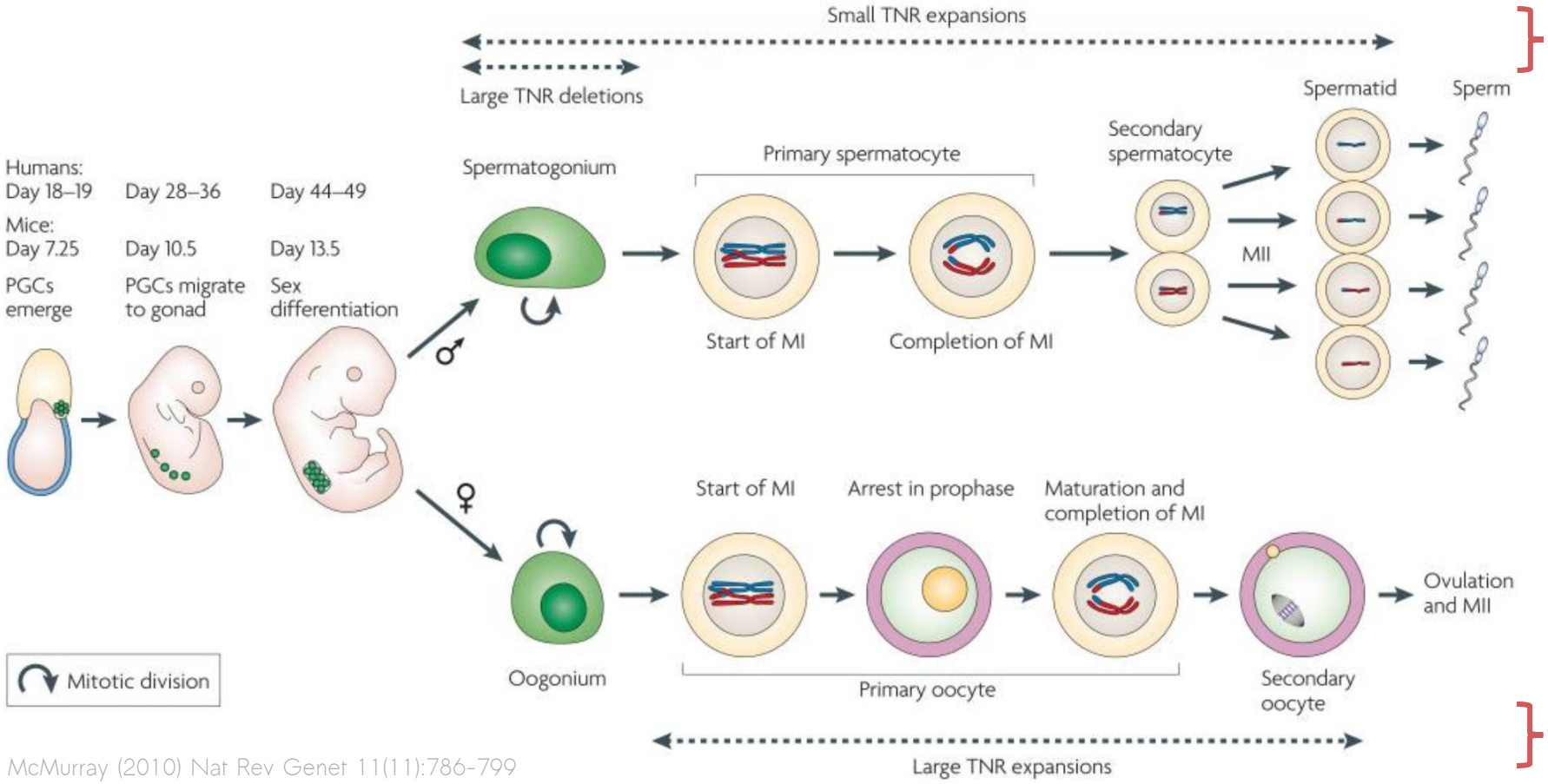
Developmental dynamics of repeat expansion stability

Different mechanisms in mother and father



McMurray (2010) Nat Rev Genet 11(11):786-799

TNR = trinucleotide repeat

Prone to:

de novo expansion during maternal oocyte development

contraction during paternal spermatogonium development

de novo expansion during paternal spermatocyte differentiation

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5. Heritability disparity suggests some *de novo* mutations. Why don't we see increased paternal age?

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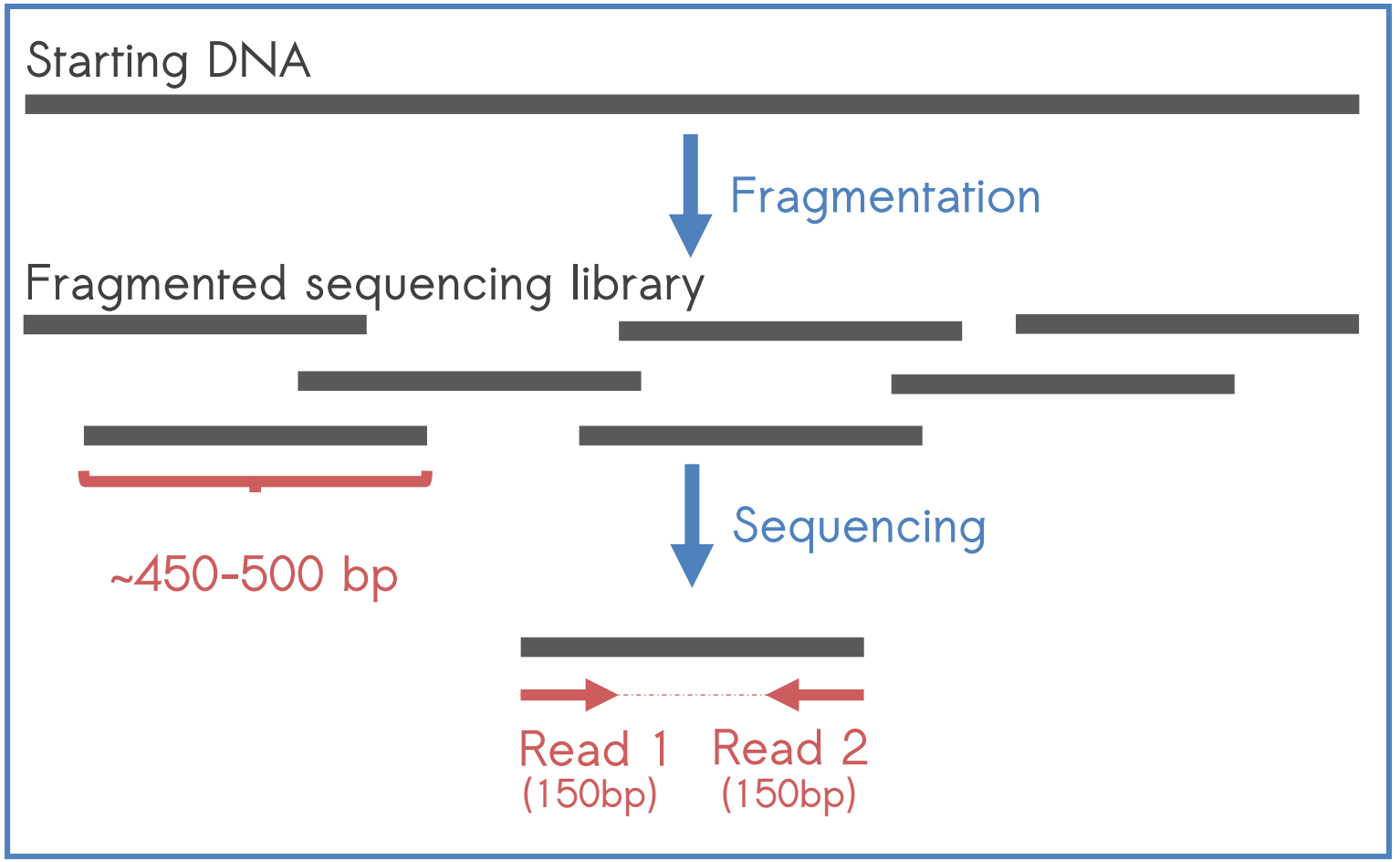
5. Heritability disparity suggests some *de novo* mutations. Why don't we see increased paternal age?
   a) Repeat expansions are prone to *de novo* instability and are not tied to paternal age

How can we find (novel) repeat expansions?

Paired-end next-generation sequencing




File Genomes View Tracks Regions Tools GenomeSpace Help
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Go
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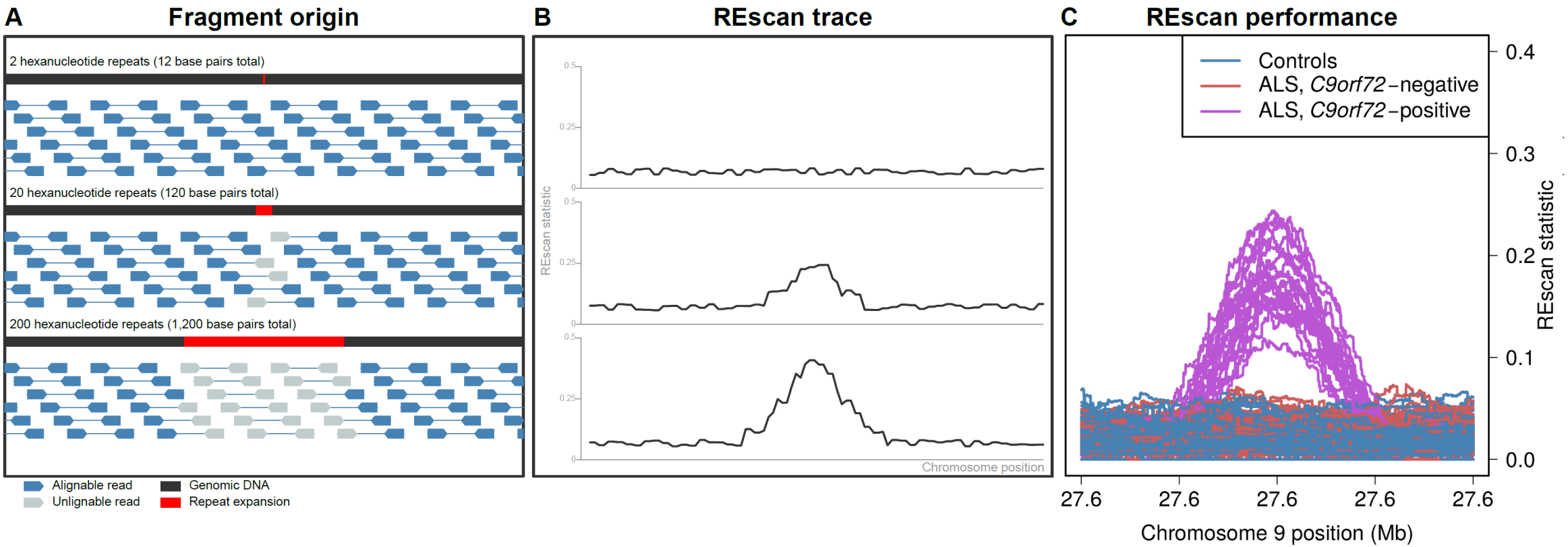
Finding repeat expansions

Using paired-end next-generation sequencing data



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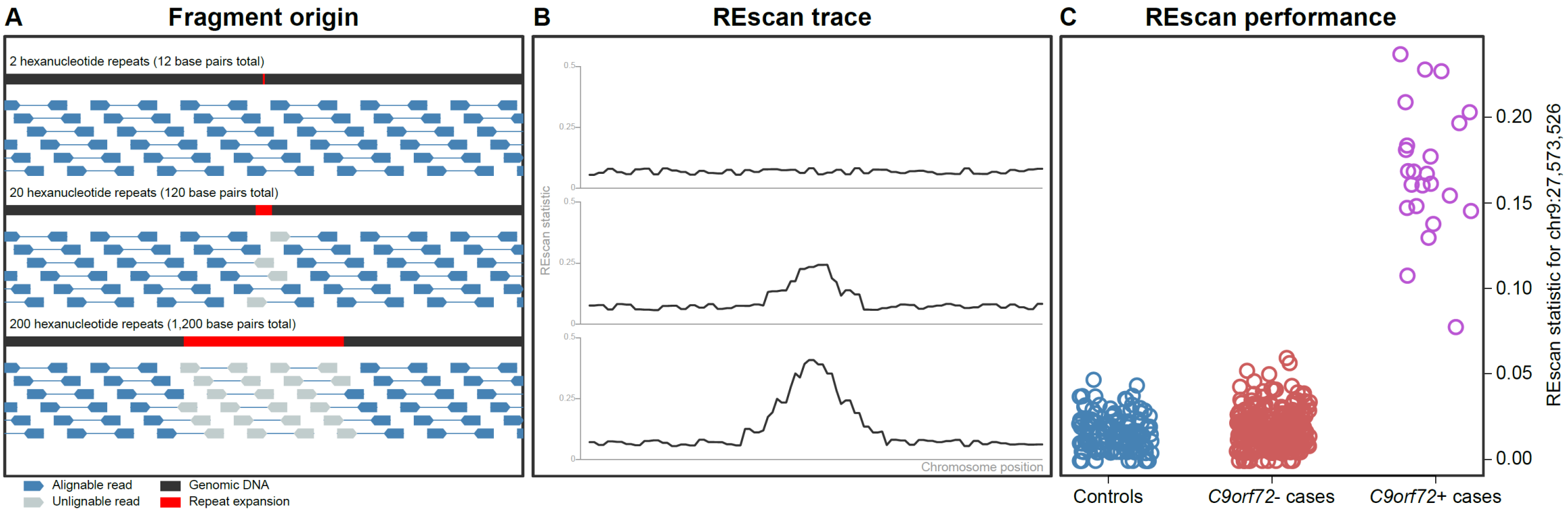


Finding repeat expansions

ExpansionHunter

Detection of long repeat expansions from PCR-free whole-genome sequence data

Egor Dolzhenko[1,#], Joke J.F.A. van Vugt[2,#], Richard J. Shaw[3,4], Mitchell A. Bekritsky[3], Marka van Blitterswijk[5], Zoya Kingsbury[3], Sean J. Humphray[3], Raymond D. Schellevis[2], William J. Brands[2], Matt Baker[5], Rosa Rademakers[5], Maarten Kooyman[6], Gijs H.P. Tazelaar[2], Michael A. van Es[2], Russell McLaughlin[7,8], William Sproviero[9], Aleksey Shatunov[9], Ashley Jones[9], Ahmad Al Khleifat[9], Alan Pittman[10], Sarah Morgan[10], Orla Hardiman[7,8], Ammar Al-Chalabi[9], Leonard H. van den Berg[2], David R. Bentley[3], Michael A. Eberle[1,*] and Jan H. Veldink[2,*]

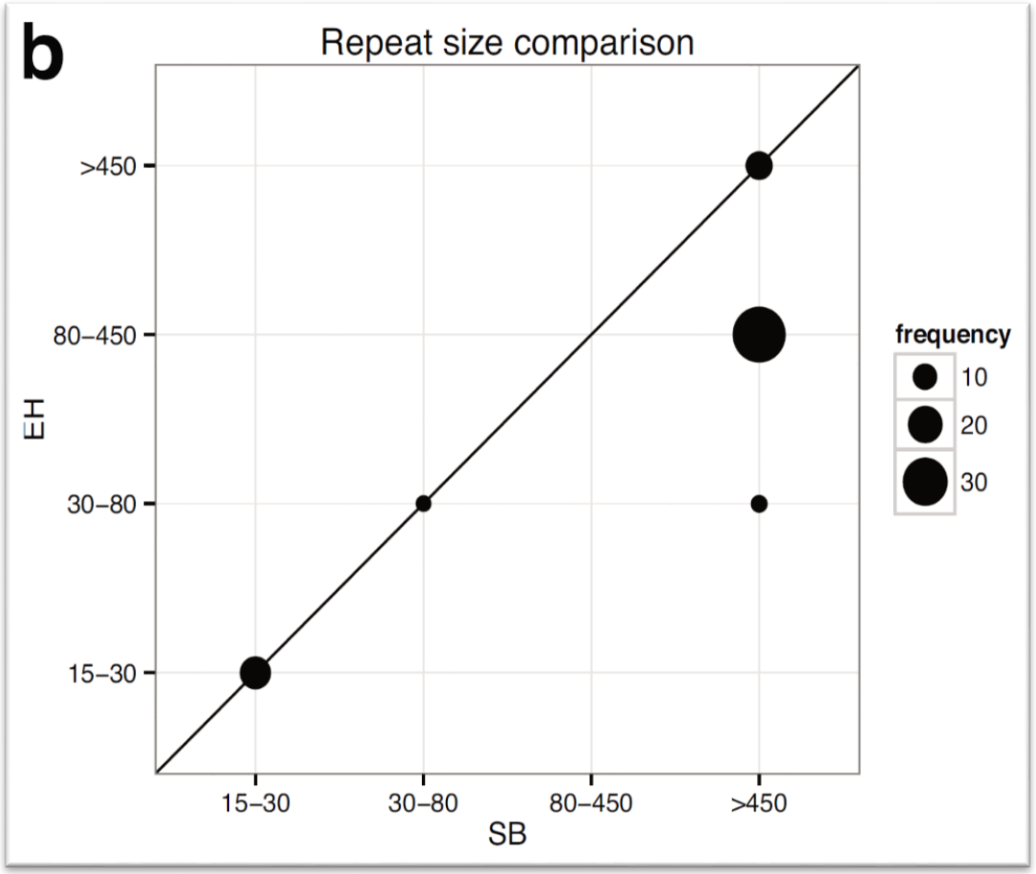
[1]Illumina Inc., 5200 Illumina Way, San Diego, CA, USA
[2]Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht, Utrecht, The Netherlands.
[3]Illumina Cambridge Ltd., Chesterford Research Park, Little Chesterford, UK
[4]Repositive Ltd., Future Business Centre, Kings Hedges Rd, Cambridge, UK
[5]Department of Neuroscience, Mayo Clinic, Jacksonville, FL, USA
[6]SURFsara, Science Park 140, Amsterdam, The Netherlands
[7]Academic Unit of Neurology, Trinity College Dublin, Trinity Biomedical Sciences Institute, Dublin, Republic of Ireland.
[8]Department of Neurology, Beaumont Hospital, Dublin, Republic of Ireland
[9]Department of Basic and Clinical Neuroscience, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[10]Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

[#]These authors contributed equally
[*]To who correspondence should be addressed

Abstract

Accurately identifying large repeat expansions including those that cause amyotrophic lateral sclerosis (ALS) and Fragile X syndrome is challenging for short-read (100-150bp) whole genome sequencing (WGS) data. A solution to this problem is an important step towards integrating WGS into precision medicine. We have developed a research tool called ExpansionHunter that, using PCR-free WGS data, can identify repeat expansions at the locus of interest, even if the expansion is larger than the read length. We applied our algorithm to WGS data from 3,001 ALS patients who have been tested for the presence of the *C9orf72* repeat expansion with repeat-primed PCR (RP-PCR). Southern blot and fragment length analysis were applied on a subset of samples to confirm the presence or absence of the repeat expansion. Compared to the RP-PCR results, our WGS-based method identified pathogenic repeat expansions (>30 GGCCCC repeats) with 98.1% sensitivity and 99.7% specificity. Further inspection identified that 11 of the 12

1

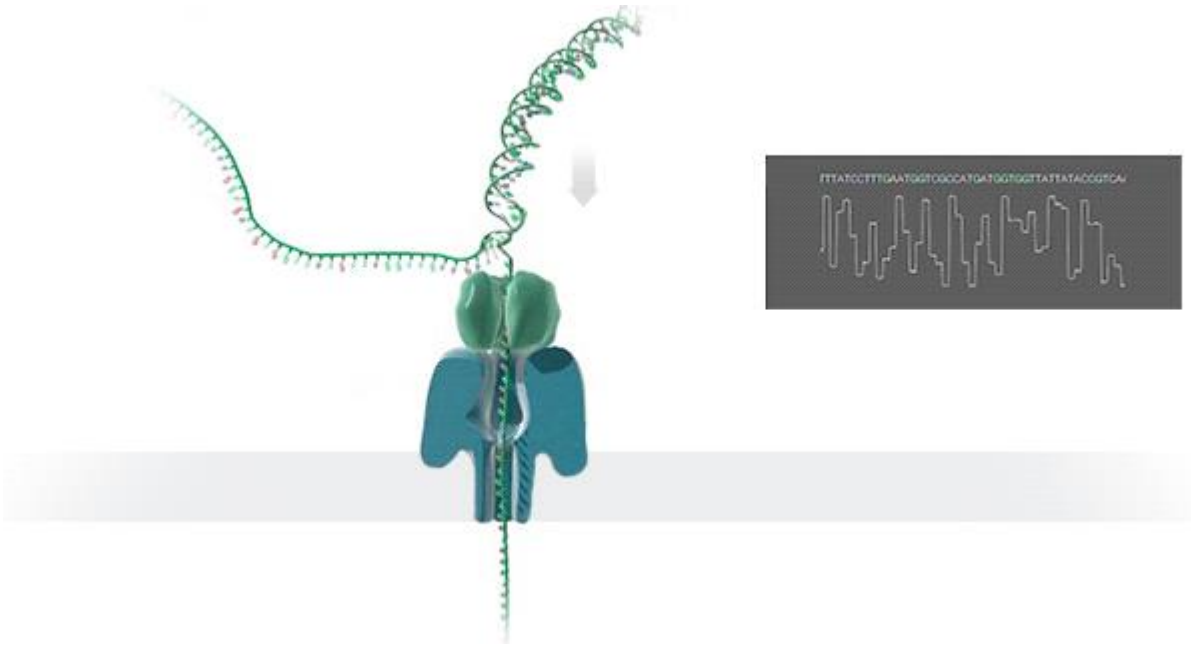


Can we directly measure repeat expansions?

From the *next* generation to the *third* generation

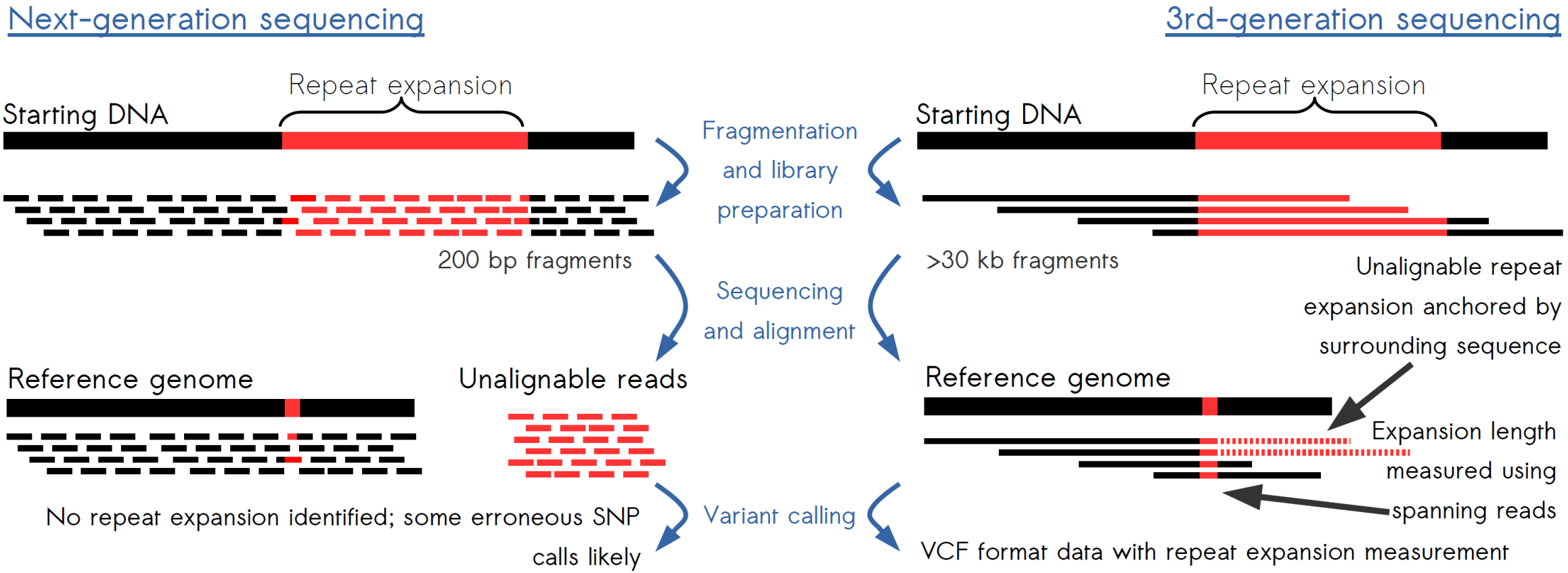
Can we directly measure repeat expansions?

3rd-generation sequencing with ultra-long reads using Oxford Nanopore MinION



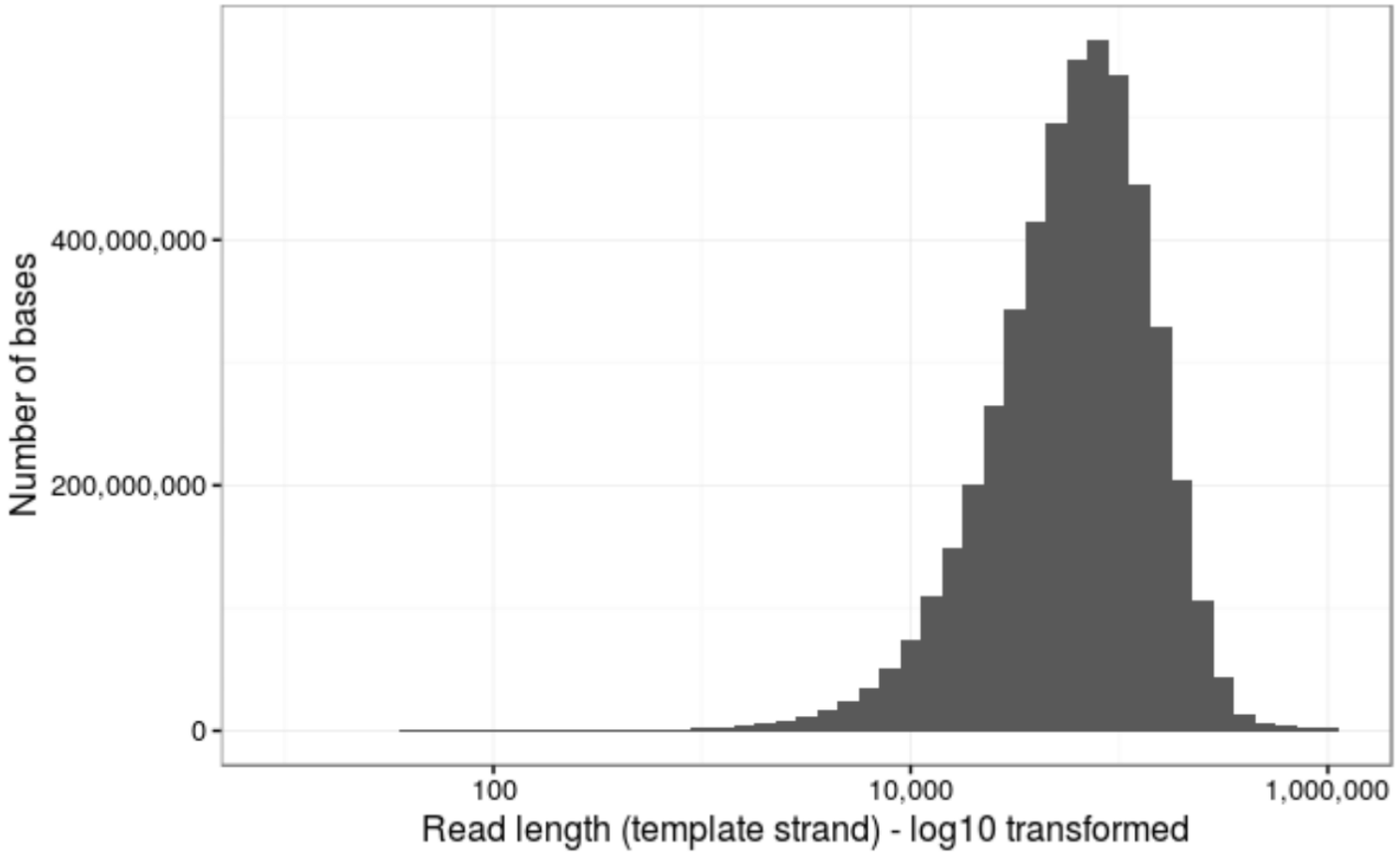
NGS vs 3GS

Spanning repeat expansions



How long is a long read?

Answer: *very*

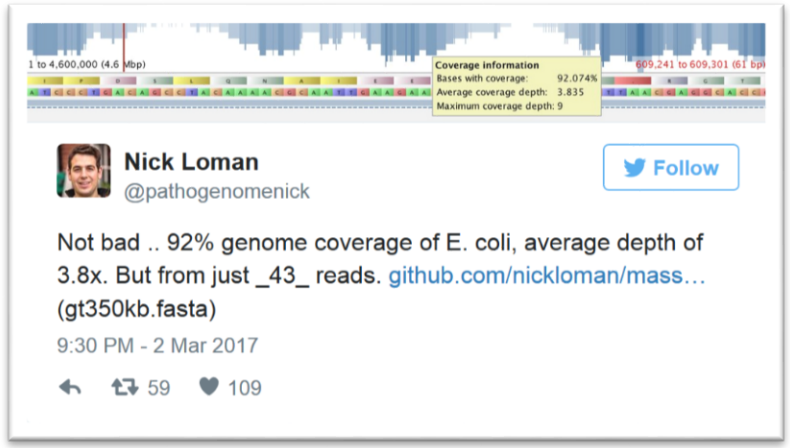


Thar she blows! Ultra long read method for nanopore sequencing

09 Mar 2017

tl;dr version

- Ultra long reads (up to 882 kb and indeed higher) can be achieved on the Oxford Nanopore MinION using traditional DNA extraction techniques and minor changes to the library preparation protocol, without the need for size selection



How long is a long read?

Answer: *very*

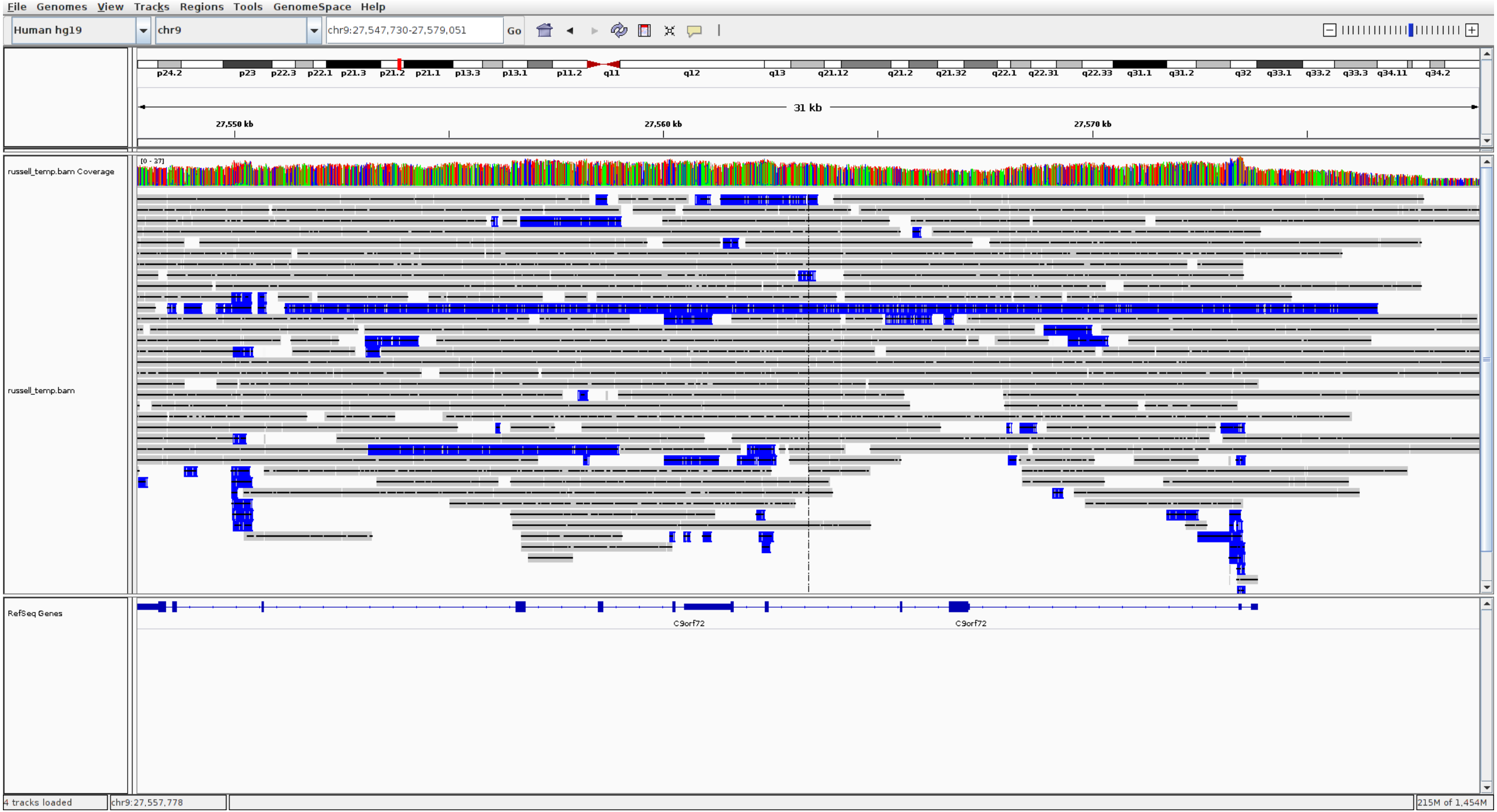
150 bp Illumina read

(banana for scale)

950,000 bp Oxford Nanopore read

(Burj Khalifa for scale)

C9orf72 locus with Oxford Nanopore


File Genomes View Tracks Regions Tools GenomeSpace Help
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chr9
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Go
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Acknowledgements

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Orla Hardiman & team
Peter Bede
Susan Byrne
Emma Corr
Mark Heverin
James Rooney
Marie Ryan
Alice Vajda

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Dan Bradley & team
Matthew Teasdale

Complex Trait Genomics
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Mark Doherty
Jenny Hengeveld

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Gijs Tazelaar
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University of Massachusetts

John Landers
Kevin Kenna & family

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The University of Dublin

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