BRIEF REPORT

Genome Aggregation Database Version 4—Allele Frequency Changes and Impact on Variant Interpretation in Dystonia

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ABSTRACT: Background: Population-scale databases majorly contribute to variant interpretation. The recently released Genome Aggregation Database (gnomAD) v4 offers a >5-fold increased sample size compared to v2.1.1. Pathogenic variants absent from v2.1.1 are now registered in v4 at a considerable rate. The implications on variant interpretation in dystonia are unknown.

Methods: All curated variants linked to the most common dominant forms of isolated dystonia were extracted from the International Parkinson's Disease and Movement Disorder Society Gene database. We compared variant population-frequencies and gene constraint metrics between gnomAD v2.1.1 and v4.

Results: The majority of dystonia-causing variants (192/247, 77.7%) remained absent from the newer gnomAD version. Of 219 variants absent from v2.1.1, 27 (12.3%) appeared for the first time in v4.1, including well-established pathogenic alleles. Gene constraints for *GNAL* and *KMT2B* significantly decreased in v4.

Conclusions: A growing number of dystonia-linked alleles are seen in gnomAD v4. The presence in population-scale data does not preclude pathogenicity.

Key Words: allele frequency; dystonia; gnomAD; *KMT2B*; variant interpretation

Population databases majorly contribute to variant interpretation in medical genetics.[1] The absence of a variant among population controls supports its pathogenicity (moderate criterion "PM2" in the American College of Medical Genetics and Genomics [ACMG] guidelines).[2] Moreover, a significantly higher prevalence of a variant in affected individuals compared with controls can be used as "strong" evidence for pathogenicity according to the ACMG "PS4" criterion.[2] The evaluation of variant frequencies in publicly available population databases has been widely adopted into clinical evidence-based frameworks and aims to reduce subjectivity in variant classification.

Despite these recommended applications, challenges are associated with the use of large-scale reference genetic data for the assessment of variants that were identified in patients with dystonia. In particular, the use of stringent frequency cutoffs (eg, requiring the absence of a variant from controls) can increase the risk of falsely categorizing a disease-causing alteration as benign or as variant of uncertain significance (VUS). Variants causing monogenic dystonia can be found in population datasets for different reasons. First, reduced penetrance, a phenomenon well known for many forms of monogenic dystonia, may result in the enrolment of asymptomatic individuals with pathogenic variation in control cohorts.[3] Second, movement abnormalities can manifest late in life, raising the possibility that individuals harboring an underlying genetic predisposition may be included as controls before symptom onset. Third, variable expressivity may result in mild phenotypes, which can remain undiagnosed in large population cohorts. Fourth, subjects included in population databases may not have been properly phenotyped for the trait of interest.

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One of the largest and most commonly queried resources, the Genome Aggregation Database (gnomAD), is updated periodically. A new gnomAD release was launched in November 2023, v4 (https://gnomad.broadinstitute.org/). This v4 version of gnomAD (meanwhile accessible as v4.1) contains sequencing data from 807,162 individuals (730,947 exomes and 76,215 genomes), a more than 5-fold increase in genomic information compared with the previous v2.1.1 release, which had become commonplace in diagnostic practice. Pathogenic variants, often absent from v2.1.1, are now registered in gnomAD at a considerable rate; for example, 14 different ClinVar-annotated (likely) pathogenic loss-of-function (LoF) changes in the neurodevelopmental disease- and dystonia-associated gene *CHD8* are found in 28 gnomAD-v4 subjects, as compared with two such variants (in one individual each) in v2.1.1. We recently made the unexpected observation of a patient with dystonia who had a probable clinically relevant de novo variant of extreme rarity according to v2.1.1, but which was later found to display an allele frequency "greater than expected" for a rare disorder in gnomAD v4.1.[4] This finding motivated us to explore the impact of the newly provided genomic information in gnomAD on variant analysis in dystonia. To this purpose, we systematically screened gnomAD v2.1.1 and v4.1 for variants described in genes linked to autosomal dominant forms of isolated dystonia based on curated data provided through the International Parkinson's Disease and Movement Disorder Society Gene Database (MDSGene).[5]

Methods

We catalogued all MDSGene-reported variants (https://www.mdsgene.org/g4d) related to six genes known to cause autosomal dominantly inherited isolated dystonia (*ANO3*, *GNAL*, *KMT2B*, *TOR1A*, *THAP1*, and *VPS16*). We considered all the variants irrespectively of their presentation with additional non-dystonia features (eg, intellectual disability in the setting of *KMT2B* and *VPS16* variants). Each entry was cross-referenced with ClinVar. Variants classified as (likely) benign according to ClinVar as well as synonymous variants were excluded. For each gene, we obtained variant observed/expected ratios, LoF observed/expected upper bound fraction (LOEUF) score, as well as probability of being loss-of-function intolerant (pLI) and missense z scores from gnomAD versions v2.1.1 and v4.1. We collected the frequencies of each reported variant in both gnomAD versions along with the scores of the following in silico tools: combined annotation dependent depletion (CADD) and rare exome variant ensemble learner (REVEL). Fisher's exact or χ^2 tests were applied as appropriate to compare constraint metrics and variant frequencies in the two gnomAD versions. Statistical significance was set at $P < 0.05$. Study related data are publicly available.

Results

From the MDSGene database, 247 variants fulfilled the inclusion criteria (as of March 2024). Of these variants, 26 (10.5%) were found in ClinVar (March 2024). Thirteen variants were classified as pathogenic or likely pathogenic (13/247, 5.3%; from now on referred to as "P/LP"), nine were classified as VUS (9/247, 3.6%), and four variants had conflicting interpretations (4/247, 1.6%).

Twenty-eight variants (28/247, 11.3%) were already listed in v2.1 (see Table 1). Six of these variants displayed a significant allele frequency decrease in v4.1, whereas two of them displayed an increased frequency in v4.1 as compared with v2.1. The remaining 20 variants showed no significant changes in allele frequencies between v2.1 and v4.1.

Of 219 variants not listed in v2.1, 27 (27/219, 12.3%) appeared for the first time in v4.1 (see Table 2). Although most of these variants occurred at an absolute allele number of n = 1 in v4.1, six of them (3 in *KMT2B*, 2 in *ANO3*, and 1 in *VPS16*) were found in ≥4 individuals.

Considering the 13 P/LP variants from ClinVar, 8 (8/13, 62%) appeared for the first time in v4.1 (0 count in v2.1). Of the five P/LP variants already reported in v2.1, two displayed a decreased frequency in v4.1.

Regarding constraint metrics, *GNAL* exhibited a significant lower constraint against both LoF and missense variants in v4.1 compared with v2.1.1 (see Supplementary Table S1). The constraint of *KMT2B* against missense variants also significantly decreased in v4.1 compared with v2.1.1 (see Supplementary Table S2). Gene-specific changes in variant frequencies are discussed below.

ANO3

Of 25 MDSGene-curated variants, seven (28%) appeared for the first time in v4.1 (see Table 1), two of which were classified as P/LP in ClinVar. Of the five variants already reported in v2.1 (5/25, 20%), one displayed a decreased frequency in v4.1. The remaining 13 variants (52%) were not reported in v2.1 or v4.1.

GNAL

Of 34 variants listed in MDSGene, one was already reported in v2.1 and displayed a reduced frequency in v4.1. The remaining 33 variants (97%) were not reported in v2.1 and v4.1.

KMT2B

Of 67 variants from MDSGene, eight (11.8%) appeared for the first time in v4.1. Five of these were frameshift LoF variants. Notably, the LoF variant p.Thr176Aspfs*8 had an absolute allele count of 11 in v4.1. Inspection of next-generation sequencing read

TABLE 1 . *Frequency comparison of the MDSGene database variants reported already in v2.1*

c.DNA	Protein	ClinVar classification	CADD	REVEL	Frequency v2.1	Frequency v4.1	*P* value
ANO3							
c.1969G>A	p.Ala657Thr	Likely pathogenic	26.5	0.472	0.00000399	0.00000685	1.0
c.2586G>T	p.Lys862Asn	Pathogenic	16.6	0.039	0.00000399	0.00001302	0.3489
c.2497A>G	p.Ile833Val		21.0	0.096	0.00001593	0.00000930	0.3116
c.2917G>C	p.Gly973Arg		28.7	0.385	0.00001065	0.00000930	0.7426
c.982>T	p.Arg328Cys		24.7	0.155	0.00005171	0.00001984	***0.0067***
GNAL							
c.44G>A	p.Gly15Asp		0.836	0.266	0.00004287	0.00002295	0.0680
KMT2B							
c.5336G>A	p.Arg1779Gln	Not provided	28.9	0.567	0.00000402	0.00000124	0.3498
THAP1							
c.407A>G	p.Asn136Ser		23.9	0.462	0.00001591	0.00002107	0.8121
c.506G>A	p.Arg169Gln	VUS	23.9	0.316	0.00001193	0.00001300	1.0
c.395T>C	p.Phe132Ser	VUS	21.5	0.506	0.00001591	0.00004027	0.0752
c.−42C>T			20.7		0.00000399	0.00003174	***0.0077***
c.86G>A	p.Arg29Gln		28.6	0.883	0.00000398	0.00000274	0.5476
c.238A>G	p.Ile80Val	VUS	16.6	0.610	0.00002784	0.00001984	0.4761
c.496G>A	p.Ala166Thr		20.1	0.410	0.00002386	0.00001611	0.4319
c.−32C>T			17.9		0.00001199	0.00000372	0.1091
c.427A>G	p.Met143Val	VUS	18.9	0.436	0.00005656	0.00003593	0.1044
c.521A>G	p.Glu174Gly		28.5	0.541	0.00000795	0.00000318	0.0900
c.50A>G	p.Asp17Gly		25.9	0.731	0.00002802	0.00001574	0.1913
TOR1A							
c.863G>A	p.Arg288Gln	Pathogenic	23.0	0.387	0.00009191	0.00009541	1.0
c.962C>T	p.Thr321Met	VUS	25.9	0.53	0.00001061	0.00007001	***<0.0001***
c.907_909delGAG	p.Glu303del	Pathogenic	19.5		0.00010605	0.00005204	***0.0014***
c.934A>G	p.Arg312Gly		21.9	0.183	0.00000398	0.00000342	1.0
c.823A>G	p.Lys275Glu	Conflicting interpretation	23.5	0.07	0.00043481	0.00026392	***<0.0001***
c.385G>A	p.Val129Ile	VUS	26.1	0.369	0.00006717	0.00002602	***0.0017***
VPS16							
c.692A>G	p.Tyr231Cys		23.9	0.406	0.00004772	0.00000991	***0.0001***
c.156C>A	p.Asn52Lys	Pathogenic	18.8	0.096	0.00024778	0.00007435	***<0.0001***
c.1903C>T	p.Arg635*	Conflicting interpretation	37.0		0.00000402	0.00000256	0.5640
c.1939C>T	p.Arg647*	Conflicting interpretation	39.0		0.00000402	0.00000310	0.5772

Significant changes in allele frequency in v4.1 are marked in bold; the blue and red shading indicate a decrease or an increase in allele frequency, respectively. Italics indicates gene names.

Abbreviations: MDSGene, International Parkinson's Disease and Movement Disorder Society Gene Database; CADD, Combined Annotation Dependent Depletion; REVEL, Rare Exome Variant Ensemble Learner; VUS: variant of uncertain significance.

TABLE 2 *MDSGene database variants listed for the first time in gnomAD v4.1*

c.DNA	Protein	ClinVar classification	Allele count/ allele number 4.1	Frequency v4.1
ANO3				
c.860G>A	p.Arg287Gln		5/1603422	0.00000312
c.674A>G	p.Asn225Ser		4/1607382	0.00000249
c.835T>A	p.Tyr279Asn		1/833108	0.00000120
c.702C>G	p.Cys234Trp	VUS	1/1458066	0.00000069
c.1943A>G	p.Asn648Ser	Likely pathogenic	1/833000	0.00000120
c.2540A>G	p.Tyr847Cys		1/1613556	0.00000062
c.1480A>T	p.Arg494Trp	Pathogenic	2/1564666	0.00000128
KMT2B				
c.3325_3325delC	p.Arg1109Glufs*73	Likely pathogenic	1/1436868	0.00000070
c.3431A>T	p.Asp1144Val		1/826814	0.00000121
c.3596_3697insC	p.Met1202Aspfs*22		2/1430130	0.00000140
c.521dupC[a]	p.Thr176Aspfs*8	Pathogenic	11/1460836	0.00000753
c.3325dupC	p.Arg1109Profs*4		2/1436898	0.00000139
c.2210T>C	p.Leu737Pro	VUS	7/1459534	0.00000480
c.4622C>T	p.Ala1541Val	Not provided	2/833098	0.00000240
c.6413_6414dupC[a]	p.Ala2139Glyfs*6	Pathogenic	4/1452802	0.00000275
THAP1				
c.11C>T	p.Ser4Phe	Pathogenic	1/833110	0.00000120
c.570delA	p. Asp191Thrfs*9		1/628476	0.00000159
c.5T>G	p.Val2Gly		1/833110	0.00000120
c.410A>	p.Tyr137Cys		1/1614142	0.00000062
c.7C>T	p.Gln3*	Pathogenic	1/1461488	0.00000068
c.17C>T	p.Ser6Phe		2/833110	0.00000240
c.77C>G	p.Pro26Arg		1/1461640	0.00000068
c.236delC	p.Thr79Lysfs*41		2/833110	0.00000240
c.266A>G	p.Lys89Arg	VUS	2/1613934	0.00000124
TOR1A				
c.692T>A	p.Ile231Asn		1/1614220	0.00000062
VPS16				
c.1988_1989insG	p.Asn663Lysfs*2	Likely pathogenic	1/1614198	0.00000062
c.559C>T	p.Arg187*	Conflicting interpretation	6/1461724	0.00000410

Abbreviations: MDSGene, International Parkinson's Disease and Movement Disorder Society Gene Database; gnomAD, Genome Aggregation Database; VUS: variant of uncertain significance.
[a]Filtered out because of poor quality in gnomAD v2.1.

data in gnomAD revealed that eight of 11 datasets had a depth of coverage of <20 at this site (read depth 12–19; variant called in 3–5 reads), whereas two of 11 datasets with a corresponding sequencing depth of >20 presented the variant in 20% of reads only, potentially indicative of mosaic events. Another LoF variant (p.Ala2139Glyfs*6) was also present in four carriers in v4.1; visualization of gnomAD sequencing data showed that the depth of coverage was <20 in all four subjects, with four or less reads affected. One

missense variant already present in v2.1 showed no relevant frequency change in v4.1. The remaining 58 variants (86.6%) were not reported in v2.1 and v4.1.

THAP1

Nine of 94 MDSGene-listed *THAP1* variants absent from v2.1 were now reported in v4.1, two of which were classified as P/LP in ClinVar. Of the 11 variants already present in v2.1, one displayed an increased frequency in v4.1 (absolute carrier number n = 51 in v4.1 vs. n = 1 in v2.1). The remaining 74 variants (78.7%) were not found in v2.1 and v4.1.

TOR1A

Nine *TOR1A* variants were reported in MDSGene. Of these, one appeared for the first time in v4.1. Of the six variants already present in v2.1, one displayed an increased and three a decreased frequency in v4.1. The only well-established disease-causing variant (p.Glu303del) displayed an approximately 2-fold frequency decrease in v4.1 compared with v2.1.

VPS16

Two of 18 variants appeared for the first time in v4.1. One was a P/LP frameshift LoF variant described in ClinVar. Four variants were already reported in v2.1: two with conflicting interpretations in ClinVar displayed no change in frequency, whereas the other two (1 P/LP; 1 unreported in ClinVar) displayed a reduced frequency in v4.1. The remaining 12 variants (66%) were not reported in v2.1 or v4.1.

Discussion

Although the ACMG guidelines contain two important criteria to support the pathogenicity of a variant based on its population frequency ("PS4" and "PM2"), there are often no specific recommendations for defining the expected (or "allowed") carrier cutoff of the variant in the context of an individual clinical disorder.[2] For example, rare variants associated with pediatric-onset diseases are expected to be depleted from population-based databases. Nevertheless, the most common variant causing childhood-onset generalized dystonia (*TOR1A* p.Glu303del) is recurrently found in gnomAD subjects (n = 84 in v4.1). Frequency-based filtering of variants is a key step for identifying monogenic disease variation from next-generation sequencing data. Indeed, the absence of a variant among population controls (PM2 criterion) is sufficient to upgrade a variant from VUS to likely pathogenic and the other way around.[2] Therefore, detailed knowledge about the allele count of variants linked to disorders such as dystonia in the general population is crucial. The v4.1 update of gnomAD is considered to provide more accurate frequency estimates based on a considerable increase in sample size. Therefore, for variant interpretation by the genetics community, the impact of new carrier rates of currently considered disease-causing variants on clinical diagnostics needs to be determined. Here, we comprehensively assessed the carrier rates of variants reported to cause isolated dystonia based on the MDSGene database according to the v2.1.1 and v4 gnomAD releases. Three core observations emerged from our evaluation. First, the majority (77.7%) of presumably dystonia-linked variants from MDSGene remained absent from gnomAD. This finding indicates that a relevant proportion of variants causing monogenic dystonia are ultra-rare or "private" alterations yet unobservable in a large sample size of population controls. Second, for many variants already listed in gnomAD v2.1.1, the v4 update did not result in a statistically significant change in allele frequencies, or at least not in an increased prevalence. Rather, a few dystonia-causing variants from MDSGene showed a decreased population frequency in v4 (eg, *TOR1A* p.Glu303del). This might be attributable to the inclusion of additional cohorts of European ancestry, such as the UK Biobank dataset, in which certain variants are less prevalent than in other populations (eg, the *TOR1A* p.Glu303del variant being most prevalent among Ashkenazi Jews[6]). Third, a non-neglectable number of variants listed in MDSGene, including many that were cross-referenced as P/LP alterations in ClinVar, appeared for the first time in gnomAD v4. This notion reinforces the conclusion that the (rare) presence of a variant in gnomAD does not indicate that it is benign. We also noted unexpected carrier rates for *KMT2B* LoF variants in gnomAD v4 (eg, for p.Thr176Aspfs*8; 11 carriers) which has previously been discovered as a de novo event in early-onset neurodevelopmental dystonia.[7] A closer examination of the gnomAD data suggested the presence of sequencing artifacts or mosaic states as possible explanations for some of these relatively high allele counts, adding further layers of complexity to variant interpretation using large-scale sequencing data. To overcome the intrinsic challenges of variant analysis with the use of DNA sequencing-level data alone, the implementation of additional markers for pathogenicity analysis will be a promising strategy. An example is the analysis of genome-wide methylation profiles from blood-extracted DNA to assess the consequences of variants in *KMT2B*,[8] including alterations with moderate-to-low effect sizes. Interestingly, the *KMT2B* missense variant p.Ala1541Val, unreported in gnomAD v2.1.1 but present in two carriers in v4, was shown to cause more subtle methylation changes in a family with incompletely penetrant dystonia.[8,9]

In summary, we provide a systematic assessment of population frequencies of documented dystonia-causing variants to continue improving the interpretability of variants identified in affected individuals. We found

that a sizable portion of dystonia-linked variants now appear in the recently released v4 version of gnomAD, highlighting a role for variable penetrance and expressivity mechanisms and underlining the importance of further research into the prevalence and effects of rare variants carried by patients with dystonia.

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Data Availability Statement

The data that support the findings of this study are available in gnomAD at https://gnomad.broadinstitute.org/. as well as at https://www.mdsgene.org/.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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