

Is the pathogenic Androgen Receptor CAG repeat expansion underestimated in the general population?

Matteo Zanovello

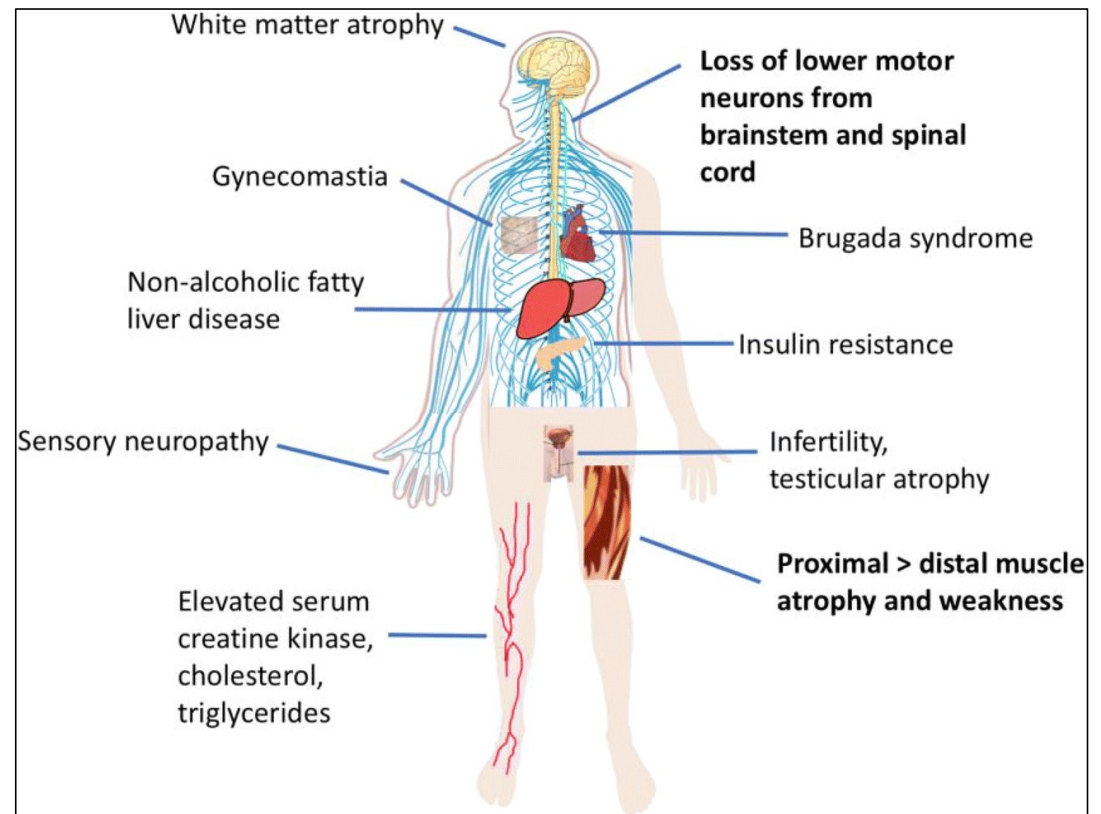
Spinal and bulbar muscular atrophy (SBMA)

CAG repeat (exon 1 - Androgen Receptor) ≥ 37

Poly(Gln) tract

Slowly progressive LMN symptoms

Associated with non-neurological conditions
(insulin resistance, fatty liver, metabolic syndrome)



Arnold and Merry, 2019

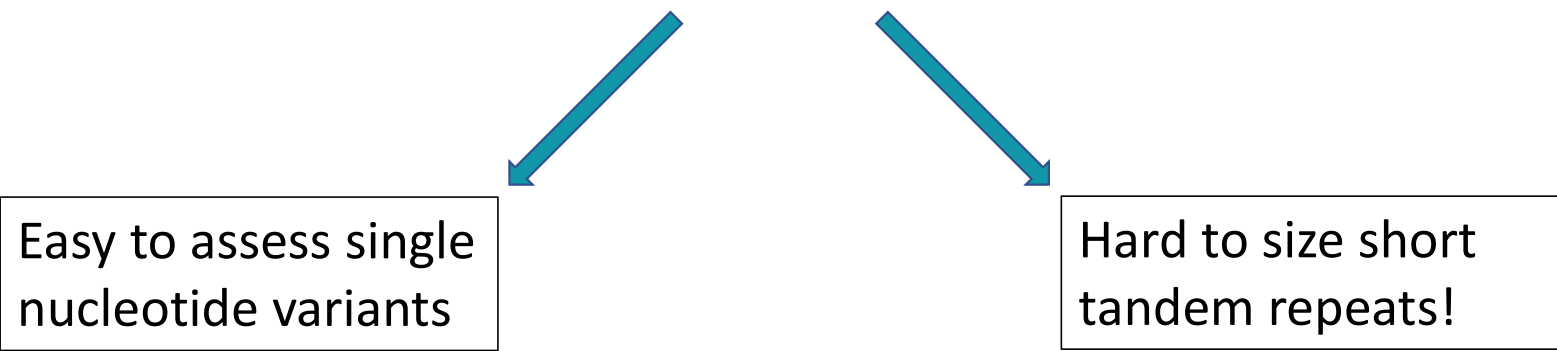
SBMA epidemiology

SBMA prevalence according to epidemiological studies			
AREA	PREVALENCE	METHOD	REFERENCES
Worldwide	1-2/100,000 1/300,000 1/30,303 (male adjusted)	Estimates	<i>Fishbeck, 1997</i> ncbi.nlm.nih.gov orpha.net
Veneto (Italy)	1/80,645 1/38,760 (male adjusted)	Perspective prevalence survey	<i>Bertolin et al, 2019</i>
Reggio Emilia (Italy)	1/62,500 1/30,303 (male adjusted)	Perspective prevalence survey	<i>Guidetti et al, 2001</i>
Slovakia	1/41,700	Perspective prevalence survey	<i>Zelinkova et al, 2016</i>
Vasa region (Finland)	1/6,538	Perspective prevalence survey	<i>Udd et al, 1998</i>

Unknown prevalence of repeat expansion in the population

Unknown prevalence of repeat expansion in the population

Genomic repositories and whole-genome sequencing (WGS)



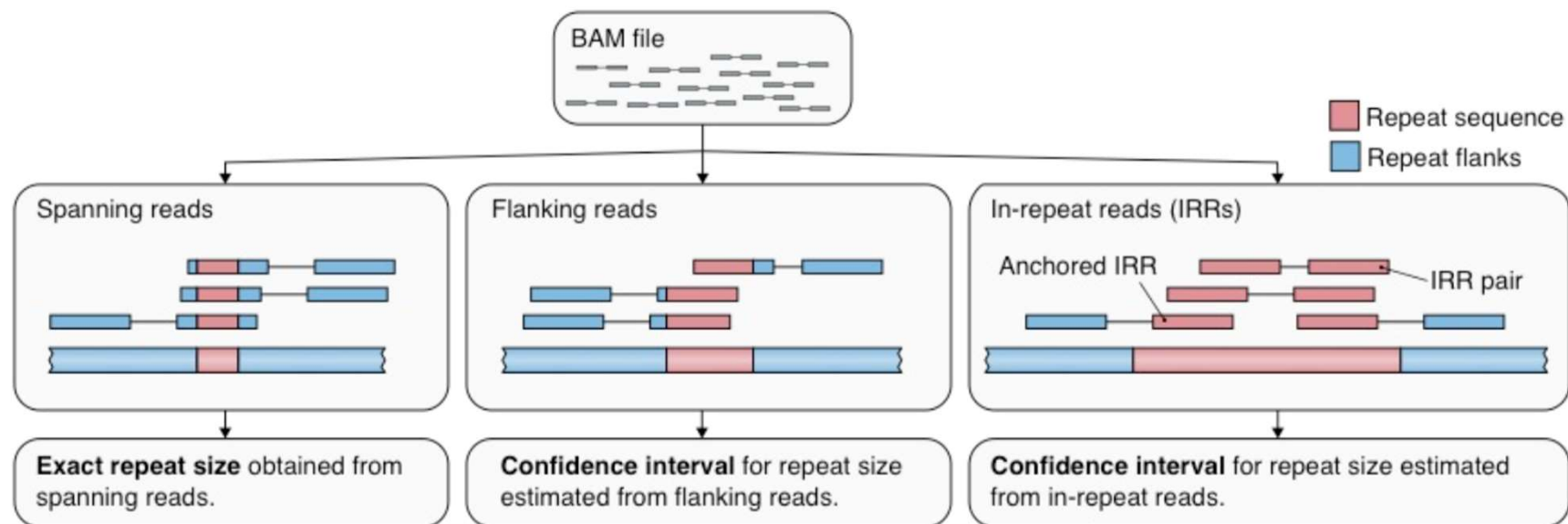
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graph TD; A[Genomic repositories and whole-genome sequencing (WGS)] --> B[Easy to assess single nucleotide variants]; A --> C[Hard to size short tandem repeats!]
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Easy to assess single nucleotide variants

Hard to size short tandem repeats!

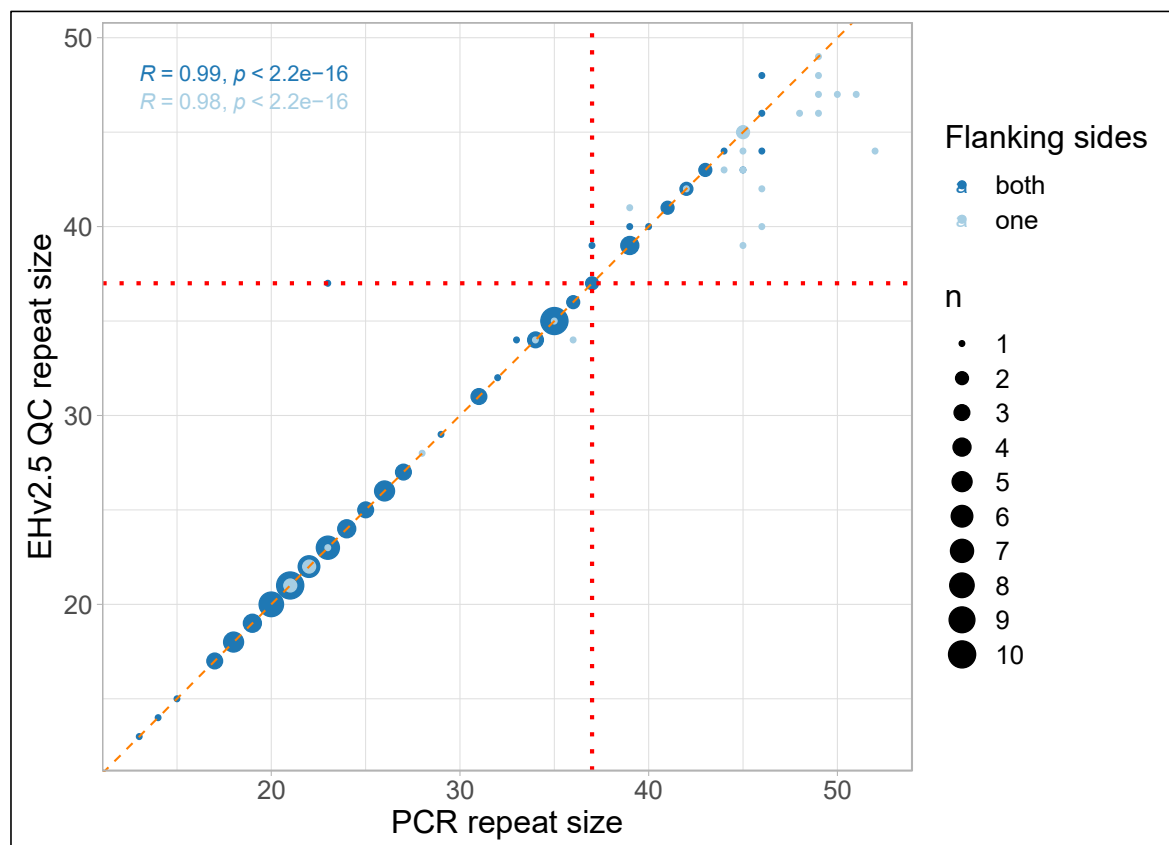
ExpansionHunter (Illumina, Inc. 2016)

Recently developed bioinformatics tool based on **whole-genome sequencing (WGS)** data
SBMA diagnosis gold standard: **PCR**



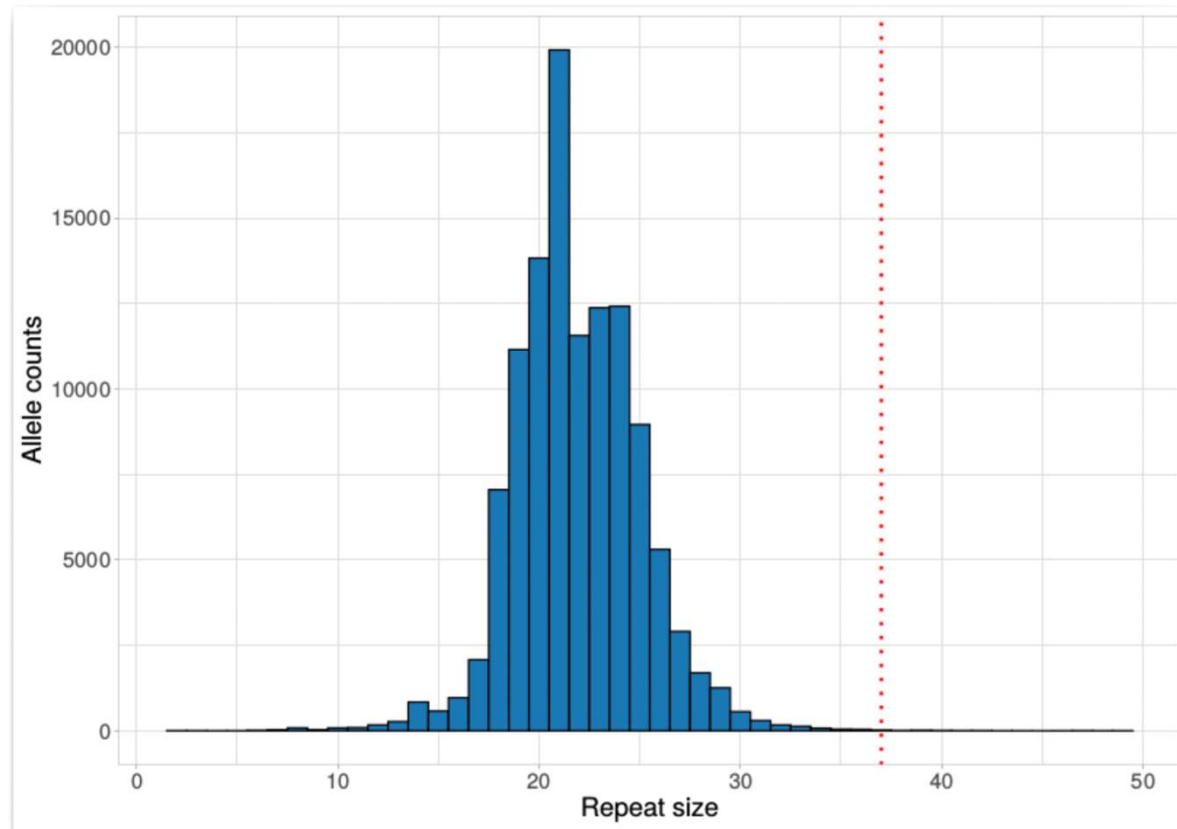
Dolzhenko et al, 2017; Dolzhenko et al, 2019

Pipeline benchmarking against PCR

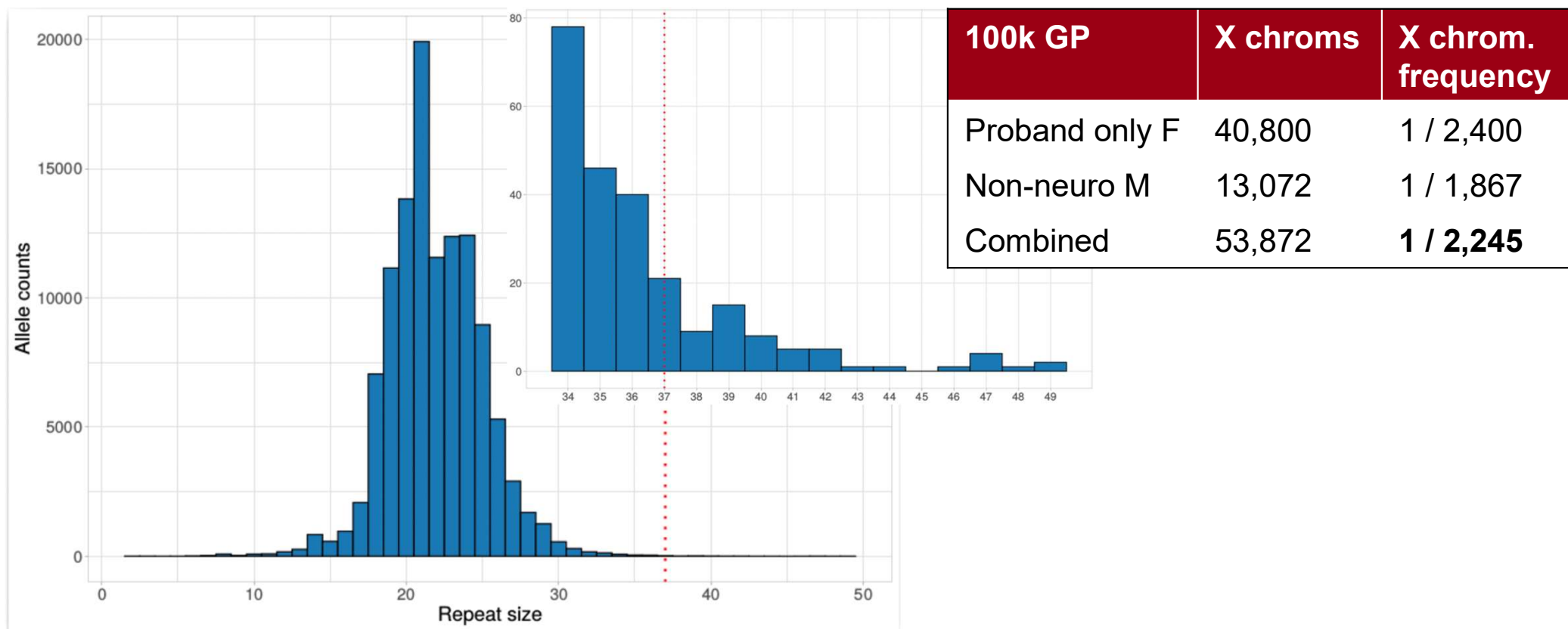


	Value	95% CI
Sensitivity	100%	91.4% - 100%
Specificity	98.9%	96.8% - 100%
PPV	97.6%	92.8% - 100%

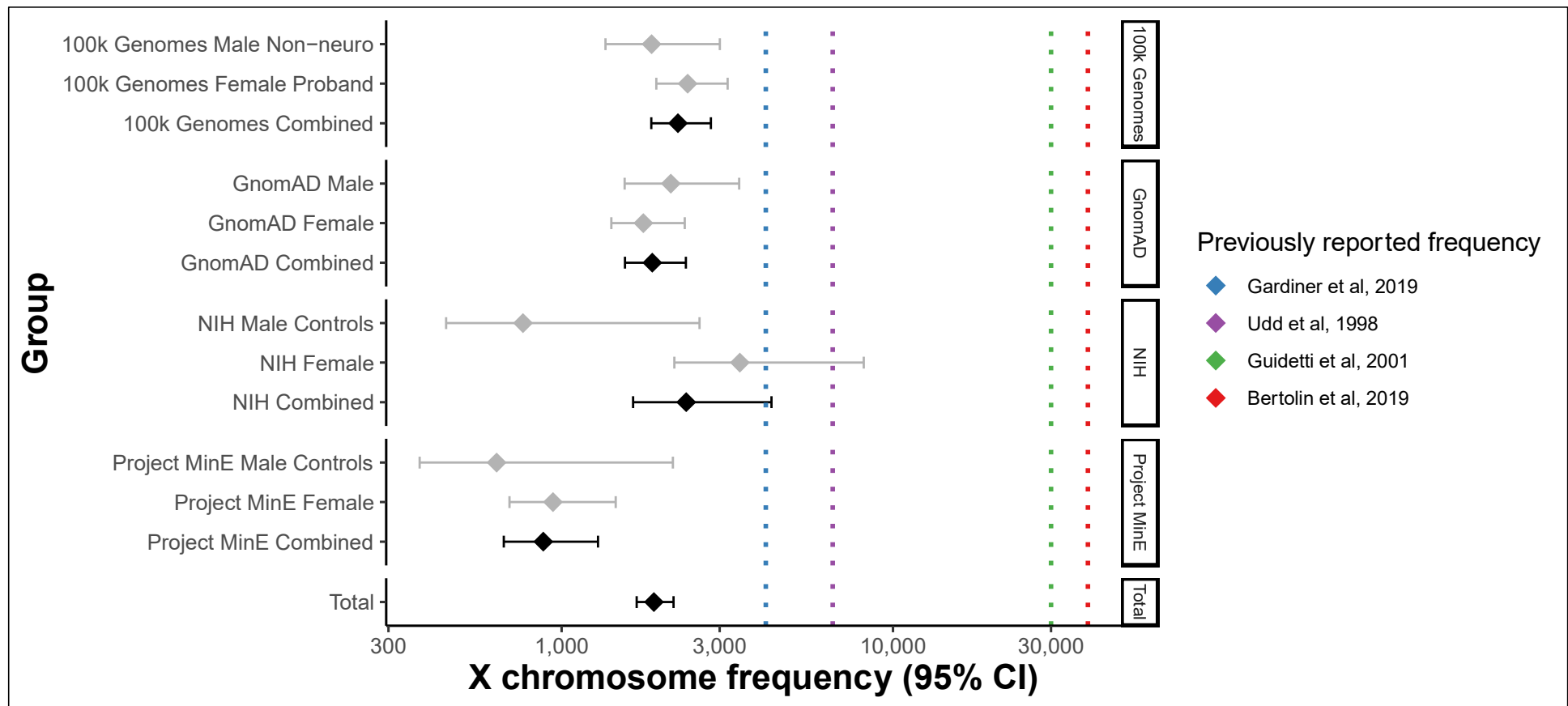
Allelic distribution on 75,035 genomes



Allelic distribution on 75,035 genomes



Replication cohorts confirm the finding



Conclusions

Disease prevalence $\neq$ Frequency of pathogenic repeat expansion

- a) underdiagnosis of the condition
- b) reduced disease penetrance
- c) **pleomorphic clinical manifestations**

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