appendix e-1

HRM and Sanger Sequencing. HRM was performed with the LightCycler 480 Real-Time PCR system and High Resolution Master Mix (Roche; Indianapolis, IN, USA). Reactions were performed in either 96- or 384-well plates, using 40 ng of template DNA, 1× HRM Master Mix, 2.5 mM $MgCl_2$, and 200 nM of each primer in a 10-µl reaction volume. Melting curves and difference plots were analyzed by at least two investigators blinded to phenotype. Shifted melting curves were further investigated using ExoSAP-IT® (Affymetrix; Santa Clara, CA, USA)-cleaned PCR products and bidirectional Sanger sequencing.

In Silico Analyses. SIFT (http://sift.jcvi.org/) is a sequence homology-based tool that sorts intolerant from tolerant amino acid substitutions and predicts whether an amino acid substitution at a particular position in a protein will have a phenotypic effect. MutationTaster (http://www.mutationtaster.org) applies a naïve Bayes classifier to data derived from evolutionary conversation, splice-site changes, loss of protein features and changes that might affect the amount of messenger RNA to predict disease potential. PolyPhen-2 (http://genetics.bwh.harvard.edu/pph2/) predicts pathogenicity by applying a probabilistic classifier to sequence- and structure-based information. CADD (http://cadd.gs.washington.edu/) predicts pathogenicity of the variants from the whole genome by training a linear kernel support vector machine (SVM) to differentiate evolutionarily derived possibly benign alleles from simulated conceivably deleterious variants. CADD raw scores offer superior resolution across the entire spectrum of scores and are suggested for use in large case-control studies of single or multiple genes. In contrast, scaled CADD Scores (PHRED-like), which range from 0 to 99, may be most useful for identifying causal variants within an individual exome or genome. A scaled CADD score of 10 corresponds to the top 10% deleterious variants whereas a score of 20 corresponds to the top 1% of deleterious variants and so forth.

Population Controls. The EVS dataset is comprised of 2203 African-American and 4300 European-American unrelated individuals. The EVS cohort includes controls, extremes of specific traits such as cholesterol and blood pressure and specific diseases such as myocardial infarction and stroke. The 1KG cohort includes individuals of Asian, African and European ancestry. 1KG samples are mostly anonymous and have no associated phenotypic data. ExAC provides data on 60,706 unrelated individuals sequenced as part of various disease-specific and population genetic studies. In general, SVs reported in EVS, 1KG and ExAC have not been confirmed with bidirectional Sanger sequencing.

Table e-1
Clinical diagnoses and demographics for additional screening of *TOR1A* Exon 5

Clinical diagnosis	Number (age of onset)[a]	Family history[b]	Gender		Race/Ethnicity			Sequence Variant (n)[c]
			Male	Female	Caucasian	Jewish	Other	
Spasmodic dysphonia	128 (48.8 ± 8.8, 13-80)	13.3%	40	88	114	2	12	
Cervical dystonia	319 (44.4 ± 7.1, 10 -85)	13.2%	77	242	301	5	13	c. 907_909delGAG (1)
Blepharospasm	145 (57.7 ± 5.2, 11-79)	7.6%	47	98	142	0	3	
Writer's cramp	13 (34.8 ± 13.2, 7-60)	7.7%	8	5	11	0	2	
Other primary focal dystonia	58 (44.1 ± 10.8, 1-84)	17.2%	18	40	51	1	6	
Segmental dystonia	85 (44.1 ± 8.6, 5-78)	18.8%	23	62	73	0	12	c.962C>T (1)
Multifocal & generalized	24 (22.2 ± 9.9, 1-68)	33.3%	7	17	18	3	3	c. 907_909delGAG (2)
Dystonia totals	**772 (46.7 ± 10.0, 1-85)**	**13.6%**	**220**	**552**	**710**	**11**	**51**	
Other movement disorders	214 (48.4 ± 10.6, 1-76)	NA	102	112	189	3	22	
Neurologically-normal controls	174 (53.3 ± 10.1, 18-87)[d]	NA	68	106	118	2	56	
Grand total	**1160**							

[a]Mean +/- standard error, range (yrs).
[b]First- or second-degree relative with dystonia.
[c](n) - number of subjects with identified SV
[d]Age at study enrollment.
NA = not available or applicable.

Table e-2
Primers for Sanger Sequencing and High Resolution Melting

Primer	Sequence (5'→3')	Locus	Exon	Product (bp)
GNAL_E1aF	aatgcaaaatgaccctctgg	NC_000018 11689089-109		
GNAL_E1aR	ccggggcgtcagccgac	NC_000018 11689973-957	Exon 1a	885 (with GNAL_E1aF)
GNAL_E2F	cctgctctgaatcggaaaac	NC_000018 11752280-299		
GNAL_E2R	atttcctacacgcgggttc	NC_000018 11752751-733	Exon 2	472 (with GNAL_E2F)
GNAL_E3F	ccggctagtggtgagagatg	NC_000018 11752783-802		
GNAL_E3R	aagcacttttgggacgtctg	NC_000018 11752995-976	Exon 3	213 (with GNAL_E3F)
GNAL_E4F	ggaaatttaaaatcccactcaa	NC_000018 11753547-568		
GNAL_E5R	aaaatggttccatctttcact	NC_000018 11753995-975	Exons 4 & 5	449 (with GNAL_E4F)
GNAL_E6F	tttgcagtttctttttcctttt	NC_000018 11824835-856		
GNAL_E6R	tgcatgcaatcatattcttcaa	NC_000018 11825069-048	Exon 6	235 (with GNAL_E6F)
GNAL_E7F	gggaaagtgggcagagaac	NC_000018 11862344-362		
GNAL_E7R	tctcaaagtttctggtgtgtgg	NC_000018 11862493-472	Exon 7	150 (with GNAL_E7F)
GNAL_E8F	atacccgggctttaccttga	NC_000018 11864464-483		
GNAL_E8R	gaagccccttaaacctcac	NC_000018 11864687-668	Exon 8	224 (with GNAL_E8F)
GNAL_E9F	atgtgtgaacgctggaacct	NC_000018 11867062-081		
GNAL_E9R	tgctgagtgttagaattcactcc	NC_000018 11867278-256	Exon 9	217 (with GNAL_E9F)
GNAL_E10F	ctgagtagctgctgggtgtg	NC_000018 11868457-476		
GNAL_E10R	cctggcctgagcgtatttt	NC_000018 11868736-718	Exon 10	280 (with GNAL_E10F)
GNAL_E11F	ctatgttagaggcactttcatg	NC_000018 11872201-222		
GNAL_E11R	aaacaattctattcctcaatcat	NC_000018 11872443-421	Exon 11	570 (with GNAL_E11F)
GNAL_E12F	ccttctgtgttttcgtagagttg	NC_000018 11876547-569		
GNAL_E12R	gaagggaggtagaaaaacaaagg	NC_000018 11876727-705	Exon 12	181 (with GNAL_E12F)
GNAL_E13F	tccttccccagagtacatgc	NC_000018 11880928-947		
GNAL_E13R	agagactctgcctcctaccat	NC_000018 11881218-198	Exon 13	291 (with GNAL_E13F)
THAP1_E1F	aagaagcgagggaatccaac	NT_007995 13018721-702		
THAP1_E1R	ccccaccccggctgaga	NT_007995 13018509-525	Exon 1	213 (withTHAP1_1F)
THAP1_E2F	tttgggtgcctttatttattt	NT_007995 13014975-955		
THAP1_E2R	caaaaagcaacccaatatttta	NT_007995 13014683-704	Exon 2	293 (with THAP1_2F)
THAP1_E3F	tggtcagtccacagattctttt	NT_007995 13013940-919		
THAP1_E3R	tgtggtattgccccattaga	NT_007995 13013452-471	Exon 3	489 (with THAP1_3F)
TOR1A_E5F	cagcaccttgtttcttcttcc	NC_000009 132576505-525		
TOR1A_E5R	ccaactccaggcagtgactc	NC_000009 132576212-231	Exon 5	283 (with TOR1A_5F)