

Table 1: Demographic characteristics of the identified Dystonia and Control cohorts.

Diagnosis	N	Age			Gender	
		Mean	Standard Deviation	Range	Male	Female
Dystonia	1572	59	8.1	40-70	583	989
Idiopathic Familial Dystonia	3	66	3.5	62-68	1	2
Idiopathic Non-familial Dystonia	1	58	-	-	0	1
Cervical Dystonia	775	55.8	8.1	40-70	283	492
Idiopathic Orofacial Dystonia	6	47.7	8.8	40-64	3	3
Blepharospasm	131	60.4	7.3	42-70	40	91
Idiopathic torsion dystonia	1	47	-	-	0	1
Writer's cramp	4	53.8	2.5	51-57	1	3
Myoclonic dystonia	1	61	-	-	1	0
Dystonia with Tremor	488	59.6	7.7	40-70	201	287
Other Dystonia	8	54.9	5.9	47-65	2	6
Dystonia Unspecified	154	57.5	8.1	41-70	51	103
Control	24012	59	8.1	40-70	9123	14889

Table 2: Scores for Primary care and symptomatic psychiatric components

	Dystonia		Cervical Dystonia		Blepharospasm		Tremor		Dystonia, Unspecified		Control
		P-value		P-value		P-value		P-value		P-value	
Primary Care Diagnoses – Psychiatric Disorders											
ADHD	0	-	0	-	0	-	0	-	0	-	0
Anxiety	383 (24.4%)	<2.2x10 ⁻¹⁶ ***	200 (25.8%)	<2.2x10 ⁻¹⁶ ***	15 (11.5%)	0.002 **	160 (32.8%)	<2.2x10 ⁻¹⁶ ***	5 (3.2%)	1	518 (2.2%)
ASD	0	-	0	-	0	-	0	-	0	-	2 (0.008%)
Conduct Disorders	0	-	0	-	0	-	0	-	0	-	1 (0.004%)
Depression	485 (30.9%)	<2.2x10 ⁻¹⁶ ***	259 (33.4%)	<2.2x10 ⁻¹⁶ ***	20 (15.3%)	0.002 **	196 (40.2%)	<2.2x10 ⁻¹⁶ ***	7 (4.5%)	0.876	692 (2.9%)
Eating Disorders	20 (1.3%)	0.002 **	12 (1.5%)	0.002 **	1 (0.8%)	0.360	7 (1.4%)	0.002 **	0	-	14 (0.05%)
Serious Mental illness	38 (2.4%)	0.002 **	12 (1.5%)	0.002 **	2 (1.5%)	0.087	21 (4.3%)	0.002 **	3 (1.9%)	0.004**	31 (0.01%)
Substance Use Disorder	74 (4.7%)	<2.2x10 ⁻¹⁶ ***	32 (4.1%)	<2.2x10 ⁻¹⁶ ***	4 (3.1%)	0.195	36 (7.4%)	<2.2x10 ⁻¹⁶ ***	2 (1.3%)	1	215 (0.9%)
Psychiatric Symptoms											
Nervous person	448/1510 (29.7%)	1.37x10 ⁻⁵ ***	205/748 (27.4%)	0.515	35/127 (27.6%)	1	148/466 (31.8%)	2.00x10 ⁻³ ***	55/146 (37.7%)	0.002 **	5602/2327 8 (24.1%)
Worrying/anxious feelings	951/1520 (62.6%)	2.59x10 ⁻³ ***	465/752 (61.8%)	0.327	73/125 (58.4%)	1	301/470 (64.0%)	0.008**	98/149 (65.8%)	0.725	13445/233 14 (57.7%)
Feels tense/"Highly strung"	359/1488 (24.1%)	6.40x10 ⁻⁹ ***	164/738 (22.2%)	0.024*	28/123 (22.8%)	1	122/466 (26.2%)	3.76x10 ⁻⁵ ***	41/139 (29.5%)	0.056	4085/2309 6 (17.7%)
Worries too long after embarrassment	765/1485 (51.5%)	0.274	361/730 (49.5%)	1	66/123 (53.7%)	1	253/465 (54.4%)	0.151	78/145 (53.8%)	1	11091/229 19 (48.4%)
Suffers from nerves	417/1485 (28.1%)	5.54x10 ⁻¹⁰ ***	190/739 (25.7%)	0.020*	34/126 (27.0%)	1	143/457 (31.3%)	9.61x10 ⁻⁷ ***	47/142 (33.1%)	0.006**	4787/2299 2 (20.8%)
Irritability	419/1469 (28.5%)	1	194/721 (26.9%)	1	27/125 (21.6%)	1	148/458 (32.1%)	0.314	46/144 (31.9%)	1	6237/2289 4 (27.2%)
Miserableness	725/1537 (47.2%)	0.093	352/757 (42.9%)	1	51/128 (39.8%)	1	243/479 (50.7%)	0.029*	68/150 (45.3%)	1	10274/235 53 (43.6%)
Fed-up feelings	728/1529 (47.6%)	2.61x10 ⁻⁷ ***	358/759 (47.2%)	0.002**	53/126 (42.1%)	1	241/475 (50.7%)	7.31x10 ⁻⁵ ***	65/146 (44.5%)	1	9431/2340 3 (40.3%)
Guilty feelings	509/1513 (33.6%)	0.011*	249/749 (33.2%)	0.421	55/126 (43.7%)	0.010*	155/468 (33.1%)	1	48/148 (32.4%)	1	6888/2331 2 (29.5%)
Mood swings	780/1527 (51.1%)	3.69x10 ⁻⁴ ***	392/753 (52.1%)	0.006**	53/128 (41.4%)	1	253/476 (53.2%)	0.015*	71/147 (48.3%)	1	10623/233 29 (45.5%)
Loneliness/isolation	370/1529 (24.2%)	5.59x10 ⁻⁶ ***	163/754 (21.6%)	0.890	36/130 (27.7%)	0.193	126/474 (26.6%)	1.96x10 ⁻⁴ ***	40/149 (26.8%)	0.238	4448/2352 7 (18.9%)
Seen GP/doctor for nerves, anxiety, tension, or depression	676/1547 (43.7%)	1.26x10 ⁻¹⁰ ***	306/764 (40.1%)	0.071	53/127 (41.7%)	1	237/480 (49.4%)	1.72x10 ⁻⁹ ***	72/152 (47.4%)	0.028*	8348/2378 0 (35.1%)

Seen a psychiatrist for nerves, anxiety, tension, or depression	278/1558 (17.8%)	7.05x10 ⁻¹⁴ ***	114/769 (14.8%)	0.069	26/127 (20.5%)	0.033*	100/486 (20.6%)	1.30x10 ⁻⁸ ***	35/151 (23.2%)	1.76x10 ⁻⁴ ***	2741/2386 5 (11.5%)
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Legend: P-values are all vs control and are represented as post Bonferroni correction for multiple comparisons, *p<0.05; **p<0.01; ***p<0.001, ADHD: Attention Deficit Hyperactivity Disorder, GP: General Practitioner

Table 3: Comparison of pain, sleep and cognition scores between dystonia and control cohorts

	Dystonia		Cervical Dystonia		Blepharospasm		Tremor		Dystonia, Unspecified		Control
	n (%)	P-value	n (%)	P-value	n (%)	P-value	n (%)	P-value	n (%)	P-value	n (%)
Pain	1129/1565 (72.1%)	2.29x10 ⁻¹⁹ ***	560/774 (72.3%)	7.09x10 ⁻¹¹ ***	86/131 (65.6%)	0.283	347/485 (71.5%)	1.51x10 ⁻⁶ ***	121/151 (80.1%)	1.60x10 ⁻⁶ ***	14519/23911 (60.7%)
Headache	430/1565 (27.5%)	6.63x10 ⁻¹⁰ ***	220/774 (28.4%)	1.08x10 ⁻⁶ ***	29/131 (22.1%)	1	136/485 (28.0%)	5.54x10 ⁻⁴ ***	41/151 (27.2%)	0.458	4912/23911 (20.5%)
Facial pain	60/1565 (3.8%)	4.47x10 ⁻⁷ ***	18/774 (2.3%)	1	13/131 (9.9%)	0.004**	17/485 (3.5%)	0.094	11/151 (7.3%)	0.004**	439/23911 (1.8%)
Neck/shoulder pain	551/1565 (35.2%)	4.82x10 ⁻²³ ***	268/774 (34.6%)	5.80x10 ⁻¹¹ ***	37/131 (28.2%)	1	164/485 (33.8%)	3.84x10 ⁻⁶ ***	71/151 (47.0%)	4.50x10 ⁻¹⁰ ***	5701/23911 (23.8%)
Back pain	493/1565 (31.5%)	3.22 x10 ⁻⁶ ***	230/774 (39.7%)	0.101	46/131 (35.1%)	0.143	163/485 (33.6%)	7.57x10 ⁻⁴ ***	49/151 (32.5%)	0.565	6137/23911 (25.7%)
Stomach/abdominal pain	201/1565 (12.8%)	4.66x10 ⁻⁷ ***	100/774 (12.9%)	6.50x10 ⁻⁴ ***	15/131 (11.5%)	1	59/485 (12.2%)	0.089	25/151 (16.6%)	0.010*	2094/23911 (8.8%)
Hip pain	260/1565 (16.6%)	6.33x10 ⁻⁹ ***	100/774 (12.9%)	1	26/131 (19.8%)	0.032*	95/485 (19.6%)	3.12x10 ⁻⁷ ***	35/151 (23.2%)	9.12x10 ⁻⁵ ***	2730/23911 (11.4%)
Knee pain	402/1565 (25.7%)	1.30x10 ⁻³ ***	196/774 (25.3%)	0.119	31/131 (23.7%)	1	130/485 (26.8%)	0.055	42/151 (27.8%)	0.636	5162/23911 (21.6%)
Pain all over	59/1565 (3.8%)	4.80x10 ⁻⁸ ***	22/774 (2.8%)	0.196	2/131 (1.5%)	1	22/485 (4.5%)	4.80x10 ⁻⁵ ***	12/151 (7.9%)	0.004**	407/23911 (1.7%)
Sleep											
Insomnia	1263/1569 (80.5%)	0.006**	621/775 (80.1%)	0.210	104/131 (79.4%)	1	403/486 (82.9%)	0.011*	120/153 (78.4%)	1	18421/23942 (76.4%)
Chronotype	554/1395 (39.7%)	0.575	283/695 (40.7%)	0.495	42/118 (35.6%)	1	179/433 (41.3%)	0.845	47/131 (35.9%)	1	7997/21289 (37.6%)
Sleep Duration	594/1553 (38.2%)	2.63x10 ⁻⁶ ***	267/772 (34.6%)	0.789	46/129 (35.7%)	1	208/478 (43.5%)	7.50x10 ⁻⁷ ***	68/149 (45.6%)	0.003**	7639/23825 (32.1%)
Snoring	550/1423 (38.7%)	0.303	282/716 (39.4%)	0.413	44/113 (38.6%)	1	163/440 (37.0%)	1	54/136 (39.7%)	1	8029/22213 (36.1%)
Daytime sleepiness	72/1553 (4.7%)	4.61x10 ⁻⁴ ***	30/769 (3.9%)	0.570	3/126 (2.4%)	1	29/481 (6.0%)	4.03x10 ⁻⁴ ***	10/153 (6.5%)	0.065	683/23855 (2.9%)
Sleep Pattern											
Health Sleep pattern	402/1249 (32.2%)	4.90x10 ⁻⁴ ***	208/642 (32.4%)	0.016*	34/99 (34.3%)	0.639	116/379 (30.6%)	0.011*	37/114 (32.5%)	0.350	7306/19674 (37.1%)
Intermediate sleep pattern	766/1249 (61.3%)	0.049*	397/642 (61.8%)	0.095	57/99 (57.6%)	0.939	237/379 (62.5%)	0.124	67/114 (58.8%)	1	11502/19674 (58.5%)
Poor sleep pattern	81/1249 (6.5%)	7.67x10 ⁻⁴ ***	37/642 (5.8%)	0.121	8/99 (8.1%)	0.083	26/379 (6.9%)	0.030*	10/114 (8.8%)	0.042*	866/19674 (4.40%)
Sleep score	3(2-4)	9.16x10 ⁻⁸ ***	3(2-4)	4.37x10 ⁻⁴ ***	3(2-4)	0.517	3(2-4)	3.01x10 ⁻⁵ ***	3(2-4)	0.056	3(3-4)

Cognition	Median (range) [n]	p-value	Median (range) [n]	p-value	Median (range) [n]	p-value	Median (range) [n]	p-value	Median (range) [n]	p-value	Median (range) [n]
Numeric Memory	7(6-7) [91]	1	7(6-8) [29]	0.282	7(6.5-7) [11]	1	6(6-7) [30]	0.600	6(5.5-7) [19]	0.524	7(6-8) [2466]
Prospective Memory	2(1-2) [437]	0.287	2(2-2) [218]	1	2(1-2) [37]	1	2(1-2) [128]	0.396	2(1-2) [50]	0.077	2(2-2) [8307]
Good Recall	317/437 (72.5%)	0.090	168/218 (77.1%)	0.833	25/37 (67.6%)	0.300	90/128 (70.3%)	0.147	31/50 (62.0%)	0.029*	6331/8307 (76.2%)
Intermediate Recall	93/437 (21.3%)	0.238	37/218 (17.0%)	0.531	12/37 (32.4%)	0.059	28/128 (21.9%)	0.458	15/50 (30.0%)	0.069	1569/8307 (18.9%)
Bad Recall	27/437 (6.2%)	0.277	13/218 (6.0%)	0.577	0/37 (0.0%)	-	10/128 (7.8%)	0.193	4/50 (8.0%)	0.291	407/8307 (4.9%)
Fluid Intelligence	6(4-7) [413]	0.018*	6(4-7.75) [206]	1	5(4-5) [36]	0.306	6(4-7) [123]	0.342	5(4-7) [45]	0.268	6(4-7) [8008]
Pairs Matching											
Trial 1	0(0-1) [1567]	0.128	0(0-1) [775]	1	0(0-1) [131]	1	0(0-1) [485]	0.001**	0(0-1) [152]	1	0(0-1) [23795]
Trial 2	3(2-6) [1567]	0.820	4(2-6) [775]	0.640	3(2-5) [131]	1	3(2-6) [485]	1	4su(2-6) [152]	1	3(2-6) [23795]

Legend: P-values are all vs control and are represented as post Bonferroni correction for multiple comparisons

*p<0.05; **p<0.01; ***p<0.001

Table 4: Number of individuals from the complete genetic cohort (n=179028) and dystonia cohort (n=485) with genetic variants in 32 genes that have previously been associated with dystonia

Gene	Location	OMIM number	Synonymous variants		Missense Variants						Loss of Function Variants		Other non-synonymous Variants	
			S	R	MPC<2		MPC 2-3		MPC >3		S	R	S	R
					S	R	S	R	S	R				
<i>SLC2A1</i>	1p34.2	138140	36; 0	114; 1	31; 0	82; 0	18; 0	34; 0	0; 0	0; 0	2; 0	0; 0	0; 0	0; 0
<i>HPCA</i>	1p35.1	142622	12; 0	43; 0	19; 1	42; 0	9; 0	5; 0	0; 0	0; 0	1; 0	3; 0	1; 0	0; 0
<i>MECR</i>	1p35.3	608205	20; 0	61; 0	64; 0	152; 1	0; 0	0; 0	0; 0	0; 0	14; 0	27; 0	4; 0	3; 0
<i>SPR</i>	2p13.2	182125	21; 0	36; 0	44; 0	77; 0	0; 0	0; 0	0; 0	0; 0	4; 0	12; 0	2; 0	2; 0
<i>EIF2AK2</i>	2p22.2	176871	25; 0	60; 0	68; 0	135; 0	0; 0	0; 0	0; 0	0; 0	14; 0	18; 0	1; 0	0; 0
<i>PRKRA</i>	2q31.2	603424	16; 0	25; 0	22; 0	58; 1	2; 0	0; 0	0; 0	0; 0	4; 0	5; 0	3; 0	2; 0
<i>PNKD</i>	2q35	609023	34; 0	71; 0	58; 0	166; 0	0; 0	0; 0	0; 0	0; 0	12; 0	21; 0	1; 0	9; 0
<i>COL6A3</i>	2q37.3	120250	189; 0	553; 2	484; 0	1222; 8	0; 0	0; 0	0; 0	0; 0	35; 0	65; 0	4; 0	14; 0
<i>ADCY5</i>	3q21.1	600293	93; 0	280; 1	153; 0	291; 2	40; 0	58; 0	3; 0	22; 0	17; 0	14; 0	6; 0	23; 0
<i>VPS41</i>	7p14.1	605485	44; 0	90; 1	110; 0	212; 3	0; 0	0; 0	0; 0	0; 0	20; 0	30; 0	2; 0	4; 0
<i>SGCE</i>	7q21.3	604149	25; 1	42; 0	62; 0	137; 0	0; 0	0; 0	0; 0	0; 0	13; 0	16; 0	2; 0	3; 0
<i>RELN</i>	7q22.1	600514	195; 0	429; 0	507; 1	882; 2	6; 0	9; 0	0; 0	0; 0	31; 0	20; 0	8; 0	14; 0
<i>THAP1</i>	8p11.21	609520	10; 0	13; 0	21; 0	61; 0	0; 0	0; 0	0; 0	0; 0	3; 0	2; 0	2; 0	0; 0
<i>TOR1A</i>	9q34.11	605204	27; 0	46; 0	51; 0	111; 1	0; 0	0; 0	0; 0	0; 0	8; 0	28; 0	2; 0	2; 0
<i>CIZ1</i>	9q34.11	611420	56; 1	124; 0	107; 0	233; 0	0; 0	0; 0	0; 0	0; 0	24; 0	12; 0	5; 0	17; 0
<i>KCNMA1</i>	10q22.3	600150	95; 0	243; 0	66; 0	171; 0	49; 0	50; 0	3; 0	0; 0	22; 0	19; 0	9; 0	33; 0
<i>ANO3</i>	11p14.3	610110	71; 0	122; 0	115; 0	221; 1	19; 1	25; 0	0; 0	0; 0	25; 1	45; 0	2; 0	2; 0
<i>TH</i>	11p15.5	191290	35; 0	91; 1	92; 1	252; 0	2; 0	0; 0	0; 0	0; 0	10; 0	19; 0	2; 0	0; 0
<i>KCNA1</i>	12p13.32	176260	35; 1	78; 0	25; 0	46; 0	30; 0	25; 0	0; 0	4; 0	7; 0	3; 0	2; 0	0; 0
<i>SCN8A</i>	12q13.13	600702	136; 1	236; 1	86; 1	230; 2	65; 0	124; 1	6; 0	2; 0	7; 0	10; 0	2; 0	0; 0
<i>NKX2-1</i>	14q13.3	600635	34; 0	67; 0	0; 0	0; 0	0; 0	0; 0	0; 0	0; 0	1; 0	6; 0	0; 0	9; 0
<i>GCH1</i>	14q22.2	600225	15; 0	65; 0	21; 0	54; 0	11; 0	9; 0	0; 0	0; 0	4; 0	7; 0	1; 0	3; 0
<i>PRRT2</i>	16p11.2	614386	19; 0	77; 0	79; 1	155; 1	0; 0	0; 0	0; 0	0; 0	6; 0	11; 0	2; 0	0; 0
<i>GNAL</i>	18p11.21	139312	24; 0	65; 0	27; 0	37; 1	25; 0	41; 0	3; 0	0; 0	5; 0	2; 0	3; 0	0; 0
<i>CACNA1A</i>	19p13.13	601011	180; 0	439; 1	251; 0	594; 3	109; 1	179; 0	2; 0	0; 0	18; 0	12; 0	4; 0	24; 0
<i>TUBB4A</i>	19p13.3	602662	28; 0	129; 0	23; 0	56; 0	24; 1	18; 1	8; 0	5; 0	12; 0	9; 0	2; 0	10; 0
<i>KMT2B</i>	19q13.12	606834	235; 0	584; 2	0; 0	0; 0	0; 0	0; 0	0; 0	0; 0	6; 0	0; 0	10; 0	30; 0
<i>ATP1A3</i>	19q13.2	182350	95; 0	209; 1	32; 0	71; 1	47; 0	44; 0	5; 0	4; 0	9; 0	6; 0	1; 0	0; 0
<i>VPS16</i>	20p13	608550	56; 0	108; 1	99; 1	348; 1	0; 0	0; 0	0; 0	0; 0	15; 0	17; 0	0; 0	10; 0
<i>KCTD17</i>	22q12.3	616386	9; 0	41; 0	27; 0	58; 1	7; 0	27; 0	0; 0	0; 0	7; 0	3; 0	6; 0	2; 0

<i>ATF4</i>	22q13.1	604064	47; 0	97; 1	81; 0	210; 1	0; 0	0; 0	0; 0	0; 0	10; 0	19; 0	3; 0	15; 0
<i>TAF1</i>	Xq13.1	313650	72; 0	124; 0	95; 0	163; 1	34; 0	41; 0	7; 0	9; 0	1; 0	2; 0	4; 0	4; 0

Legend: Number of variants identified per gene. Results given as overall whole exome sequencing (WES) dataset (n=200,643); dystonia cohort (n=638) with each set of values presented as whole cohort (inclusive of dystonia cohort); dystonia cohort only. MPC: missense badness, PolyPhen-2, and Constraint pathogenicity classifier. R: Rare variant (present 2-5 times in the dataset), S: Singleton variants (present once in the dataset). Other non-synonymous variants include inframe deletion, inframe insertion, stop loss and start loss variants