Contribution of Large Genomic Deletions to Recessive Mendelian Disease Carrier Burden within a Healthy Population

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American College of Medical Genetics and Genomics
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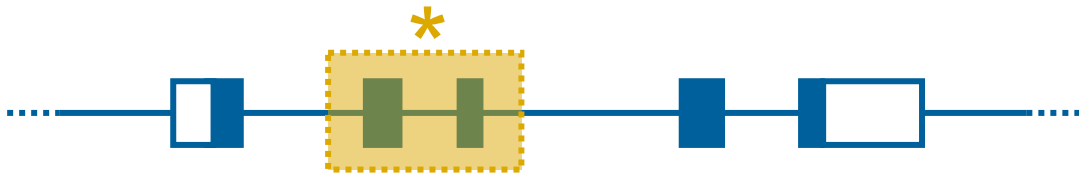
Introduction: Intragenic deletions



- Copy number variants (CNVs) have been overlooked in published case studies, diagnostic testing, & carrier screening for multiple hereditary disorders:
  - Require specialized protocols to detect with high accuracy
  - Contribution may be considered negligible
- Full contribution to carrier rates remains to be determined for some genetic diseases and ethnic populations
  - Available literature: average 3.6%, median 0%, across 169 recessive Mendelian diseases examined
- **Goal:** Examine population CNV carrier rates among an ethnically diverse cohort of individuals across a range of serious and clinically actionable Mendelian diseases

Methods

346,182 patients:
routine Expanded Carrier Screening

NGS:
176 Mendelian recessive disorders

Variant calling:
incl. CNVs
(leveraging NGS read-depth values)

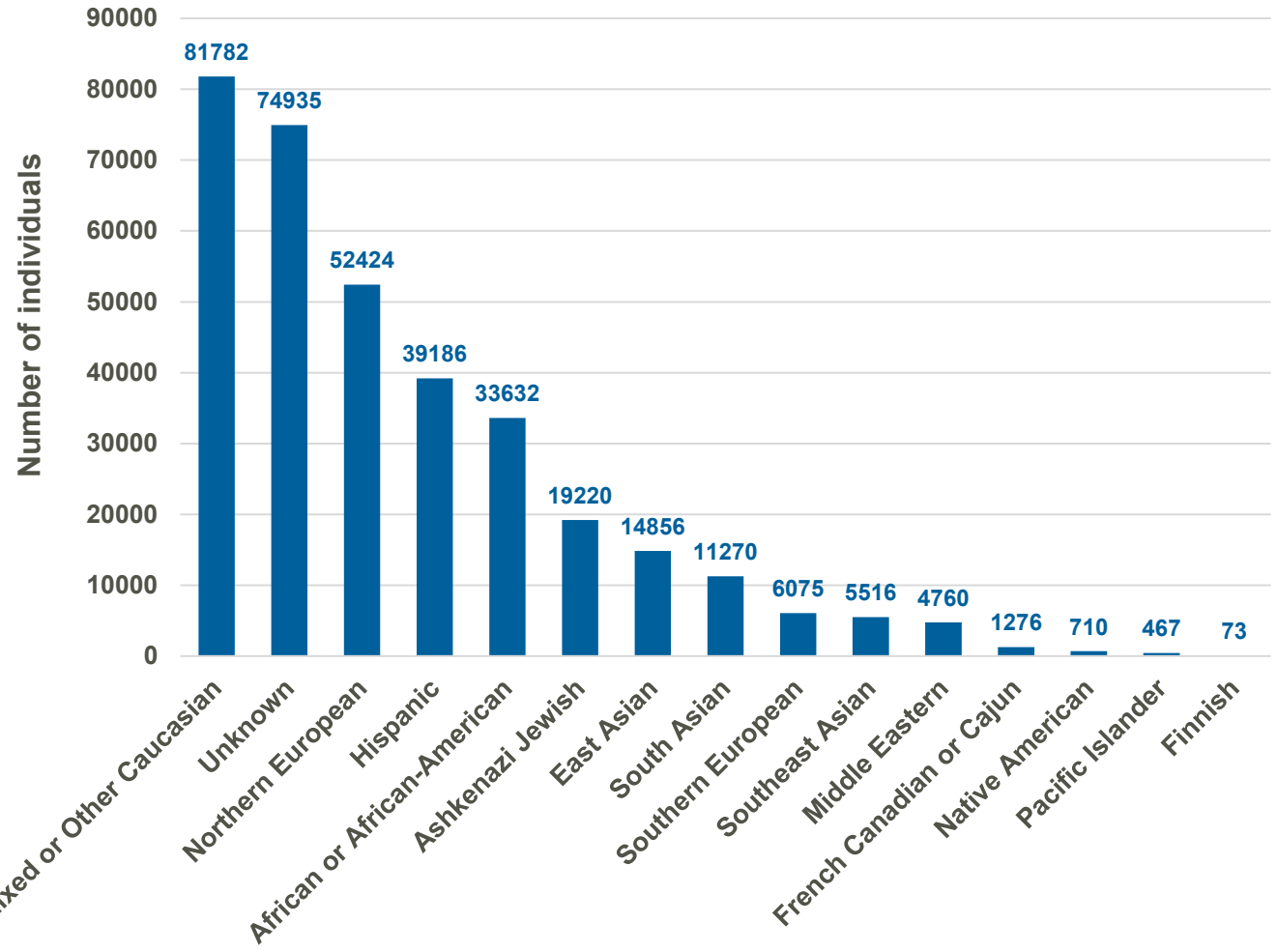
ACMG-based classification

Results from **169* genes** were interrogated

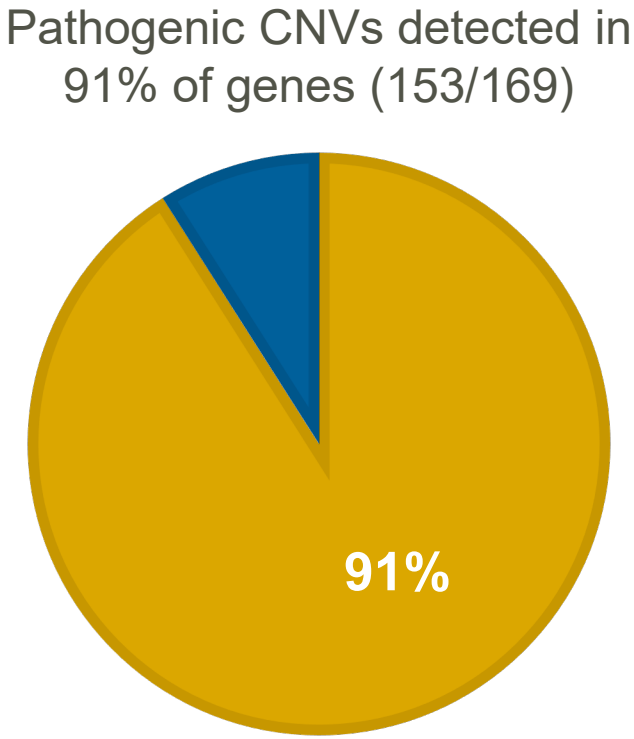
Contribution of **CNV dels & dups†**

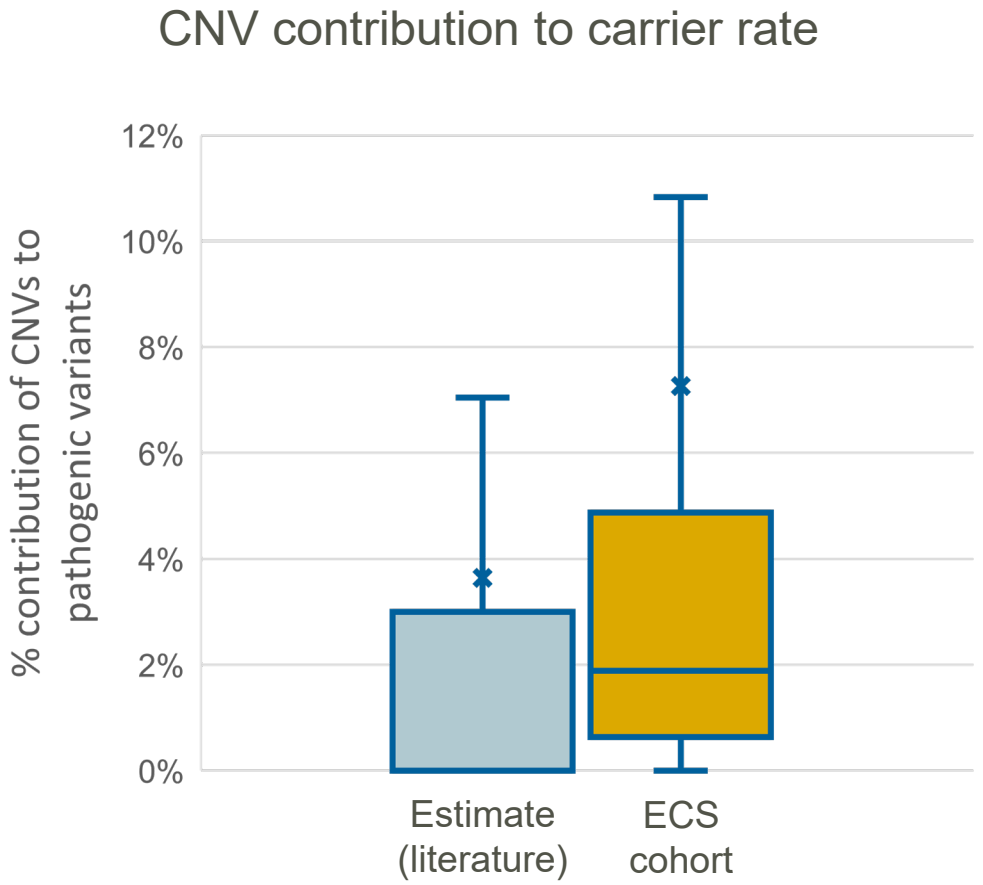
* 7 genes excluded due to specialized assay design or because loss-of-function was not a disease mechanism
† CNV duplications for *CFTR* & *DMD*

Results: Self-reported ethnicity among 346,182 patients

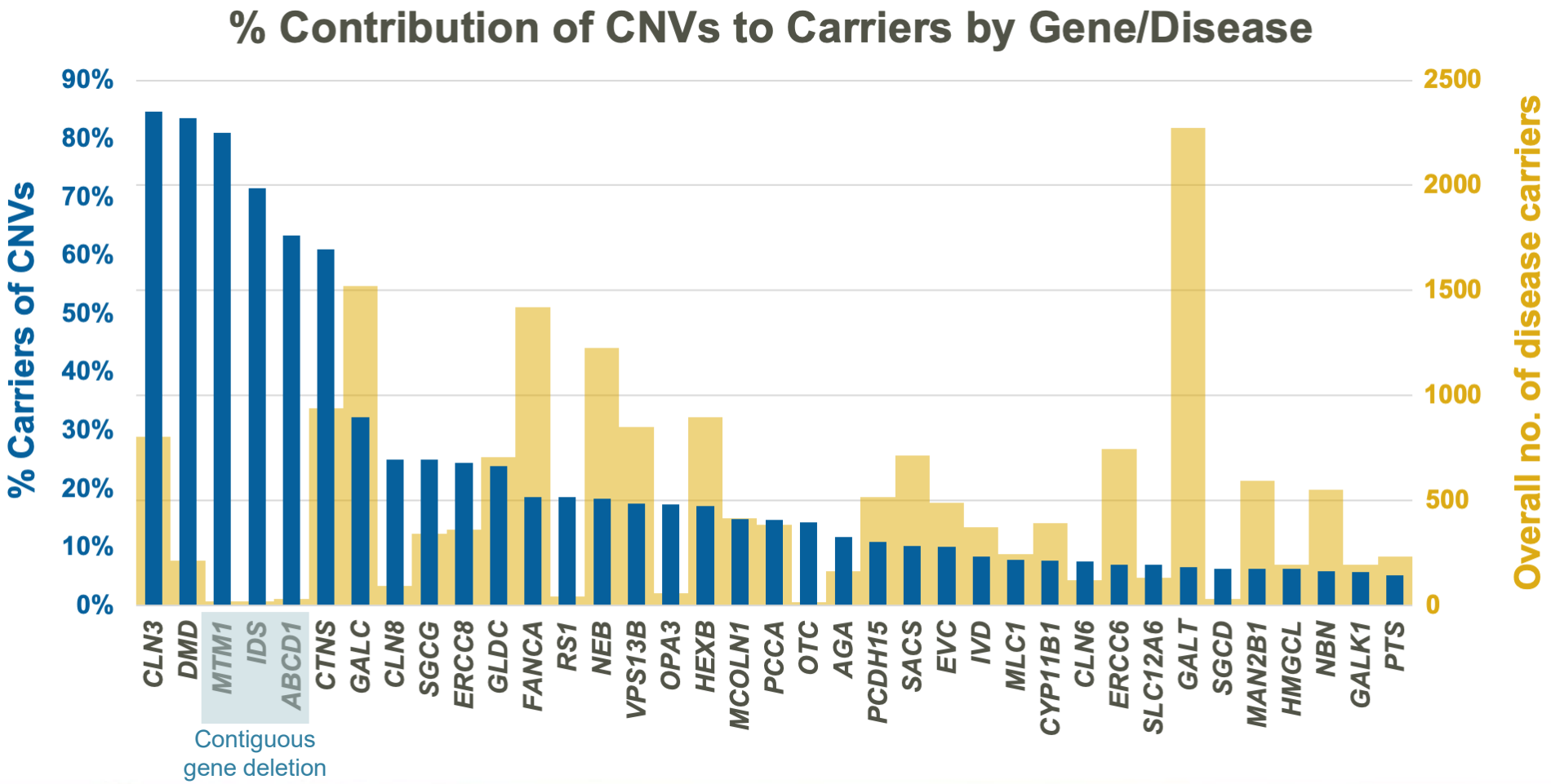


Widespread contribution of CNVs to population carrier burden



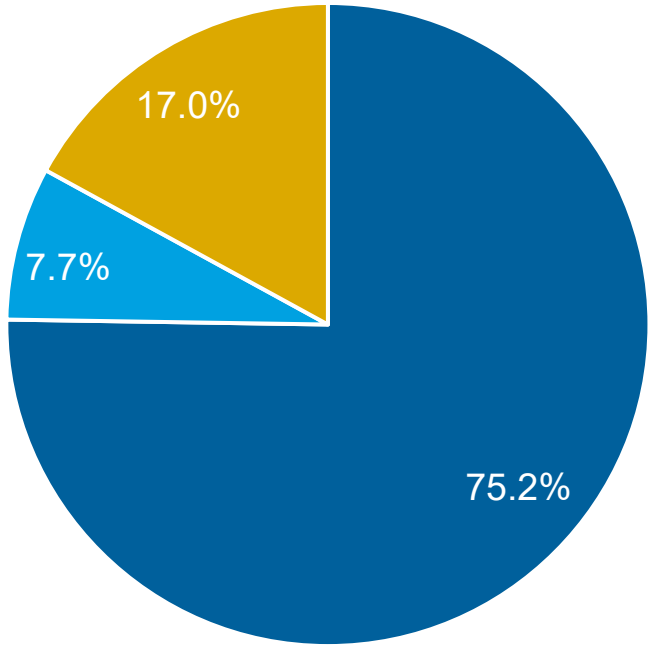


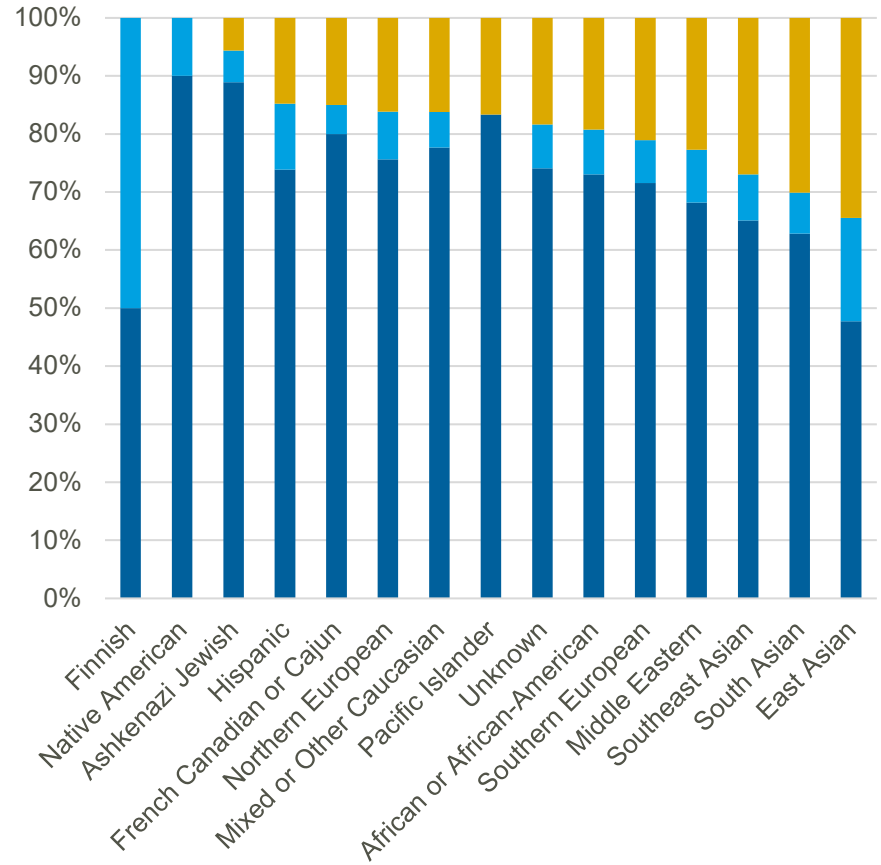
CNV contribution exceeded 5% for 37 genes



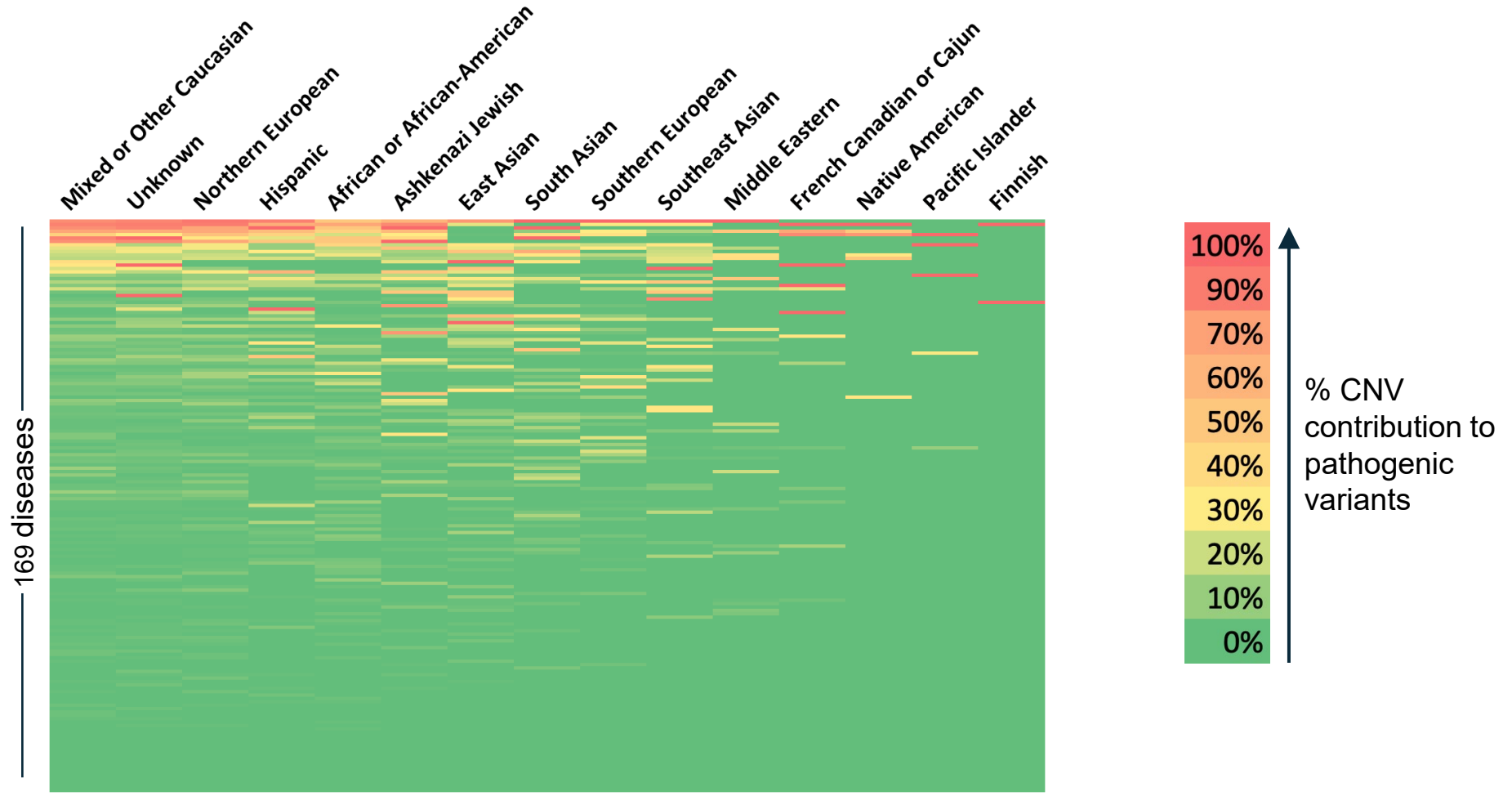
17% of pathogenic CNVs are completely novel

CNV Classification	Published Cases
Likely Pathogenic *without* case support	–
Likely Pathogenic *with* case support	
Known Pathogenic	

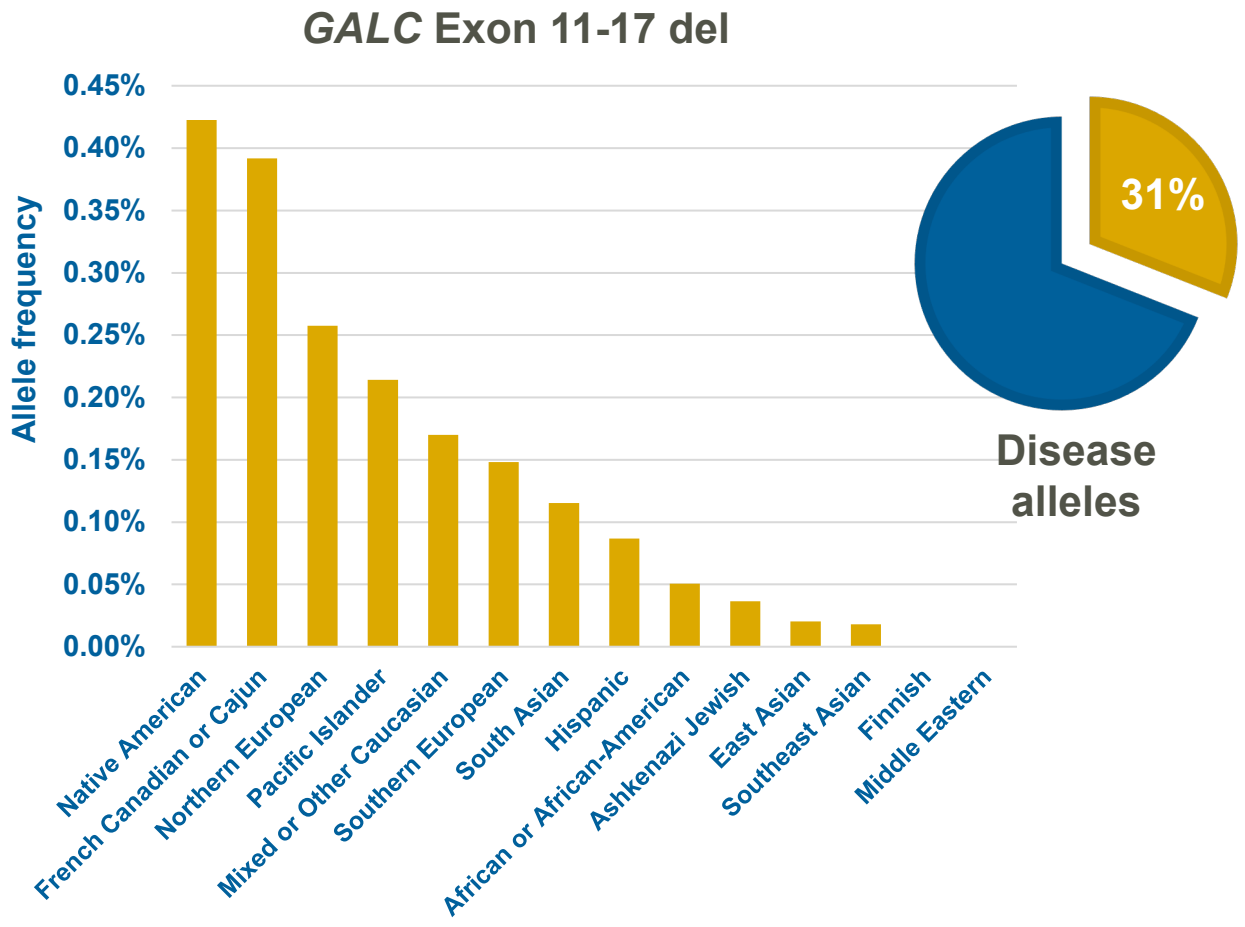




Landscape of CNV contribution: 169 diseases



Recurrent CNVs: Multiethnic



Example: ***GALC* 30 kb del**

- Krabbe disease
- frame N/A (involves last coding exon)
- **31%** disease alleles for total cohort
- seen in **89%** of ethnicities
- Luzi *et al.* 1995, Tappino *et al.* 2010:
  - reported as frequent in Caucasians

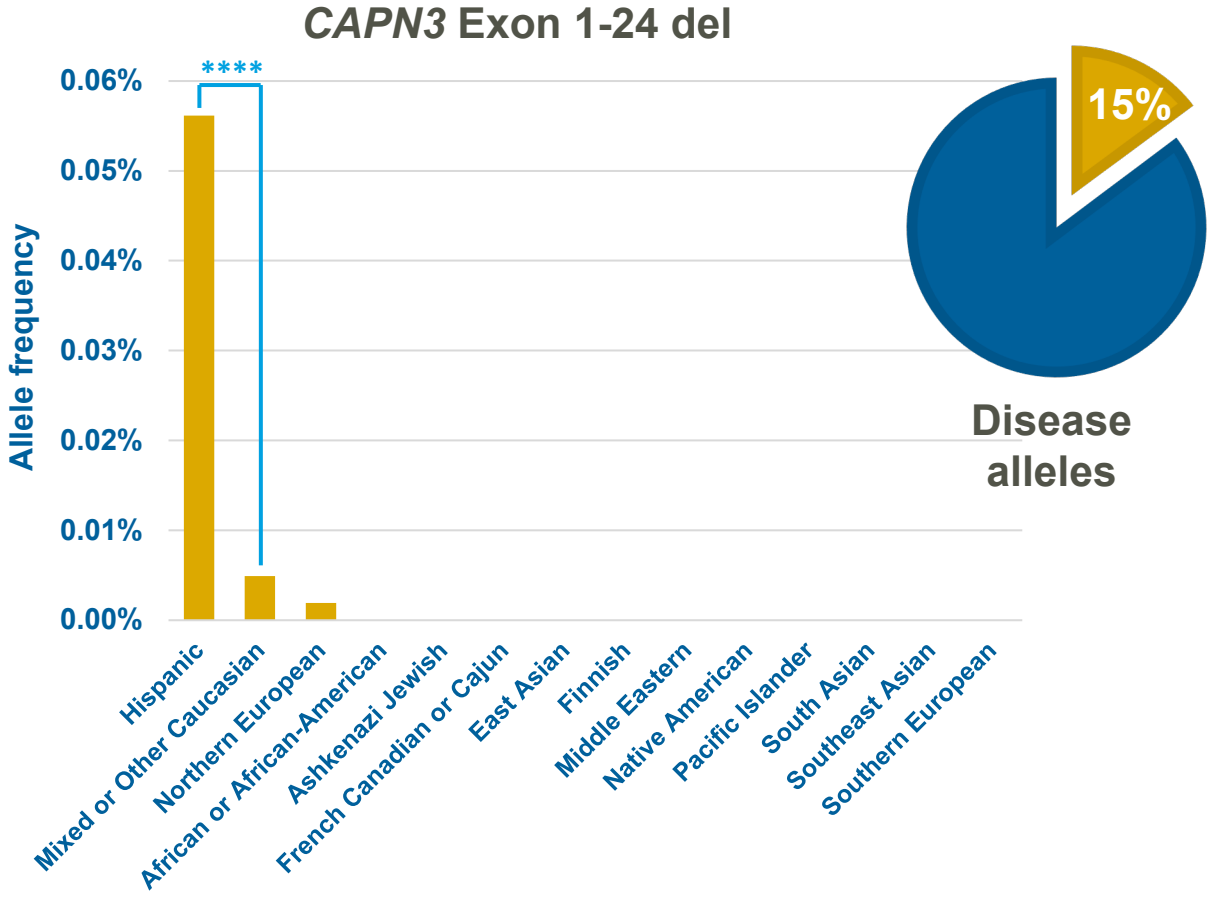
Recurrent CNVs: Multiethnic

CNV	Pop freq	% ethnicities	% all carriers	Frame	Published evidence (PMIDs)
GALC Exon 11-17 del	0.14%	86%	31%	N/A (last coding exon)	'30kb deletion' reported as frequent in Caucasians. Nonrecurrent appearance (8634707, 20886637)
CLN3 Exon 8-9 del	0.19%	71%	82%	OUT-OF-FRAME	'1 kb deletion' reported as a founder mutation in a common European ancestor (22545070)
CTNS 57 kb deletion	0.16%	71%	58%	N/A (1st coding exon)	57 kb deletion reported as a Caucasian founder mutation, but reported in some non-European populations (10417278, 30949462)
HEXB Exon 1-5 del	0.04%	71%	16%	N/A (1st coding exon)	Recombination between two Alu sequences. Suggested French or French-Canadian founder origin (2147027)
HBB Exon 1-3 del	0.05%	71%	2%	WHOLE GENE	Deletions of varying size have been reported in a large number of ethnicities (23637309)
GJB2-D13S1830 del	0.04%	71%	2%	PROMOTER	Founder effect in Ashkenazi Jews and a suggested common founder for countries in Western Europe (14571368)

Recurrent CNVs: Known ethnicity-specific

CNV	Ethnicity -specific	Sub-pop freq	% all carriers	Frame	Signifi-cance (p-value)	Published evidence (PMIDs)
NEB Exon 55 del	Ashkenazi Jewish	7.4E-03	75%	IN-FRAME	2.56E-65	Ashkenazi Jewish founder (15221447, 19232495)
GALT Exon 1-11 del	Ashkenazi Jewish	5.6E-03	76%	WHOLE GENE (bipartite structure)	1.91E-57	Ashkenazi Jewish founder (11286505, 17079880)
MCOLN1 Exon 1-7 del	Ashkenazi Jewish	2.3E-03	26%	N/A (1st coding exon)	4.01E-21	Ashkenazi Jewish founder (10973263, 11551108)
ERCC8 Exon 4 del	East Asian	4.7E-04	30%	OUT-OF-FRAME	2.53E-04	East Asian founder rearrangement involving IVS4 (28333167, 29057985)

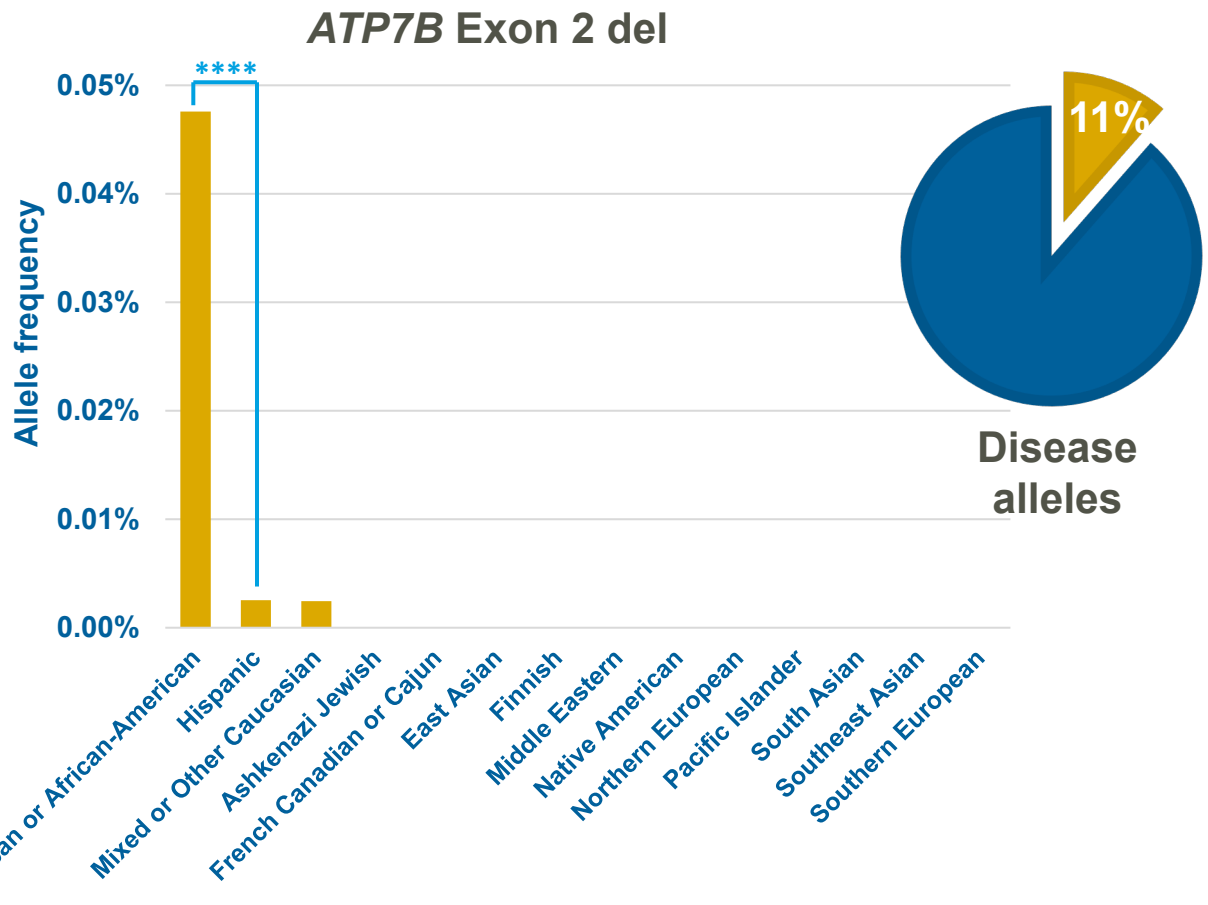
Recurrent CNVs: Novel ethnicity-specific



***CAPN3* Exon 1-24 del**

- Calpainopathy
- whole gene del
- observed **22** times in **Hispanic** patients
- **15%** disease alleles for this ethnicity
- **Reported in different ethnicity:**
  - Jaka *et al.* 2014: 2 Spanish families - authors suggest as possible founder in south of Spain

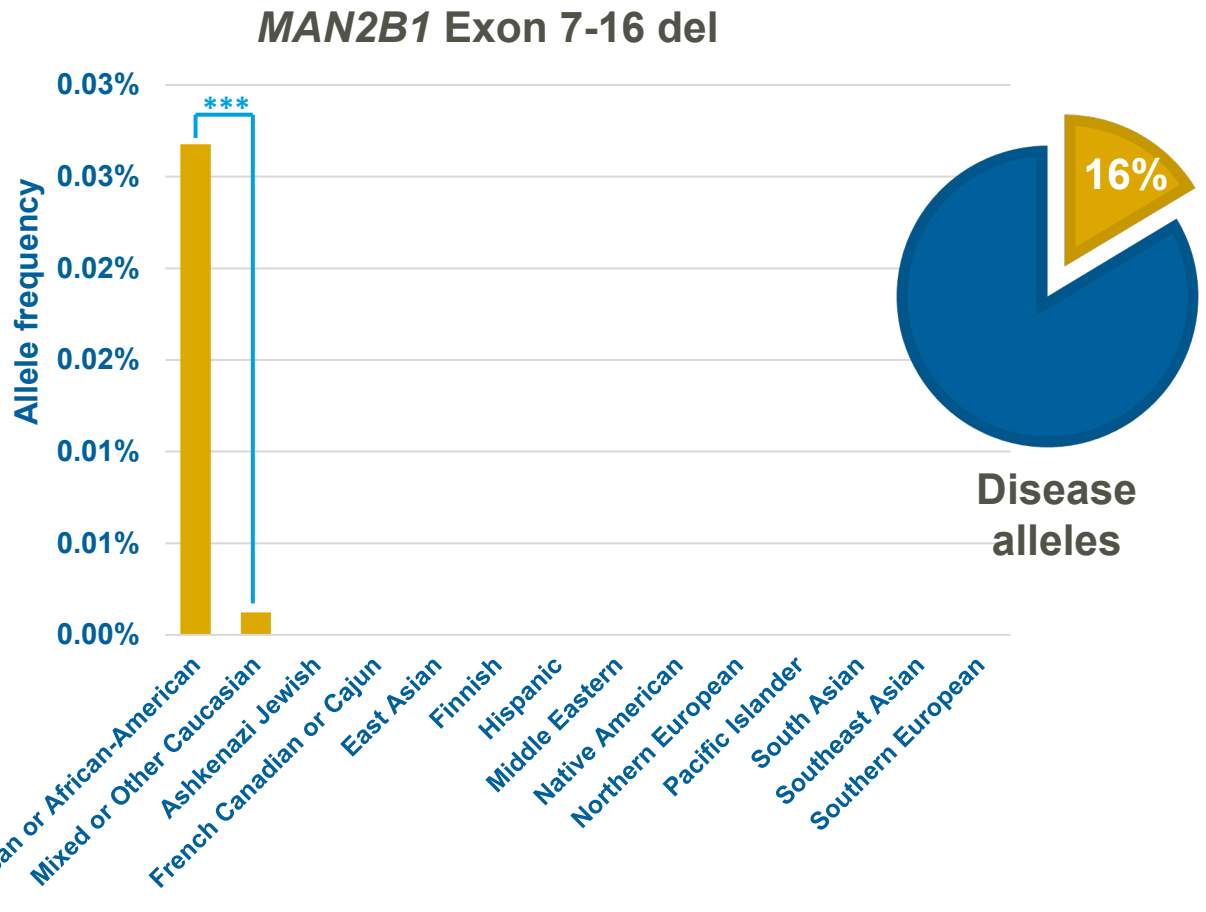
Recurrent CNVs: Novel ethnicity-specific



***ATP7B* Exon 2 del**

- Wilson disease
- out-of-frame
- observed **16** times in **African or African-American** patients
- **11%** disease alleles for this ethnicity
- **Reported in different ethnicity:**
  - Hua *et al.* 2016, Chen *et al.* 2019: 4 Chinese cases

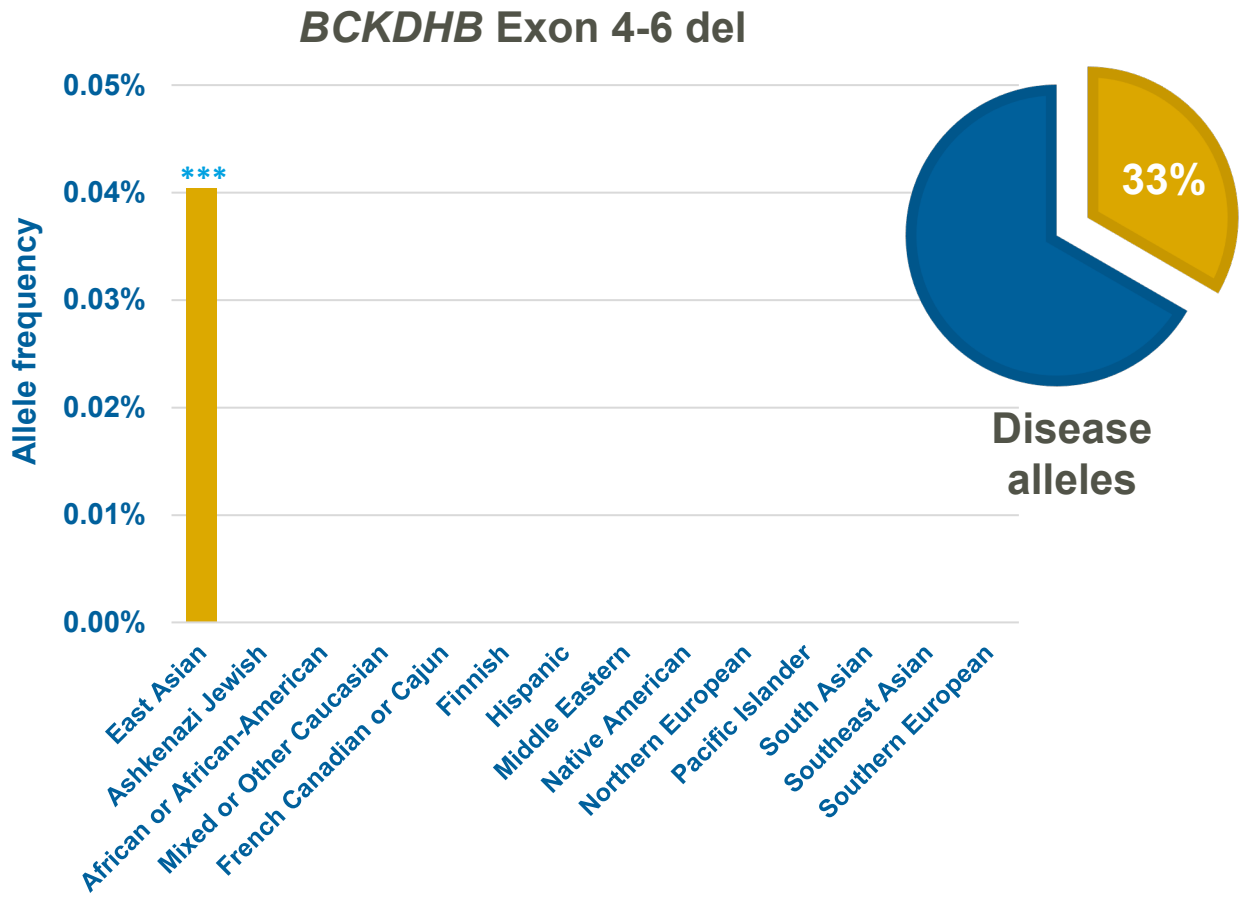
Recurrent CNVs: Novel ethnicity-specific



***MAN2B1* Exon 7-16 del**

- Alpha-mannosidosis
- in-frame (37% protein)
- observed **9** times in **African or African-American** patients
- **16%** disease alleles for this ethnicity
- Not found in the literature:
  - Cases with encompassed deletions only

Recurrent CNVs: Novel ethnicity-specific



***BCKDHB* Exon 4-6 del**

- Maple syrup urine disease type Ib
- in-frame (34% protein)
- observed **6** times in **East Asian** patients
- **33%** disease alleles for this ethnicity
- **Reported in different ethnicity:**
  - Abiri *et al.* 2019: 1 Iranian case

Conclusions

- Contribution of CNVs to population carrier burden is widespread for serious and clinically actionable Mendelian diseases.
- Recurrent CNVs make a previously unappreciated and clinically relevant contribution to ethnicity-specific disease allele frequency.
- Highlights the need to incorporate CNV calling in testing paradigms to maximize detection rates across the broad spectrum of patients and healthy adult individuals.

Acknowledgements

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