Improving Our Understanding of Autosomal Recessive Condition Frequencies:

Lessons Learned from the Rare Genomes Project's Prevalence Study of *GBE1*-Related Disease

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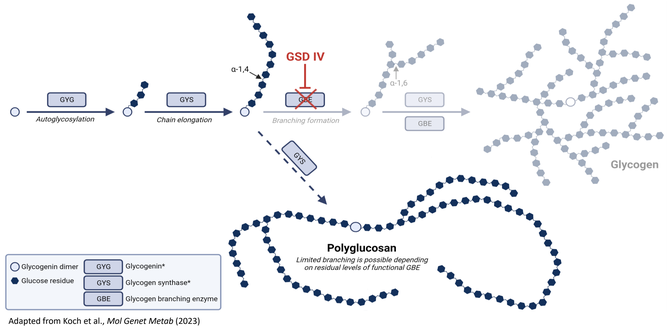
Background

Glycogen storage disease type IV (GSD IV) is caused by deficient glycogen branching enzyme activity



Adapted from Koch et al., *Mol Genet Metab* (2023)

An autosomal recessive disease that exhibits phenotypic heterogeneity

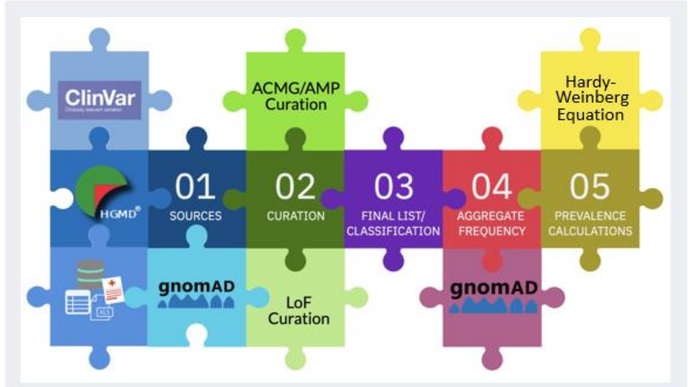
- Spectrum of clinical involvement: hepatic, neurologic, muscular, and cardiac
- Caused by a variety of pathogenic variants and large gene deletions in *GBE1*
- Varies in severity and age of onset

GBE1-related disease is traditionally categorized by pediatric-onset form ("GSD IV") versus adult-onset form ("APBD")

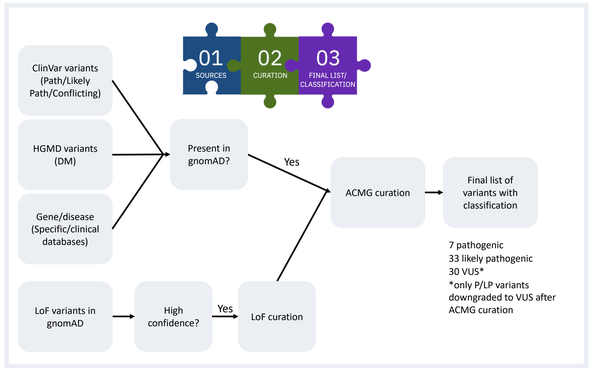
- Pediatric-onset GSD IV: presents at different stages (in utero to adolescence)
- Adult Polyglucosan Body Disease (APBD): adult-onset neurodegenerative disease common in the Ashkenazi Jewish population (high frequency of p.Y329S variant)
- An epidemiological study of all *GBE1*-related disease phenotypes has not been performed

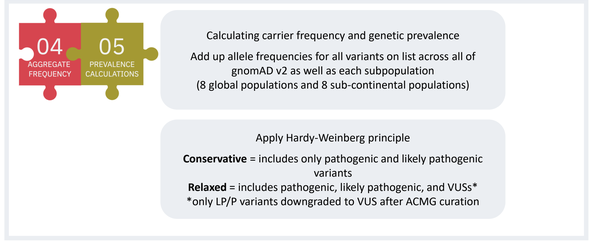
Methods

Using variant databases to estimate disease genetic prevalence for recessive disease conditions



With the ongoing research of potential treatments, it is critical to understand the global genetic prevalence of GBE1-related disease to support therapeutic development





Results & Conclusions

Global carrier frequency and genetic prevalence by *GBE1*-related disease and populations

		All *GBE1*-Related Disease				GSD IV				APBD			
	# of alleles	Conservative frequency	Relaxed frequency	Conservative prevalence	Relaxed prevalence	Conservative frequency	Relaxed frequency	Conservative prevalence	Relaxed prevalence	Conservative frequency	Relaxed frequency	Conservative prevalence	Relaxed prevalence
All Populations	282,896	**1/284**	**1/185**	**1/323,188**	**1/136,970**	**1/436**	**1/298**	**1/760,995**	**1/355,934**	**1/1072**	**1/406**	**1/4,596,833**	**1/657,834**
African	24,970	1/991	1/594	1/3,929,926	1/1,412.478	1/2528	1/1353	1/25,570,585	1/7,322,957	1/4586	1/1343	1/84,118,601	1/7,212,225
Latino	35,440	1/347	1/214	1/480,712	1/183,469	1/439	1/237	1/770,814	1/225,180	-	1/5587	-	1/124,873,532
Ashkenazi Jewish	10,370	1/49	1/47	1/9,414	1/8,887	1/2003	1/2003	1/16,047,465	1/1,6047,465	1/50	1/49	1/10,098	1/9,525
East Asian	19,954	1/1333	1/307	1/7,104,668	1/376,406	1/5785	1/193	1/133,866,212	1/148,388	1/9578	1/9578	1/36,695,1846	1/366,951,846
Korean	3,818	-	1/616	-	1/1,518,341	-	1/308	-	1/379,585	-	-	-	-
Other East Asian	14,424	1/1021	1/263	1/4,165,781	1/276,561	1/4451	1/170	1/79,251,681	1/116,048	1/6875	1/6875	1/189,063,918	1/189,063,918
Finnish	25,124	1/477	1/269	1/909,736	1/289,611	1/524	1/524	1/1,097,357	1/1,097,357	-	1/375	-	1/563,904
non-Finnish European	129,200	1/256	1/168	1/261,179	1/113,477	1/300	1/249	1/360,586	1/248,191	1/2758	1/411	1/30,417,796	1/676,412
Bulgarian	2,670	1/439	1/176	1/771,334	1/124,152	1/1291	1/1291	1/6,666,609	1/6,666,609	1/665	1/264	1/1,771,536	1/278,084
Estonian	4,834	1/400	1/240	1/640,882	1/231,309	1/599	1/401	1/1,437,595	1/641,940	1/1205	1/481	1/5,803,281	1/926,212
North-western European	50,820	1/311	1/200	1/386.500	1/160,707	1/366	1/293	1/534,999	1/343,254	1/4615	1/498	1/85,193,469	1/992,817
Other non-Finnish European	33,132	1/283	1/169	1/319,390	1/113,674	1/325	1/257	1/421,668	1/264,372	1/3081	1/345	1/37,968,827	1/477,145
Southern European	11,610	1/705	1/212	1/1,987,488	1/179,531	1/1396	1/471	1/7,798,364	1/886,137	1/2851	1/415	1/32,518,018	1/689,962
Swedish	26,134	1/150	1/125	1/90,191	1/62,451	1/160	1/156	1/101,774	1/96,928	1/6469	1/450	1/167,403,535	1/808.966
Other	7,228	1/156	1/125	1/97,048	1/62,083	1/228	1/179	1/208,796	1/128,300	1/602	1/354	1/1,449,633	1/501.839
South Asia	30,616	1/2249	1/370	1/20,232,556	1/547.166	1/4376	1/1179	1/76610,374	1/5,559,802	1/14,744	1/473	1/869,547,264	1/894.969

Estimated number of affected individuals by *GBE1*-related disease based on 2022 world population (7.9 billion)*

*gnomAD is not representative of the entire world population and therefore, this number is only an estimate

All *GBE1*-Related Disease	GSD IV	APBD
Conservative estimate of affected individuals	**Conservative estimate of affected individuals**	**Conservative estimate of affected individuals**
26,075	11,454	1,719

~1,100 of those are expected to be from Ashkenazi Jewish genetic ancestry group

Limitations:

- Only includes variants present in gnomAD
- Not all VUSs are included in the analysis, though we believe that the VUSs that are most likely to turn likely pathogenic/pathogenic are included
- Some populations and subpopulations are missing from gnomAD and more diversity of reference data is needed
- This calculation assumes random mating and does not take into account the increased rates of consanguinity in some cultures

Estimated global carrier frequency:
~1 in 284 individuals

The global genetic prevalence of GBE1-related disease:
~1 in 323,000 individuals

Individuals with GBE1-related disease
~26,000 individuals

View the conservative results on the public GeniE platform
genie.broadinstitute.org/public-lists/

The estimated genetic prevalence reports are publicly available through the Genetic Prevalence Estimator (GeniE) tool which enables users to estimate carrier frequency and genetic prevalence for recessive conditions.

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Have questions or manage a patient with GBE deficiency?

Contact Rebecca Koch, PhD, RDN, LDN at Duke University
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