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**RESEARCH ARTICLE** 

# The Role of TOR1A Polymorphisms in Dystonia: A Systematic Review and Meta-Analysis

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## Abstract

## Importance

A number of genetic loci were found to be associated with dystonia. Quite a few studies have been contacted to examine possible contribution of TOR1A variants to the risk of dystonia, but their results remain conflicting. The aim of the present study was to systematically evaluate the effect of TOR1A gene SNPs on dystonia and its phenotypic subtypes regarding the body distribution.

## Methods

We performed a systematic review of Pubmed database to identify all available studies that reported genotype frequencies of TOR1A SNPs in dystonia. In total 16 studies were included in the quantitative analysis. Odds ratios (ORs) were calculated in each study to estimate the influence of TOR1A SNPs genotypes on the risk of dystonia. The fixed-effects model and the random effects model, in case of high heterogeneity, for recessive and dominant mode of inheritance as well as the free generalized odds ratio (OR<sub>G</sub>) model were used to calculate both the pooled point estimate in each study and the overall estimates.

## Results

Rs1182 was found to be associated with focal dystonia in recessive mode of inheritance [Odds Ratio, OR (95% confidence interval, C.I.): 1.83 (1.14–2.93), Pz = 0.01]. In addition, rs1801968 was associated with writer's cramp in both recessive and dominant modes [OR (95%C.I.): 5.99 (2.08–17.21), Pz = 0.00009] and [2.48 (1.36–4.51), Pz = 0.003) respectively and in model free-approach [OR<sub>G</sub> (95%C.I.): 2.58 (1.45–4.58)].

## Conclusions

Our meta-analysis revealed a significant implication of rs1182 and rs1801968 TOR1A variants in the development of focal dystonia and writer's cramp respectively. TOR1A gene variants seem to be implicated in dystonia phenotype.

## Introduction

Dystonia is a common but heterogeneous movement disorder. It is estimated to be the third most frequent movement disorder worldwide [1]. However, for most dystonia cases the nature and cause remains largely unknown [2]. Increased cortex plasticity through the entire sensorimotor system [3, 4] and functional modifications of the olivo-cerebellar pathway [5] were recognized as endophenotypes of dystonia. Moreover, reduced integrity of cerebello-thalamocortical tracts has been observed in symptomatic and asymptomatic carriers of dystonia-linked genes mutations [6].

Recently, a new general definition and a new classification of dystonia have been proposed [7]. Classification is now based on two distinct axes: the etiology and the clinical features, which include age at onset, body distribution, temporal pattern and coexistence of other movement disorders. The widely used term "primary" has been replaced with the term "isolated", where dystonia is the only motor feature, not counting tremor [7].

TOR1A gene (also known as DYT1) covers an 11k bp region in chr9 and it is consisted of 5 exons. TOR1A protein, called TorsinA belongs to the family of the AAA+ ATPases that can be found in the endoplasmic reticulum and nuclear envelope of most cells [8] including cells of the central nervous system [1] and are associated with a variety of cellular activities [9]. The function of TorsinA and how TOR1A gene mutations lead to dystonia is poorly understood. However, it seems that TorsinA is implicated in several molecular and cellular procedures, such as the interactions between cytoskeleton and membrane, important functions of the endoplasmic reticulum (reaction to stress, secretory pathway, protein degradation, neurites' expansion) and of the nuclear envelope (membrane formation and cell migration) [1, 8].

Relatively few genetic loci have been identified as potential causing factors of hereditary forms of isolated and combined dystonia, with a wide variation in the mode of inheritance, clinical features, body distribution and age of onset. The DYT1 (TOR1A) form of hereditary dystonia is mainly a generalized (and rarely focal) dystonia, which is inherited by an autosomal dominant mode [10]. Regarding sporadic dystonia, a number of genes have been linked to dystonia phenotypes including but not limited to TOR1A, b-cystathionine synthase (CBS), GTP cyclohydrolase1 (GCH1), dopamine D5 receptor (DRB5) and brain-derive neurotrophic factor (BDNF) genes [11–21]. Moreover, apolipoprotein E (APOE) gene has been reported to modulate the age at onset of primary dystonia [22]. However, TOR1A gene remains the most extensively studied and related to a variety of phenotypes but with conflicting results [23].

Two meta-analyses evaluated, so far, the effects of TOR1A gene variants on primary dystonia [14, 24], whereas there is also one pooled analysis in adult-onset primary focal dystonia [23]. In the first meta-analysis no significant association was found [14], whereas in the second meta-analysis a borderline significant association was reported for the rs1801968 in the subgroup of patients with primary dystonia that also had a positive family history [24]. Similarly, the pooled analysis that examined the effect of rs2296793 and rs1801968 variants on adultonset primary focal dystonia also did not reveal any significant difference between cases and controls [23]. The previous two meta-analyses [14, 24] used as a clinical outcome endpoint all forms of primary dystonia together without focusing on each dystonia sub-phenotype such as cervical dystonia, blepharospasm or writer's cramp. Moreover, the pooled analysis of adult-onset primary focal dystonia cases [23] studied only two (rs2296793, rs1801968) of TOR1A gene variants and part of the available studies was used. In the present meta-analysis we aimed to study the effect of all available TOR1A gene SNPs on the risk of dystonia and its sub-phenotypes. Our meta-analysis has included five additional studies that have been published recently and were not included in the previous meta-analyses.

## Methods

#### Data extraction

Eligible case-control candidate gene association studies (GAS) were selected by searching Pubmed database. The combination of search strings that was used included the following terms: "dystonia" and "tor1a" and "polymorphism". The complete search algorithm is available in the **S1 Appendix**. We imposed no language or other restrictions. Last literature search was performed on September 9th, 2016. The reference lists of all retrieved articles were additionally examined to identify studies that may have been missed by the initial database search. The inclusion criteria were a) case-control studies, in which cases were clinically diagnosed of having dystonia and controls were neurologically healthy, b) studies reporting single nucleotide polymorphisms in the TOR1A gene and c) studies that mentioned in the text the genotype frequencies from patients and controls. Studies with incomplete data or without genotype frequencies were excluded from meta-analysis. The initial phenotypic classifications of participants in each study were maintained.

The following information was extracted from each study: author, year of publication, ethnicity of the studied population, numbers of cases and controls, age at disease onset, mean age and gender distribution, genotype frequencies, tested polymorphisms, family history of the participants, method of diagnosis, screening or not of TOR1A  $\Delta$ GAG mutation, deviation or not from the Hardy-Weinberg Equilibrium (HWE), and tested dystonia phenotypes.

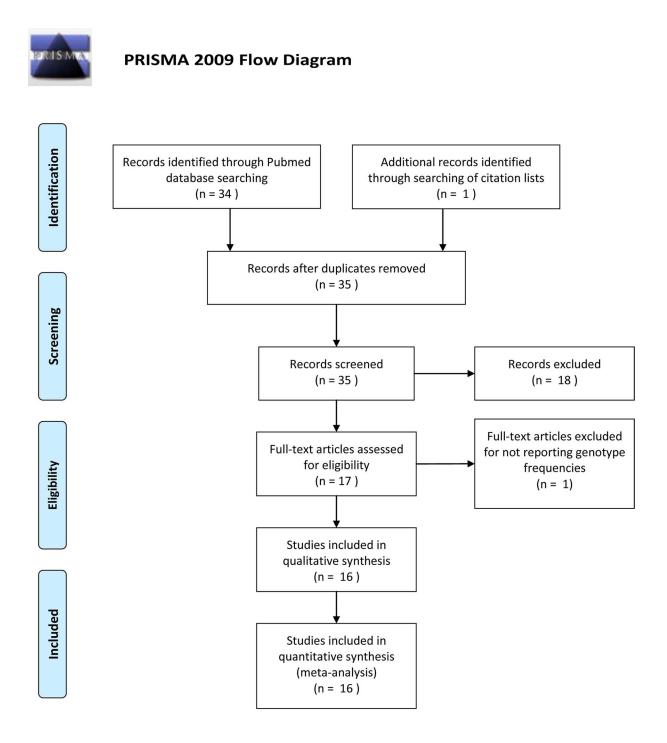
All individual studies were reviewed and the risk of possible bias was assessed. The flowchart presenting the selection procedure of eligible studies is presented in Fig 1.

### Statistical analysis

Dystonia cases were stratified according to the five following phenotypic qualitative traits: a) an overall dystonia group, b) an overall focal dystonia group (containing cervical dystonia, ble-pharospam, writer's cramp and other focal dystonias) and the three following focal dystonias' subgroups c) the cervical dystonia group, d) the blepharospasm group and f) the writer's cramp group. In each of the previous phenotypic traits, available TOR1A polymorphisms were tested in the meta-analysis. The association between the TOR1A SNPs and the above mentioned dystonia traits was estimated by calculating the pooled odds ratio (OR) and 95% confidence interval (CI) assuming the dominant [(mt/mt+wt/mt) vs (wt/wt)] and the recessive [(mt/mt) vs (wt/mt+wt/wt)] genetic modes of inheritance. The significance of the OR was determined by the Z test (p<0.05 was considered statistically significant). Additionally, the generalized odds ratio (OR<sub>G</sub>) and the corresponding 95%C.I. were applied in order to quantify the association between genotype distribution and disease. OR<sub>G</sub> is an inheritance model free approach that estimates the mutational load in cases compared to the controls [25, 26]. ORs and OR<sub>G</sub>s with the corresponding 95 C.I. were also calculated in every individual eligible GAS.

The statistical heterogeneity of the studies was calculated with the Cochran's Q and  $I^2$  index. The random-effects model (the DerSimonian and Laird method [27]) was applied if





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Fig 1. Flow chart presenting the selection of eligible studies.

there was an indication of substantial heterogeneity ( $P_Q < 0.10$  and/or  $I^2 > 75\%$ ). Otherwise the fixed-effects model (the Mantel-Haenszel method [28]) was used.

Test for possible publication bias was graphically assessed using the funnel plot. Furthermore, it was evaluated by the linear regression asymmetry test by Egger [29], when it was applicable, with p<0.10 considered to be representative of statistically significant publication bias.

All statistical analyses were performed in Review Manager (RevMan) Version 5.2 software [The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark (<u>http://tech.cochrane.org/revman</u>)]. The OR<sub>G</sub> was calculated with ORGGASMA (<u>www.biomath.uth.gr</u>) software. The PRISMA guidelines for reporting reviews and meta-analyses (<u>S2 Appendix</u>) were applied in this meta-analysis.

## Results

#### Study selection and study characteristics

Pubmed database search yielded 34 studies published between September 1997 and March 2016. After title and abstract screening by 2 independent reviewers (VS and ED), 16 potentially eligible studies for the meta-analysis were retained. One additional study was extracted from the references of the identified studies and was included in the meta-analysis [30]. However, one study was excluded from further analysis, as it did not report genotype frequencies [31] and therefore 16 studies were finally included in the quantitative meta-analysis [14, 16, 20, 23, 24, 30, 32–41], involving in total 3103 dystonia cases and 3628 healthy controls. In total 9 TOR1A SNPs have been investigated so far (rs1801968 and rs2296793 in ten studies, rs1182 and rs3842225 in nine, rs13283584, rs11787741 and rs13297609 in two and rs2287367 and rs1043186 in one study). One study revealed an association of a haplotype (constructed from rs2296793, rs1182 and rs3842225) with sporadic dystonia [36] while another one revealed a strong association of rs13283584 with idiopathic dystonia [38]. Association of rs1801968 with primary dystonia was reported in three studies [33, 39, 41] while another one revealed significant association only in cases with positive family history [32]. Association or a tendency for association of rs1182 was reported in three studies [37, 38, 40].

The majority of the studies were conducted in Chinese (n = 5) [20, 23, 34, 35, 41] and German (n = 4) [16, 30, 32, 38] populations. 10 studies reported inclusion of patients with positive family history of dystonia [20, 24, 32–35, 38–41] dystonia and in one study [41] was reported inclusion of participants positive for the  $\Delta$ GAG TOR1A mutation. The characteristics of the included studies are summarized in <u>S1 Table</u>. Detailed information of the tested TOR1A SNPs is presented in <u>S2 Table</u>. There was no reported deviation from HWE in controls at any protocol. At another one, where two different populations were tested, we analyzed them separately in the meta-analysis [37].

#### Tests of heterogeneity

Significant heterogeneity was revealed in the total dystonia group for a number of SNPs: rs1801968 ( $I^2 = 53\%$ ,  $P_Q = 0.03$  for dominant mode and  $I^2 = 54.63\%$ ,  $P_Q = 0.002$  for model free), rs2296793 ( $I^2 = 42\%$ ,  $P_Q < 0.07$  for recessive mode), rs1182 ( $I^2 = 72\%$ ,  $P_Q = 0.00002$  for dominant mode,  $I^2 = 42\%$ ,  $P_Q = 0.08$  for recessive mode and  $I^2 = 81.98\%$ ,  $P_Q < 0.0001$  for model free), rs13283584 ( $I^2 = 79\%$  and  $P_Q = 0.03$  for both dominant and recessive modes and  $I^2 = 65.72\%$ ,  $P_Q = 0.09$  for model free), rs11787741 ( $I^2 = 79\%$ ,  $P_Q = 0.03$  for recessive mode). No significant heterogeneity was observed in the entire focal dystonia group and in the focal dystonia subgroups (cervical dystonia, blepharospasm and writer's cramp). In case of considerable heterogeneity, the random-effects models were applied as previously described.

## **Publication bias**

Funnel plots, which are presented in Fig 2 for the overall dystonia group and in Fig 3 for the focal dystonia group and focal dystonia subgroups, did not reveal any significant asymmetry for any tested SNP in the dominant or recessive modes. Results from Egger's test (S3 Appendix) revealed no publication bias (P>0.10) in the dominant or recessive modes.

### Overall dystonia group analysis and subgroup analyses

The main results of meta-analysis for all available SNPs in the overall dystonia group are presented as forest plots in **Fig 4**. A tendency towards association was found for rs1182 in the recessive inheritance mode [Odds Ratio, OR (95% confidence interval, C.I.): 1.60 (0.98–2.62)]. The main meta-analysis results for the entire focal dystonia group and the focal dystonia subgroups (cervical dystonia, blepharospasm and writer's cramp) are shown in **Fig 5**. The respectively results after the meta-analysis with the model-fee approach and the genotypes frequencies, are showed at **Table 1** for the overall dystonia group and at **Table 2** for the focal dystonia group and focal dystonia's subtypes. Overall, rs1182 was found to be associated with focal dystonia in recessive mode [OR (95%C.I.): 1.83 (1.14–2.93),  $P_z = 0.01$ ]. Moreover, rs1801968 has found to be associated with writer's cramp in both recessive and dominant modes [OR (95%C.I.): 5.99 (2.08–17.21),  $P_z = 0.00009$ ] and [OR (95%C.I.): 2.48 (1.36–4.51),  $P_z = 0.003$ )] respectively and in model free-approach [ORG (95%C.I.): 2.58 (1.45–4.58)].

## Discussion

In the present meta-analysis, that included a relatively large number of participants, we investigated the effect of TOR1A gene SNPs on the risk of dystonia, as well as on the risk of focal dystonia and its subtypes (cervical dystonia, blepharospasm and writer's cramp). Our study detected a significant influence of a specific variant of TOR1A gene, rs1182, on the risk of focal dystonia. It also showed and that there is a strong association between rs1801968 and the development of task specific writer's cramp focal dystonia. To the best of our knowledge, this is the first meta-analysis examining the effect of TOR1A gene polymorphisms on the abovementioned disorders.

Quite a few polymorphisms across TOR1A gene have been examined for possible association with dystonia, but the results from candidate gene association studies (CGASs) remain conflicting [20, 23]. Additionally, in the first meta-analysis and in a pooled analysis regarding TOR1A SNPs and dystonia no significant association was revealed [14, 23]. However, in a second meta-analysis a marginal statistical significance was revealed for rs1801968 only in a subgroup of patients with primary dystonia that also had a positive family history [24]. The lack of replication and the inconsistency of the results among CGASs, meta- and pooled- analyses about TOR1A gene and dystonia could be attributed to a number of reasons. Small sample sizes, low statistical power to detect associations and different ethnic backgrounds may have contributed to these discrepancies [24, 31]. Our study pooled patients from different ethnic groups. Specifically, rs1182 exhibited a significant effect in a cohort with focal dystonia (n = 880) consisting of a variety of nationalities (Caucasians, Africans, Americans, Hispanic, Italians, Chinese, Dutch and Slavs). Also, rs1801968 was found to be associated with writer's cramp in a cohort (n = 55) of German and Chinese patients. The large clinical phenotypic spectrum of dystonia and the fact that a dystonia patient can be assign in more than one phenotypic group [7, 14] could be an additional factor leading to conflicting results [14, 23]. In our study rs1801968 was found to be associated only with writer's cramp sub-phenotype and not with the entire focal dystonia phenotype. Moreover, the variability in the penetrance of

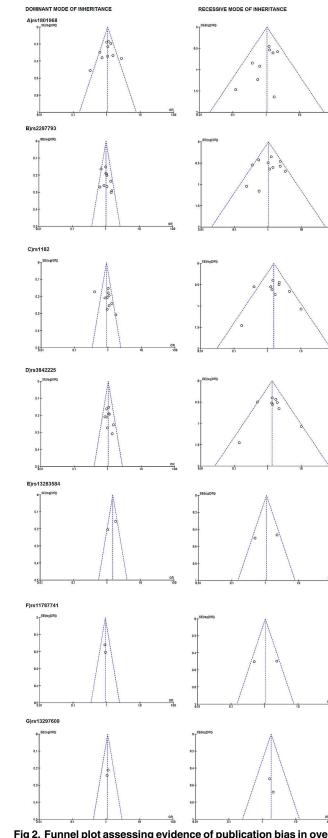


Fig 2. Funnel plot assessing evidence of publication bias in overall studies for TOR1A SNPs included in meta-analysis for overall dystonia group, in dominant and recessive modes of inheritance. SE, standard error; OR, odds ratio.

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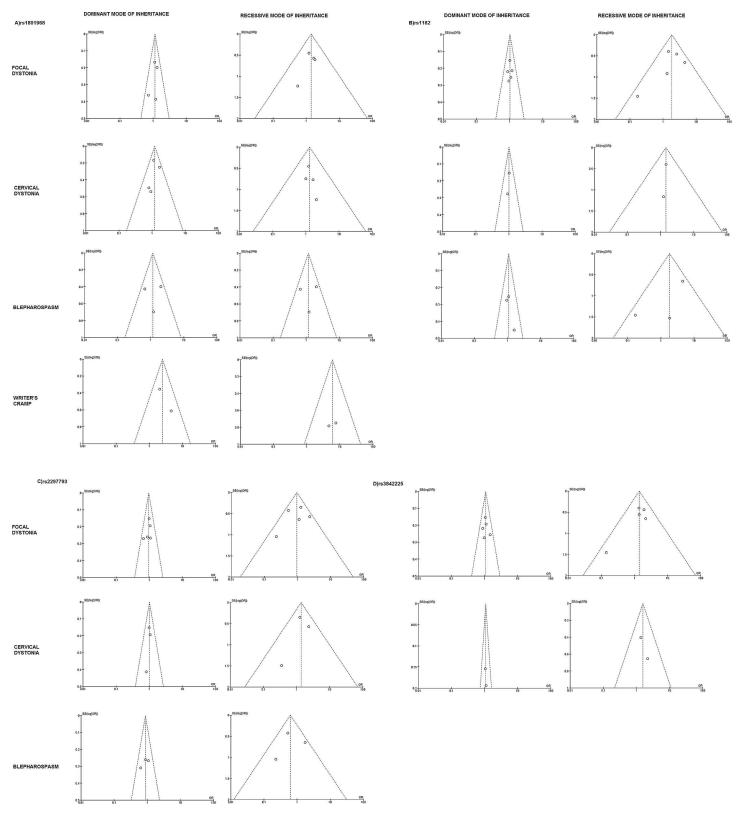


Fig 3. Funnel plot assessing evidence of publication bias in overall studies for TOR1A SNPs included in meta-analysis for entire focal dystonia group and focal dystonia subgroups (cervical dystonia, blepharospasm and writer's cramp), in dominant and recessive modes of inheritance. SE, standard error; OR, odds ratio.

#### DOMINANT MODE OF INHERITANCE

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RECESSIVE MODE OF INHERITANCE

DOMINANT MODE OF INHERITANCE	RECESSIVE MODE OF INHERITANCE		
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Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           uby or Subgroup         Events         Total         Events         Total         H, Fixed, 95% CI           arimon 2005         34         46         32         99         4.2%         1.37 (Dr 5, 2.50)           mm 2006         79         223         87         255         12.2%         1.06 (D, 7), 1.54           arimon 2007 U.S. series         28         73         97         250         1.85 (%, 0.80) (0.6), 1.49           evenand 2012         73         198         71         197         10.7%         0.95 (0.6), 1.44	Display         Dystonia         Control         Odds Ratio           Study or Subgroup         Dystonia         Control         Odds Ratio         Odds Ratio           Study or Subgroup         Events         Total         Weight HL, fixed, 95% CI         ML, Fixed, 95% CI           Clarimon 2005         8         6         1         99         1.4%         10.0 (1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1		
Sterogenety Tau <sup>2</sup> = 0.11: ChP = 31.90, df = 9 (P = 0.0002); P = 72%         Interpretation of the sterio of the s	Distantia         Control         Odds Ratio           Study or Subgroup         Events         Total         Weight         M-4, Tixed, 95% CI           Claimon 2005         8         8         1         99         1.4%         10.05 [1.2, 82.08]           Hague 2006         8         23         7         255         10.07 [1.2, 82.08]         M-4, Fixed, 95% CI           Claimon 2005         8         24         251         22.2%         0.50 [0.1, 1.34]         10.1 [1.2, 82.08]           Claimon 2007 US, series         7         251         122.2%         0.50 [0.1, 1.34]         10.1 [1.2, 1.2]         10.1 [1.2, 1.2]           Claimon 2007 US, series         0.1         1.26         9.4%         1.38 [0.47, 4.13]         11.24         10.5%         11.24 [1.2, 4.3]           Newman 2012         12         12.6         186         197         9.5%         1.51 [1.2, 4.3]         11.25         12.5%         11.25         12.5%		
Up:s3842225         Dystonia         Control         Odds Ratio           uby or Subgroup         Events         Total         Ventoria         Control           animon 2006         79         223         87         259         48         632         99         4.2%         1.37 (0.75, 2.50)           animon 2006         79         223         87         255         12.2%         1.06 (0.73, 1.54)           animon 2006         87         223         87         255         12.2%         1.06 (0.73, 1.54)           animon 2007 U.S. series         28         73         97         250         1.85 (%)         0.83 (0.63, 1.44)           evenanz 2012         73         198         71         197         7363         130         11.86 (%)         0.83 (0.65, 1.26)           evenanz 2015         87         218         73         118         1.18 (%)         0.83 (0.65, 1.26)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)         4.44 (0.94)	Display         Dystonia         Control         Odds Ratio           Study or Subgroup         Dystonia         Control         Odds Ratio           Clarinon 2005         8         6         1         91         1.4%         10.51         1.4%         10.51         0.4         10.1         0.1         0.1         0.1         0.1         0.1         1.01		
Dist 3842225         Dystonia         Control         Odds Ratio           uby or Subgroup         Events         Total         Vents         0.01         0.1         1         10         1           num 2006         79         223         87         255         12.2%         1.06 (0.7), 1.54           mimo 2006         79         223         87         255         12.2%         1.06 (0.7), 1.54           mimo 2006         79         223         87         255         11         85% 0.08 (0.6), 1.64           arimon 2007 U.S. series         28         73         97         250         1.85 (0.8) (0.8) (0.6), 1.44           evenanz 2012         73         198         71         187         10.7%         0.95 (0.6), 1.44           evenanz 2015         87         218         73         118         1.86 (0.8), 1.44         4           uoz 2015         71         201         95         229         1.17%         1.12 (0.76, 1.63)         4           uoz 2015         71         201         95         29         1.7%         1.12 (0.76, 1.63)         4         4           uoz 2015         71         201         95         29         1.7%         1.12	Distribution         Dystonia         Control         Odds Ratio           Study or Subgroup         Events         Total         Weight         M-H, Fixed, 95% CI           Clarimon 2005         8         6         1         91         1.4%         10.51         0.1         0.1         0.1           Hague 2006         8         23         7         255         10.7%         1.32(9.47, 3.70)         0.4%         1.39(1.47, 3.20, 4.74, 3.20)           Hague 2006         5         2.43         7         255         10.7%         1.32(9.47, 3.20)         0.4%         0.44(1.02, 1.23, 2.208)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.4%         0.44(1.24, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)         0.44(1.41, 4.13)<		
Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Control         Odds Ratio           bit or overall effect Z = 0.36 (P = 0.72)         Dystonia         Dystonia         Dystonia           bit overall effect Z = 0.36 (P = 0.72)         Dystonia         Dystonia         Dystonia           bit overall effect Z = 0.37         Dystonia         Dystonia         Dystonia         Dystonia           bit overall effect Z = 0.37	Display         Dystonia         Control         Odds Ratio           -         Study or Subgroup         Events         Total Vegith         Mail         Account of the state of the		
terogenety: Tau"= 0.11; Chi" = 31 80, df = 9 (P = 0.0002); P = 72%.           to for overall effect Z = 0.50 (P = 0.72)           Ins38422225         Dystemia         Control         Odds Ratio           odds Ratio         Odds Ratio           Ins38422225         Dystemia         Control         Odds Ratio           Ins38422225         Dystemia         Control         Odds Ratio           Odds 79         223         M 273         10 / 10           Ins 2006         7         20         0.34         0 / 253         11 / 256         Odds Ratio           Intro 2005         7         223         P         0         0.34         0         0.34         0         0           Intro 2007 U.S. series         23         S         0.25         0.27         1         0         0         0         0         0         0         0 <td>Display         Dystonia Test for overall effect Z = 1.87 (P = 0.06); P = 42%         Odds Ratio Display         Odds Ratio Favours Dystonia         Odds Ratio Favours Dystonia           Study or Subgroup         Dystonia Events         Control         Odds Ratio ML, Fixed, 95% Cl         Odds Ratio ML, Fixed, 95% Cl           Clarimon 2005         8         6         1         99         1.4%         1.05 (1.2%)         ML, Fixed, 95% Cl           Clarimon 2005         8         6         1         99         1.4%         1.05 (1.2%)         0.01 (1.2%)           Clarimon 2005         8         6         1         99         1.4%         1.05 (1.2%)         0.01 (1.2%)           Clarimon 2007 DS         5         243         1         521         1.2%         5.00 (1.2%)         0.01 (1.2%)           Clarimon 2007 DS, series         73         1         250         8.8%         0.14 (0.01, 2.43)         0.05 (1.2%)           Clarimon 2007 JS, series         13         13         135 (1.3%)         1.37 (1.2%)         1.38 (1.2%)         1.37 (1.2%)         1.4%         1.39 (0.1, 2.43)         0.01         0.1         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01</td>	Display         Dystonia Test for overall effect Z = 1.87 (P = 0.06); P = 42%         Odds Ratio Display         Odds Ratio Favours Dystonia         Odds Ratio Favours Dystonia           Study or Subgroup         Dystonia Events         Control         Odds Ratio ML, Fixed, 95% Cl         Odds Ratio ML, Fixed, 95% Cl           Clarimon 2005         8         6         1         99         1.4%         1.05 (1.2%)         ML, Fixed, 95% Cl           Clarimon 2005         8         6         1         99         1.4%         1.05 (1.2%)         0.01 (1.2%)           Clarimon 2005         8         6         1         99         1.4%         1.05 (1.2%)         0.01 (1.2%)           Clarimon 2007 DS         5         243         1         521         1.2%         5.00 (1.2%)         0.01 (1.2%)           Clarimon 2007 DS, series         73         1         250         8.8%         0.14 (0.01, 2.43)         0.05 (1.2%)           Clarimon 2007 JS, series         13         13         135 (1.3%)         1.37 (1.2%)         1.38 (1.2%)         1.37 (1.2%)         1.4%         1.39 (0.1, 2.43)         0.01         0.1         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01         0.01		
terogenetity: Tau#=0.11; Ch#= 31.90, df= 9 (P = 0.0002); P = 72%.           bystonia         Control           to description           termine 2005         34 485 32 98 42% 13 10 1075, 250           Mark to description           Mark to description<	Display         Dystonia         Control         Odds Ratio           Study or Subgroup         Dystonia         Control         Odds Ratio           Clarimon 2005         8         86         1         98         14%         10.01         0.1         <		
terogenety: Tau"= 0.11; Chi* = 31.90, df = 9 (P = 0.0002); P = 72%.           to overall effect Z = 0.36 (P = 0.72)           Ins38422225         Dystonia         Control         Odds Ratio           uty or Subgroup         Dystonia         Control         Odds Ratio           Martine 2005         34 96 32 99 42%         131 075, 250           gue 2006         79 223 87 255 12.2%         Odds Ratio           Multiple Figure 2010         Odds Ratio           Odds 79 223 87 255 12.2%         105 0.03%, 0.98 0.73, 1.54           arrinon 2007 U.S. series         28 73 97 250 6.3%         0.98 0.98 0.83, 1.44           arrinon 2007 U.S. series         218 71 187 10.7%         0.99 0.83, 1.44           outors 5 71 201 95 228 11.7%         1.01 0.73, 1.53           arrinon 2007 file series         0.93           arrinon 2007 file series         0.93         0.93         0.93         0.93         0.93         0.93         0.93         0.93         0.93 <th <<="" colspan="2" td=""><td>Display         Dystonia Test for overall effect Z = 1.87 (P = 0.06); P = 2.08); P = 42%         Display         Odds Ratio Favours Dystonia         Odds Ratio Control           Study or Subgroup         Dystonia Events         Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control           Study or Subgroup         Dystonia Events         Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control           Clairinon 2005         8         8         1         99         1.4%         10.50 (1.23, 82.09)           Hague 2006         8         223         7         255         10.7%         1.32 (0.47, 3.70)           Clairinon 2007 US. series         0         73         11         250         8.8%         0.14 (0.01, 2.43)           Clairinon 2007 US asines         13         13         13.08 (1.36%, 1.37) (1.24, 4.14)         1.36 (1.56, 2.03)           Timetaeva 2015         15         228         10.00%         1.35 (0.96, 1.88)         1.37 (1.24, 4.14)           Total (P5% Ch         1728         2252 (100.0%         1.35 (0.96, 1.88)         1.37 (0.16, 1.787)           Total (P5% Ch         1728         2252 (100.0%         1.35 (0.96, 1.88)         1.37 (0.16, 1.787)           Total (P5% Ch</td></th>	<td>Display         Dystonia Test for overall effect Z = 1.87 (P = 0.06); P = 2.08); P = 42%         Display         Odds Ratio Favours Dystonia         Odds Ratio Control           Study or Subgroup         Dystonia Events         Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control           Study or Subgroup         Dystonia Events         Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control           Clairinon 2005         8         8         1         99         1.4%         10.50 (1.23, 82.09)           Hague 2006         8         223         7         255         10.7%         1.32 (0.47, 3.70)           Clairinon 2007 US. series         0         73         11         250         8.8%         0.14 (0.01, 2.43)           Clairinon 2007 US asines         13         13         13.08 (1.36%, 1.37) (1.24, 4.14)         1.36 (1.56, 2.03)           Timetaeva 2015         15         228         10.00%         1.35 (0.96, 1.88)         1.37 (1.24, 4.14)           Total (P5% Ch         1728         2252 (100.0%         1.35 (0.96, 1.88)         1.37 (0.16, 1.787)           Total (P5% Ch         1728         2252 (100.0%         1.35 (0.96, 1.88)         1.37 (0.16, 1.787)           Total (P5% Ch</td>		Display         Dystonia Test for overall effect Z = 1.87 (P = 0.06); P = 2.08); P = 42%         Display         Odds Ratio Favours Dystonia         Odds Ratio Control           Study or Subgroup         Dystonia Events         Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control           Study or Subgroup         Dystonia Events         Control         Odds Ratio Control         Odds Ratio Control         Odds Ratio Control           Clairinon 2005         8         8         1         99         1.4%         10.50 (1.23, 82.09)           Hague 2006         8         223         7         255         10.7%         1.32 (0.47, 3.70)           Clairinon 2007 US. series         0         73         11         250         8.8%         0.14 (0.01, 2.43)           Clairinon 2007 US asines         13         13         13.08 (1.36%, 1.37) (1.24, 4.14)         1.36 (1.56, 2.03)           Timetaeva 2015         15         228         10.00%         1.35 (0.96, 1.88)         1.37 (1.24, 4.14)           Total (P5% Ch         1728         2252 (100.0%         1.35 (0.96, 1.88)         1.37 (0.16, 1.787)           Total (P5% Ch         1728         2252 (100.0%         1.35 (0.96, 1.88)         1.37 (0.16, 1.787)           Total (P5% Ch
terogenetry: Tax#=0.11; Ch#= 31 90, df= 9 (P = 0.0002); P = 72%.           to control           to control           Odds Ratio           to control           to control           to control           to control           to control           Odds Ratio           to control           Mode Statio           to control           Mode Statio           to control           Mode Statio           to control           to con	Display         Dystonia Test for overall effect: Z = 1.87 (P = 0.06); P = 0.08); P = 42%         Display         Odds Ratio           Study or Subgroup         Dystonia Events         Control         Odds Ratio         Odds Ratio           Clarimon 2005         8         6         1         99         1.4%         10.01         0.1         0.1         0.1           Hague 2006         8         233         7         255         10.7%         1.32 (0.47, 3.70)         M.H. Fixed, 95% Cl           Karm 2007         Sin as         1         351         1.58         1.22%         5.00 (1.91, 1.34)         0.14%         0.14 (0.1, 2.43)           Clarimon 2007 US series         0         73         1         250         8.9% (3.14%, 1.32, 0.47, 3.70)         0.4%         1.38 (1.5%, 1.23%, 0.23, 0.33)           Clarimon 2007 US series         0         73         1         250         8.9% (3.14%, 0.17, 4.14)         0.4%         1.38 (0.17, 7.17)         1.42%         1.75 (0.7, 4.14)         0.01		
terogenety: Tau"= 0.11; Ch <sup>2+</sup> = 31.90, df = 9 (P = 0.0002); P = 72%.           to control         Odds Ratio           Odds Ratio           dy of Subgroup         Centrol         Odds Ratio           O	Display         Dystonia         Control         Odds Ratio           Study or Subgroup         Dystonia         Control         Odds Ratio         Odds Ratio           Clairinon 2005         8         66         1         99         1/4%         10.95% Cl           Hague 2006         8         223         7         255         10.7%         13.20 A/3, 320.00           Hague 2006         8         223         7         255         10.7%         13.20 A/3, 320.00           Hague 2006         8         21         21         223         6.50 (1.91, 1.34)         1.4%         10.95 (1.34)           Clairinon 2007 U.S. series         0         73         11         20         8.8%         0.140 (D1, 2.43)         1.4%           Clairinon 2007 U.S. series         13         13         10.87 (1.35% (1.7, 1.37))         1.4%         1.39 (1.7, 2.53)         0.14 (1.05), 1.341         1.4%         1.39 (1.4%, 1.33)         1.4%         1.39 (1.7, 2.53)         0.14 (1.05), 1.771         1.4%         1.20 (1.5, 1.7, 717)         1.4%         1.2%         1.2% (1.6, 1.7, 717)         1.4%         1.39 (1.6, 1.7, 717)         1.44 (1.6, 1.5, 1.7, 717)         1.44 (1.6, 1.5, 1.7, 717)         1.44 (1.6, 1.5, 1.7, 717)         1.41 (1.5, 1.5, 1.7, 717)         1.53 (1.3, 2.2,		
Isrogeneity: Tau"= 0.11; Ch² = 31.90, df = 9 (P = 0.0002); P = 72%.         Dot 0.1         0.1         0.1         10         1           It for overall effect: Z = 0.56 (P = 0.72)         Dystonia         Control         Odds Ratio         Odds Ratio         Odds Ratio           It or overall effect: Z = 0.56 (P = 0.72)         Events         Total         Veripti M H, Fixed, 95% CI         MH, Fixed, 95% CI         MH, Fixed, 95% CI           Immo 2005         34         46         32         99         42%         1.37 (D 75, 2.50)         MH, Fixed, 95% CI           Immo 2006         73         223         87         255         1.25%         1.06 (D 73, 1.44)           Immo 2007 Hains series         22         73         94         236         0.39 (D 85, 1.24)           Immo 2015         87         71         170         70         171         174         1.56         0.31 (D 16, 1.44)           Introp 2015         87         718         718         711         1.76         1.12 (D 76, 1.63)           Ist oreal effect: Z = 0.56 (P = 0.77); P = 0%.         1.12 (D 76, 1.63)         1.00         1.14 (D 81, 2.34)         1.00           Ist oreal effect: Z = 0.56 (P = 0.77); P = 0%.         1.33 (D 35, 2.49)         0.44 (D 40, 1.43)         1.40         1.40	Image: Description of the second s		
Introduction: Tar = 0.11; Ch <sup>2</sup> = 31.90, of = 9 (P = 0.0002); P = 72%.           Introduction: Tar = 0.11; Ch <sup>2</sup> = 31.90, of = 9 (P = 0.0002); P = 72%.           Introduction: Tar = 0.11; Ch <sup>2</sup> = 31.90, of = 9 (P = 0.0002); P = 72%.           Introduction: Tar = 0.11; Ch <sup>2</sup> = 31.90, of = 9 (P = 0.0002); P = 72%.           Introduction: Tar = 0.0000; P = 72%.           Introduction: Tar = 0.0000; P = 72%.           Odds Ratio           Odds Ra	Digits         Helerogeneity: Tax"=0.25; Chi"=15.48, df = 9 (P = 0.08); P = 42%         Digits         <		
terogeneity: Tau" = 0.11; Chi" = 31 90, df = 9 (P = 0.0002); P = 72%. It for overall effect Z = 0.36 (P = 0.72) TS38422225 ty or Shiftyroup ty or Shiftyroup	Interference       Dystonia       Control       Odds Ratio         Study or Subgroup       Dystonia       Control       Odds Ratio       Odds Ratio         Study or Subgroup       Dystonia       Control       Odds Ratio       Odds Ratio         Clarimon 2005       8       223       7       255       10.7%       1.32 (0.47, 3.70)         Haque 2006       8       223       7       255       10.7%       1.32 (0.47, 3.70)         Harm 2007 U.S. series       0       73       11       200       8.8%       1.490 (1.42%, 1.27%)         Claimon 2007 U.S. series       0       73       11       200       8.9%       1.414, Fixed, 95% CI         Claimon 2007 U.S. series       0       73       11       250       8.9%       1.414, Fixed, 95% CI         Claimon 2007 U.S. series       0       73       11       250       8.9%       1.420, 1.78, 1.34         Trest or overall effect Z = 1.74 (P = 0.08)       75       14       2015, 1.43       1.75       1.250, 1.83         Total (95% CI)       1728       2252       100.0%, 1.35 [0.96, 1.89]       1.01       1.57 [0.27, 0.30]       1.01       1.01       1.01       1.01       1.01       1.01       1.01       1.01		
erogeneity: Tau" = 0.11; Chi" = 31.80, df = 9 (P = 0.0002); P = 72%.       0.01	Image: Description of the set of t		
erogeneity: Tau" = 0.11; Ch <sup>2</sup> = 31.90, df = 9 (P = 0.0002); P = 72%. If for overall effect Z = 0.36 (P = 0.72) <b>FS38422225</b> <u>byrstonia</u> <u>Control</u> <u>Odds Ratio</u> <u>Odds Ratio</u> <u>Odds Ratio</u> <u>M14, Fixed, 95% C1</u> <u>M14, </u>	Image: Description of the set of t		
Iterogeneity: Tau <sup>2</sup> = 0.11; Ch <sup>2</sup> = 31.90, df = 9 (P = 0.0002); P = 72%. <sup>10</sup> 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1 0.1	Did       Helerogeneity: Tax"= 0.25; Ch"= 15.48, df= 9 (P = 0.08); P= 42%         Test for overall effect Z=1.87 (P= 0.06)       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total       Control       Odds Ratio       Odds Ratio         Claimon 2005       8       823       7       255       10.7%       132 (0.47, 3.70)         Hague 2006       8       223       7       255       10.7%       132 (0.47, 3.70)         Ham 2007 U.S. series       0       73       11       250       8.8%       0.14 (0.01, 2.43)         Claimon 2007 U.S. series       0       73       11       250       8.8%       1.39 (0.17, 3.13)         Claimon 2007 U.S. series       0       132 (0.47, 3.70)       14.17% (0.45, 12.44)       14.17% (0.45, 12.44)         Claimon 2007 U.S. series       0       73       11.250       8.8%       0.14 (0.01, 2.43)         Total (95% Ch)       1728       2252       100.01%       1.35 (0.96, 1.89)       1.35 (0.96, 1.89)         Total (95% Ch)       1728       2252       100.0%       1.07 (0.25, 4.69)       0.04 (0.1, 7.87)         Total (95% Ch)       1728       2250       0.50 (0.10, 1.34)       0.44 (0.44, 1.43)       0.44 (0.44, 1.44)         Nemma 2012		
terogenety: Tax <sup>2</sup> = 0.11; Ch <sup>2</sup> = 31.90, df = 9 (P = 0.0002); P = 72%. It for overall effect Z = 0.36 (P = 0.72) <b>ITS38422225</b> Dystonia Control Odds Ratio Odds Ratio Odds Ratio Odds Ratio Odds Ratio MH, Fixed, 95% CI MH, Fi	$\frac{1}{100} = \frac{1}{100} + \frac{1}$		
terogenety: Tax"=0.11; Ch# = 31 80, df = 9 (P = 0.0002); P = 72%.       torowersil effect Z = 0.36 (P = 0.72)       ITS38422225     Dystonia     Centrol     Odds Ratio       dy or Subgroup     Dystonia     Centrol     Odds Ratio       Market S Total Events     Total Weight MH, Fixed, 95% CI       Minima Zooo     Odds Ratio       Market S Total Events     Odds Ratio       Odds Ratio <th col<="" td=""><td>Did       Helerogeneity: Tax"= 0.25; Ch"= 15.48, df= 9 (P = 0.08); P= 42%         Test for overall effect Z=1.87 (P= 0.06)       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total       Control       Odds Ratio       Odds Ratio         Claimon 2005       8       823       7       255       10.7%       132 (0.47, 3.70)         Hague 2006       8       223       7       255       10.7%       132 (0.47, 3.70)         Ham 2007 U.S. series       0       73       11       250       8.8%       0.14 (0.01, 2.43)         Claimon 2007 U.S. series       0       73       11       250       8.8%       1.39 (0.17, 3.13)         Claimon 2007 U.S. series       0       132 (0.47, 3.70)       14.17% (0.45, 12.44)       14.17% (0.45, 12.44)         Claimon 2007 U.S. series       0       73       11.250       8.8%       0.14 (0.01, 2.43)         Total (95% Ch)       1728       2252       100.01%       1.35 (0.96, 1.89)       1.35 (0.96, 1.89)         Total (95% Ch)       1728       2252       100.0%       1.07 (0.25, 4.69)       0.04 (0.1, 7.87)         Total (95% Ch)       1728       2250       0.50 (0.10, 1.34)       0.44 (0.44, 1.43)       0.44 (0.44, 1.44)         Nemma 2012</td></th>	<td>Did       Helerogeneity: Tax"= 0.25; Ch"= 15.48, df= 9 (P = 0.08); P= 42%         Test for overall effect Z=1.87 (P= 0.06)       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total       Control       Odds Ratio       Odds Ratio         Claimon 2005       8       823       7       255       10.7%       132 (0.47, 3.70)         Hague 2006       8       223       7       255       10.7%       132 (0.47, 3.70)         Ham 2007 U.S. series       0       73       11       250       8.8%       0.14 (0.01, 2.43)         Claimon 2007 U.S. series       0       73       11       250       8.8%       1.39 (0.17, 3.13)         Claimon 2007 U.S. series       0       132 (0.47, 3.70)       14.17% (0.45, 12.44)       14.17% (0.45, 12.44)         Claimon 2007 U.S. series       0       73       11.250       8.8%       0.14 (0.01, 2.43)         Total (95% Ch)       1728       2252       100.01%       1.35 (0.96, 1.89)       1.35 (0.96, 1.89)         Total (95% Ch)       1728       2252       100.0%       1.07 (0.25, 4.69)       0.04 (0.1, 7.87)         Total (95% Ch)       1728       2250       0.50 (0.10, 1.34)       0.44 (0.44, 1.43)       0.44 (0.44, 1.44)         Nemma 2012</td>	Did       Helerogeneity: Tax"= 0.25; Ch"= 15.48, df= 9 (P = 0.08); P= 42%         Test for overall effect Z=1.87 (P= 0.06)       Odds Ratio       Odds Ratio         Study or Subgroup       Events Total       Control       Odds Ratio       Odds Ratio         Claimon 2005       8       823       7       255       10.7%       132 (0.47, 3.70)         Hague 2006       8       223       7       255       10.7%       132 (0.47, 3.70)         Ham 2007 U.S. series       0       73       11       250       8.8%       0.14 (0.01, 2.43)         Claimon 2007 U.S. series       0       73       11       250       8.8%       1.39 (0.17, 3.13)         Claimon 2007 U.S. series       0       132 (0.47, 3.70)       14.17% (0.45, 12.44)       14.17% (0.45, 12.44)         Claimon 2007 U.S. series       0       73       11.250       8.8%       0.14 (0.01, 2.43)         Total (95% Ch)       1728       2252       100.01%       1.35 (0.96, 1.89)       1.35 (0.96, 1.89)         Total (95% Ch)       1728       2252       100.0%       1.07 (0.25, 4.69)       0.04 (0.1, 7.87)         Total (95% Ch)       1728       2250       0.50 (0.10, 1.34)       0.44 (0.44, 1.43)       0.44 (0.44, 1.44)         Nemma 2012	
Iterogenety: Tax"=0.11; Chi* = 31.90, df = 9 (P = 0.0002); P = 72%. <sup>10</sup> 01 01 01 01 01          Iterogenety: Tax"=0.11; Chi* = 31.90, df = 9 (P = 0.0002); P = 72%. <sup>10</sup> 01 01 01          Iterogenety: Tax"=0.11; Chi* = 31.90, df = 9 (P = 0.0002); P = 72%. <sup>10</sup> 01 01          Iterogenety: Tax"=0.11; Chi* = 31.90, df = 9 (P = 0.0002); P = 72%. <sup>10</sup> 01 01          Iterogenety: Tax"=0.11; Chi* = 31.90, df = 9 (P = 0.0002); P = 72%. <sup>10</sup> 01 01          Iterogenety: Tax"=0.11; Chi* = 31.90, df = 30 (P = 0.0002); P = 72%. <sup>10</sup> 01 05, series <sup>10</sup> 01          Iterogenety: Tax"=0.11; Chi* = 31.90, df = 30 (P = 0.0002); P = 72%. <sup>10</sup> 01 05, series <sup>10</sup> 01 05, series <sup>10</sup> 01 05, series          10001 U.S. series        28 7 3.97 250 <sup>10</sup> 55% 01 <sup>10</sup> 11 65% 01 <sup>10</sup> 141 55% 01          10001 U.S. series        28 7 18 73 <sup>10</sup> 155% 12 185% <sup>10</sup> 101, 141 <sup>10</sup> 17, 141          11 (15% 01) <sup>10</sup> 12 <sup>10</sup> 10            11 (15% 01) <sup>10</sup> 12 <sup>10</sup> 10 <sup>10</sup> 10 <sup>10</sup> 1 <sup></sup>	$\frac{1}{100} = \frac{1}{100} = \frac{1}{100} = \frac{1}{100} = \frac{1}{1000} = \frac{1}{10000} = \frac{1}{10000000000000000000000000000000000$		
$\frac{1}{100} \frac{1}{100} \frac{1}$	$\frac{1}{100} = \frac{1}{100} + \frac{1}{100} + \frac{1}{100} + \frac{1}{1000} + \frac{1}{1000} + \frac{1}{1000} + \frac{1}{1000} + \frac{1}{1000} + \frac{1}{10000} + \frac{1}{10000} + \frac{1}{10000000000000000000000000000000000$		
therogeneity: Tau"= 0.11; Ch <sup>2</sup> = 31.90, df = 9 (P = 0.0002); P = 72%. It for overall effect Z = 0.36 (P = 0.72) <b>Fig38422225</b> Dystonia Centrol Odds Ratio dy or Subgroup Events Total Events Total Weight M-H, Fixed, 95% Cl minon 2005 79 223 67 255 12.2% 106 10.73, 1.54 minon 2005 79 223 67 255 12.2% 106 10.73, 1.54 minon 2005 87 243 195 521 16.5% 108 10.73, 1.54 minon 2007 U.S. series 28 73 97 250 6.3% 0.98 10.97, 1.58 109 10.91, 2.47 minon 2005 67 243 195 521 16.5% 109 10.91, 2.47 minon 2001 5 71 201 57 1201 16.5% 109 11.5% 109 10.50, 1.63 at events 102 2 43 207 75 155 47.3% 106 10.73, 1.56 100 0dds Ratio <b>MH, Fixed, 95% Cl</b> <b>minon 2007</b> 128 2 exerts Total Events Total Weight M-H, Fixed, 95% Cl <b>minon 2007</b> 128 2 exerts Total Events Total Weight M-H, Fixed, 95% Cl <b>minon 2007</b> 17 20 57 120 57 120 57 120 57 120 57 120 57 120 57 1100 <b>rst13283584</b> Dystonia Control <b>dodds Ratio</b> <b>dodds Ratio</b> <b>do</b>	$\frac{1}{100} \frac{1}{100} \frac{1}{100} \frac{1}{100} \frac{1}{1000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{10000} \frac{1}{100000} \frac{1}{100000} \frac{1}{1000000} \frac{1}{10000000000000000000000000000000000$		
terogeneity: Tau" = 0.11; Chi" = 31 80, df = 9 (P = 0.0002); P = 72%. tfor overall effect Z = 0.36 (P = 0.72) <b>rs38422225</b> Dystonia Control Odds Ratio Odds Ratio Odds Ratio Odds Ratio Odds Ratio Odds Ratio N4, Fixed, 95% CI N4, Fixed, 95% CI N4, Fixed, 95% CI Odds Ratio	$\frac{1}{2} \frac{1}{2} \frac{1}$		
$\frac{1}{100} = \frac{1}{100} = \frac{1}$	$\frac{1}{100} = \frac{1}{100} + \frac{1}$		
$\frac{1}{100} \frac{1}{100} \frac{1}$	$\frac{1}{100} = \frac{1}{100} + \frac{1}$		

Fig 4. Odds ratios of dystonia associated with TOR1A polymorphisms in overall studies included in meta-analysis, in dominant (left) and recessive (right) modes of inheritance.

DOMINANT MODE OF INHERITANCE	RECESSIVE MODE OF INHERITANCE
Alprs18019080 (scal bytemis         Center         Center         Odds Ratio           Biogeneration         000         81         395         57         241         31.5%         132         841.17864.5%         MLL Filter 55% CT           Biogeneration         100	Total Operation         Control 1         Oads Refic         Oads Refic         Oads Refic           Biogenession 2000         9         205         4         214.8         168.012.5         101         101         0.00         100         0.00         100         0.00         100         0.00         100         24.4         102.65         100
Cenvical Dystemia         Control         Oddis Ratio         Oddis Ratio           Biogenesse         Seat         Feat         Revels         Feat         Revels         MAL (Tarset, 5% C)           Biogenesse         30         111         57         27.41         20.91         Biogenesse         Revels         MAL (Tarset, 5% C)           Wing 2016         5         32         22.01         85.01         92.02.23.41         10.01	Cenvical Dystemia         Central         Odds Ratio         D0dls Ratio           Stindy or Subgroup         Events         Tetal         Events
Struct of Sharper         Bitphorespanne         Centre for the struct with the Sharper Sharp	Bigenarropanin Statut of Sharpesin Operation         Control (Note: Total (Note: Sharpesin Chen 2012)         Control (Note: Sharpesin (Note: Sharpesin Chen 2012)         Odds (Note: Sharpesin (Note: Sharpesin Chen 2012)         Mill Flow (Note: Sharpesin (Note: Sharpes
Withort's Campo         Control         Odd/s Rulls         Odd/s Rulls         Odd/s Rulls           Brogenemics         Down         1 data         Vorsition         1 data         Vorsition         Automatic         MAIL Treed, 595 (1)         MAIL Treed, 595 (1)           Brogenemics         Down         6         41         67 (2)         41.07 (6)         207 (6)         44.11         70 (6)         45.11         70 (6)         45.11         70 (6)         45.11         70 (6)         45.11         70 (6)         45.11         70 (6)         45.11         70 (6)         100 (6)         45.11         70 (6)         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)         44.11         100 (6)	Velocity Study or Study o
B)rs1162         Facal Destes         Control         Odds Ratio         Odds Ratio         Odds Ratio           Struker Schaders         Enter         201         2	Freed Postoria         Control         Outro Table         OutroTable
Statuty ets Subjects         Centre of Destination         Centre of Destination         Centre of Destination         Destination <thdestination< <="" td=""><td>Stably or Subgroup         Control Dottorial         Control of weaks         <thcontrol of="" td="" weak<=""></thcontrol></td></thdestination<>	Stably or Subgroup         Control Dottorial         Control of weaks         Control of weaks <thcontrol of="" td="" weak<=""></thcontrol>
Billipharcesponing         Billipharcesponing         Control         Odds Rulin         Odds Rulin         Odds Rulin           Citamona 2007 US, server         28         78         72         73         72         74           Citamona 2007 US, server         29         78         72         74         76         72         74           Citamona 2007 US, server         9         22         89         24         15.95         52.97         74           Citamona 2007 US, server         9         22         89         24         15.95         15.95         74         74           Citamona 2007 US, server         9         22         89         24         15.95         15.95         74	Binghur or Stater one         Depth or optasm         Control         Odds Rutio         Odds Rutio           Clammon 2007 UIL strife         0         71         8 242         0 7 16         0 7 26         0 7 7           Clammon 2007 UIL strife         0         71         8 242         0 7 16         0 7 26
C) ps2297793 Study at Subgroup (vers)         Fec.al Dystemia (vers)         Centrol (vers)         Odds Ratio (vers)         Odds R	State or Statement         Feed Dystemia         Centre / Ideal         Centre / Model Waget         Odds Rulls         Odds Rulls           Claiments 3007 UB, meletik         Feed ID
Convolution         Control of the Ballon         Odds Ratio         Odds Ratio           Standor of Statutory         Statutory         Statutory         Mill Restat, 1951 CI         Mill Restat, 1951 CI           Statutory         Statutory         Statutory         Statutory         Mill Restat, 1951 CI         Mill Restat, 1951 CI           Statutory         Statutory         Statutory         Statutory         Statutory         Mill Restat, 1951 CI           Vinag 2016         11         22         Statutory         Statutory         Statutory           Total resetts         22         277         Nony         Nony         Statutory           Total resetts         23         242         277         Nony         Statutory         Statutory           Total resetts         23         242         177         Nony         Statutory         Statutory           Total resetts         23         242         177         Nony         Statutory         Statutory           Total resetts         23         242         177         Nony         Statutory         Statutory           Total resetts         23         242         128         128         128         128           Total resetts         23	Convolation         Convolation         Convolation         Odds Rules         Odds Rules           Statuy or Subaryon         Total         Convolation         Total         Status         Status         Mil A Total Styles         Styles         Styles         Styles         Mil A Total Styles         Mil A Total Styles
Bit photors Shape on Control on 2010 U.S. series         Control Dents         Control Monthematics         Control Dents         Control Monthematics         Control Monthematics           Calimono 2007 U.S. series         34         7.2         110         0.27         3.9%         1.0%         0.046         MAL (Incert SPG C)           Mainteen 2007 U.S. series         34         7.2         110         0.27         3.9%         1.0%         0.646         9.0%           Mainteen 2007 U.S. series         52         7.0         3.1%         0.0%         0.58         9.1%         0.0% </td <td>Staty or Subgrow         Binghor resource         Control         Weak         Odd Fails         Odd Fails           Staty or Subgrow         Events         1         72         14         247.56         044.76.85         044.76.85         044.76.85         044.76.85         044.76.85         044.76.85         044.76.85         051.05.45         051.05.45         051.05.45         051.05.45         051.05         044.76.85         051.05         044.76.85         051.05         044.76.85         051.05         045.76.85         051.05         045.76.85         051.05         045.76.85         051.05         045.76.85         051.05<!--</td--></td>	Staty or Subgrow         Binghor resource         Control         Weak         Odd Fails         Odd Fails           Staty or Subgrow         Events         1         72         14         247.56         044.76.85         044.76.85         044.76.85         044.76.85         044.76.85         044.76.85         044.76.85         051.05.45         051.05.45         051.05.45         051.05.45         051.05         044.76.85         051.05         044.76.85         051.05         044.76.85         051.05         045.76.85         051.05         045.76.85         051.05         045.76.85         051.05         045.76.85         051.05 </td
D)rs3842225 Statute & Statute Common 2010 S	Stady or Subgroup         Focal Dystems         Central         Odds Ratio         Odds Ratio           Common 2007 Loss series         0         120         127.9         139.00 / 127.9         MAL Rood, 59.01           Common 2007 Loss series         0         200         127.9         139.00 / 127.9         MAL Rood, 59.01           Timense 2015         18         201         127.9         139.00 / 127.9         139.00 / 127.9           The action of the series         10         117.9         147.9         127.9         139.00 / 127.9           The action of the series         10         117.9         117.9         127.9         139.00 / 127.9           The action of the series         10         10.00 / 127.9         139.00 / 127.9         149.00 / 127.9           The action of the series         0         129.00 / 127.9         129.00 / 127.9         149.00 / 127.9           The action of the series         0         149.00 / 127.9         149.00 / 127.9         149.00 / 127.9           Total endor         10         149.00 / 127.9         149.00 / 127.9         149.00 / 127.9         149.00 / 127.9           Total endor         10         149.00 / 127.9         149.00 / 127.9         149.00 / 127.9         149.00 / 127.9         149.00 / 127.9         149.00
Canadical Dystancia         Control         Oddes Ballo         Oddes Ballo           Grosso 2013         217         242         103         614         105         ML4, Flored, 59% CI           Jones 2013         17         242         103         614         156         103         114         104	Control State         Control Vestoria         Control Vestoria         Odds Ratio         Odds Ratio         Odds Ratio           Starty or Subgrow         Test         Feets         Test         Vestoria         No. 1723         Mil. Test 659:C1         Mil. Test 659:C1           Green: 2012         Green: 2012         15         31:74         Vestoria         127.018:S2, 320:C1         Mil. Test 659:C1         Mil. Test 659:C1           Table vestoria         15         30:1         31:74:74         21.18:82, 721         Test 659:C1         Mil. Test 659:C1           Table vestoria         25         15         15:94:74         15:98:82, 360         Test 75:74         Test 75:75         Test 75:

Fig 5. Odds ratios of entire focal dystonia group and focal dystonia subgroups (cervical dystonia, blepharospasm and writer's cramp) associated with TOR1A polymorphisms in overall studies included in meta-analysis, in dominant (left) and recessive (right) modes of inheritance.



# Table 1. Quantitate measures of genetic risk (individual study estimates and pooled effects), stratified by polymorphism of interest, for overall dystonia group, with the generalized odds ratio (OR<sub>G</sub>).

SNP	Author (Year)	Controls	6		Cases			Model-free	Model
rs1801968		wt ht mt wt				Ht	Mt	OR <sub>G</sub> (95%Cl)	
	Siblling (2003)	79	16	5	78	20	2	1.02 (0.53–1.96)	
	Naiya (2006)	52	11	0	103	6	1	0.32 (0.12-0.85)	
	Kamm (2006)	393	122	6	183	54	6	1.02 (0.72–1.45)	
	Bruggemann (2009)	184	53	4	242	90	9	1.32 (0.91 1.91)	
	Newman(2012)	150	44	3	153	50	2	1.07 (0.69–1.68)	
	Groen (2013)	267	84	9	262	91	11	1.12 (0.81–1.54)	
	Chen (2012)	86	9	5	168	29	13	1.49 (0.79–2.82)	
	Cheng (2013)	152	42	6	101	20	0	0.63 (0.36–1.11)	
	Caputo (2013)	161	39	0	24	16	0	2.80 (1.37–5.70)	
	Wang (2016)	109	20	2	102	14	1	0.73 (0.36–1.47)	
	Pooled data	1633	440	40	1146	390	45	1.06 (0.83–1.35)	Random
	Heterogenity I <sup>2</sup>							54.63%	
	Pq							0.002	
s2296793									
	Sibbing (2003)	66	29	5	56	37	7	1.49 (0.87–2.55)	
	Clarimon (2005)	64	33	3	47	31	8	1.55 (0.89–2.69)	
	Hague (2006)	159	87	9	138	77	8	1.02 (0.71–1.45)	
	Kamm (2006)	312	185	24	163	76	4	0.72(0.53–0.97)	
	Clarimon (2007) U.S.	137	96	14	39	33	1	1.00 (0.61–1.63)	
	Clarimon (2007) Italian	59	51	19	52	46	9	0.82 (0.52–1.29)	
	Newman(2012)	124	72	7	122	69	16	1.16(0.79–1.68)	
	Groen (2013)	211	131	15	213	129	19	1.02(0.77–1.35)	
	Cheng (2013)	129	68	3	68	52	1	1.39 (0.88–2.18)	
	Zhou (2015)	194	90	5	132	61	8	1.10 (0.76–1.59)	
	Wang (2016)	80	46	5	82	30	5	0.69 (0.42–1.16)	
	Pooled data		888	109	1112	641	86	1.00 (0.89–1.14)	Fixed
	Heterogenity I <sup>2</sup>							30.89%	
	Pq							0.15	
s1182									
	Clarimon (2005)	69	29	1	49	29	8	1.86(1.04–3.31)	
	Hague (2006)	169	80	5	144	73	6	1.09 (0.75–1.59)	
	Kamm (2006)	218	212	21	183	55	4	0.31 (0.22–0.44)	
	Clarimon (2007) U.S.	144	89	9	43	28	0	0.93 (0.55–1.56)	
	Clarimon (2007) Italian	79	49	3	73	40	12	1.19 (0.75–1.91)	
	Newman(2012)	117	66	6	129	62	14	1.02 (0.72–1.45)	
	Groen (2013)	225	122	11	225	120	16	1.04 0.78–1.39)	
	Chen (2012)	205	86	3	202	84	5	1.02 (0.72–1.45)	
	Cheng (2013)	136	56	8	75	40	6	1.29 (0.8–2.02)	
	Timerbaeva (2015)	91	66	7	132	66	20	0.91 (0.62–1.32)	
	Pooled data		855	74	1255	597	91	0.97 (0.72–1.30)	Random
	Heterogenity I <sup>2</sup>	1100						81.98%	- iandom
	PQ			_				<0.0001	
rs3842225				_			_	-0.0001	
JUTLEU	Clarimon (2005)	67	31	1	52	26	8	1.49 (0.84–2.66)	
	Hague (2006)	168	80	7	144	71	8	1.07 (0.74–1.54)	

(Continued)

#### Table 1. (Continued)

LOS ONE

SNP	Author (Year)	Control	s		Cases			Model-free	Model
rs1801968		wt	ht	mt	wt	Ht	Mt	OR <sub>G</sub> (95%Cl)	
	Kamm (2006)	326	174	21	156	82	5	0.91 (0.67–1.23)	
	Clarimon (2007) U.S.	153	86	11	45	28	0	0.94 (0.57–1.57)	
	Clarimon (2007) Italian	75	45	6	61	54	8	1.46 (0.91–2.33)	
	Newman(2012)	116	65	6	125	61	12	1.00 0.68-1.48)	
	Groen (2013)	231	119	11	226	122	15	1.09 (0.81–1.45)	
	Timerbaeva (2015)	91	65	8	131	69	18	0.89 (0.62 1.31)	
	Zhou (2015)	194	91	4	130	65	6	1.14 (0.78 1.65)	
	Pooled data	1421	756	75	1070	578	80	1.05 (0.93–1.20)	Fixed
	Heterogenity I <sup>2</sup>							00.0%	
	PQ							0.72	
rs13283584									
	Kamm (2006)	316	184	21	111	127	5	1.68 (1.26–2.24)	
	Newman(2012)	119	69	7	124	67	16	1.11 (0.76–1.62)	
	Pooled data	435	253	28	235	194	21	1.39 (0.93–2.08)	Random
	Heterogenity I <sup>2</sup>							65.72%	
	PQ							0.09	
rs11787741									
	Kamm (2006)	323	177	21	156	82	5	0.89 (0.66–1.20)	
	Newman(2012)	122	71	6	130	63	14	0.93 (0.68–1.46)	
	Pooled data	445	248	27	286	145	19	1.00 (0.73–1.18)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.63	
rs13297609									
	Newman(2012)	137	57	6	134	61	10	1.17 (0.79–1.74)	
	Cheng (2013)	134	62	4	79	37	5	1.11 (0.70–1.76)	
	Pooled data	271	119	10	213	98	15	1.14 (0.85–1.54)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.86	

SNP, single nucleotide polymorphism; wt, homozygotes for wild allele; ht, heterozygotes; mt, homozygotes for mutant allele; CI, confidence interval; OR<sub>G</sub>, generalized odds ratio.

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mutations, the epistasis phenomenon and the interaction between genetic and environmental factors could be responsible for the discordance of the results [1, 24, 42].

The  $\Delta$ GAG human variant of TorsinA was the first pathogenic, disease-causing mutation identified in early onset, generalized dystonia [43]. Thereafter, functional characterization of the growing number of the identified TOR1A variants in dystonia patients signifies the importance of the whole genetic variability across TOR1A gene [44]. Rs1801968 (D216H) is a functional missence coding polymorphism in exon 4 of TOR1A gene, which replaces the amino acid aspartic acid (D) with histidine (H) at residue 216 [45]. In a cell culture study, this amino acid substitution predisposes to the formation of inclusions similar to those formed by  $\Delta$ GAG mutation [45]. However, the co-existence of 216H allele and  $\Delta$ GAG mutation reduced the tendency for inclusions' formation [45]. This finding suggests that rs1801968 may have a protective role against the effect of  $\Delta$ GAG mutation and dystonia [45–47]. On the contrary, 216D allele in cis together with  $\Delta$ GAG, may predispose for developing dystonia [46, 47]. Cheng et al. reported that 216D allele was more abundant in patients with early-onset primary dystonia,



Table 2. Quantitate measures of genetic risk (individual study estimates and pooled effects), stratified by polymorphism of interest, for focal dystonia group and its subtypes, with the generalized odds ratio (OR<sub>G</sub>).

Polymorphism/	Author (Year)	Contro	ols		Cases			Model-free	Model
Phenotype									
rs1801968		wt	Ht	mt	wt	ht	mt	OR <sub>G</sub> (95%Cl)	
Focal									
Dystonia									
	Bruggemann (2009)	184	53	4	209	77	9	1.33 (0.91–1.95)	
	Chen (2012)	86	9	5	92	9	9	1.22 (0.59–2.53)	
	Groen (2013)	267	84	9	262	91	11	1.12 (0.81–1.54)	
	Wang (2016)	109	20	2	102	14	1	0.73 (0.36–1.47)	
	Pooled data	646	166	20	665	191	30	1.15 (0.92–1.43)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pa							0.52	
Cervical									
Dystonia									
	Bruggemann (2009)	184	53	4	73	35	3	1.66 (1.03–2.69)	
	Chen (2012)	86	9	5	53	4	3	0.83 (0.32–2.12)	
	Groen (2013)	267	84	9	262	91	11	1.12 (0.81–1.54)	
	Wang (2016)	109	20	2	27	4	1	0.94 (0.33–2.66)	
	Pooled data	466	166	20	425	134	18	1.21 (0.94–1.55)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pa							0.52	
Blepharospasm									
	Bruggemann (2009)	184	53	4	19	11	1	2.01 (0.94–4.27)	
	Chen (2012)	86	9	5	15	1	2	1.28 (0.34–4.83)	
	Wang (2016)	109	20	2	67	9	0	0.70 (0.31–1.58)	
	Pooled data	379	82	11	101	21	3	1.24 (0.74–2.06)	Fixed
	Heterogenity I <sup>2</sup>							42.26%	
	PQ							0.17	
Writer's									
cramp									
	Bruggemann (2009)	184	53	4	25	13	3	2.10 (1.07–4.11)	
	Chen (2012)	86	9	5	8	2	4	4.52 (1.48–13.82)	
	Pooled data	270	62	9	33	15	7	2.58 (1.45–4.58)	Fixed
	Heterogenity I <sup>2</sup>							24.90%	
	PQ							0.24	
rs1182									
Focal									
Dystonia									
	Clarimon (2007) U.S.	144	89	9	43	28	0	0.93 (0.55–1.56)	
	Clarimon (2007) Italian	79	49	3	73	40	12	1.19 (0.75–1.91)	
	Chen (2012)	205	86	3	98	48	2	1.18 (0.78–1.78)	
	Groen (2013)	225	122	11	225	120	16	1.04 (0.78–1.39)	
	Timerbaeva (2015)	91	66	7	103	54	18	0.98 (0.66 1.46)	
	Pooled data	744	412	33	542	290	48	1.06 (0.89–1.26)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	P <sub>Q</sub>							0.92	
Cervical									

(Continued)

#### Table 2. (Continued)

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Polymorphism/	Author (Year)	Contro	ols		Cases			Model-free	Model
Phenotype									
s1801968		wt	Ht	mt	wt	ht	mt	OR <sub>G</sub> (95%CI)	
Dystonia									
	Chen (2012)	205	86	3	58	22	1	0.92 (0.54–1.57)	
	Groen (2013)	225	122	11	225	120	16	1.04 (0.78–1.39)	
	Pooled data	430	208	14	283	142	17	1.01 (0.78–1.31)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.69	
Blepharospam									
	Clarimon (2007) U.S.	144	89	9	43	28	0	0.93 (0.55–1.56)	
	Clarimon (2007) Italian	79	49	3	73	40	12	1.19 (0.75–1.91)	
	Chen (2012)	205	86	3	13	9	0	1.68 (0.71–3.96)	
	Pooled data	428	224	15	129	77	12	1.14 (0.83–1.57)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.49	
s2296793									
Focal									
Dystonia									
	Clarimon (2007) U.S.	137	96	14	39	33	1	1.00 (0.61–1.63)	
	Clarimon (2007) Italian	59	51	19	52	46	9	0.82 (0.52-1.29)	
	Groen (2013)	211	131	15	213	129	19	1.02 (0.77–1.35)	
	Zhou (2015)	194	90	5	132	61	8	1.10 (0.76–1.59)	
	Wang (2016)	80	46	5	82	30	5	0.70 (0.42–1.16)	
	Pooled data	681	414	58	518	299	42	0.96 (0.80–1.14)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.61	
Cervical									
Dystonia									
	Groen (2013)	211	131	15	213	129	19	1.02 (0.77–1.35)	
	Zhou (2015)	194	90	5	132	61	8	1.10 (0.76–1.59)	
	Wang (2016)	80	46	5	21	11	0	0.84 (0.39–1.81)	
	Pooled data	485	267	25	366	201	27	1.03 (0.83–1.28)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.82	
Blepharospam									
	Clarimon (2007) U.S.	137	96	14	39	33	1	1.00 (0.61–1.63)	
	Clarimon (2007) Italian	59	51	19	52	46	9	0.82 (0.52-1.29)	
	Wang (2016)	80	46	5	54	17	5	0.70 (0.39–1.25)	
	Pooled data		193	38	145	96	15	0.85 (0.63–1.13)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.65	
s3842225									
Focal									
Dystonia									
	Clarimon (2007) U.S.	153	86	11	45	28	0	0.94 (0.57–1.57)	
	Clarimon (2007) Italian		45	6	61	54	8	1.46 (0.91–2.33)	
	Groen (2013)		119	11	226	122	15	1.09 (0.81–1.45)	

(Continued)



Polymorphism/	Author (Year)	Controls			Cases			Model-free	Model
Phenotype									
rs1801968		wt	Ht	mt	wt	ht	mt	OR <sub>G</sub> (95%CI)	
	Timerbaeva (2015)	91	65	8	102	57	16	0.97 (0.75–1.45)	
	Zhou (2015)	194	91	4	130	65	6	1.14 (0.78–1.65)	
	Pooled data	744	406	40	564	326	45	1.10 (0.93–1.31)	Fixed
	Heterogenity I <sup>2</sup>							0.00%	
	Pa							0.71	
Cervical									
Dystonia									
	Groen (2013)	231	119	11	226	122	15	1.09 (0.81–145)	Fixed
	Zhou (2015)	194	91	4	130	65	6	1.14 (0.78–1.65)	
	Pooled data	425	210	15	356	187	21	1.11 (0.88–1.39)	
	Heterogenity I <sup>2</sup>							0.00%	
	Pq							0.86	

#### Table 2. (Continued)

SNP, single nucleotide polymorphism; wt, homozygotes for wild allele; ht, heterozygotes; mt, homozygotes for mutant allele; CI, confidence interval; OR<sub>G</sub>, generalized odds ratio; Statistical significant OR<sub>G</sub>s of the pooled data are given in bold.

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while 216H allele was more frequent in the control group [41]. Furthermore, they observed that all the  $\Delta$ GAG carriers, who also carried the 216D allele, were dystonic [41]. However, the great variance in the results from studies regarding the impact of rs18019168 on dystonia [23], suggests that additional factors influence the phenotypic manifestation of this polymorphism.

Rs1182, that also reached significance in our study, is located in the 3' untranslated region (3'-UTR) of exon 5 of TOR1A gene. However, there is no known functional effect of rs1182 on expression and function of TOR1A [48] so, the precise functional role of rs1182 on primary dystonia remains unclear. In addition to the effect of rs1182 on the risk of dystonia [36–38, 40], minor rs1182 allele may also represent a genetic factor influencing the spread of blepharospasm to adjacent body regions [49]. The role of another SNP, in particular rs3842225 polymorphism, that is also located in TOR1A 3'-UTR region of exon has also been examined in dystonia patients, but with ambiguous results [20]. There is only some indications that del allele of rs3842225 in cis with D216 allele of rs1801968 may be associated with reduced risk of dystonia [31, 47]. Furthermore, Clarimon et al. conducted a population-based study and described the association between dystonia and T2 haplotype which is consists of the minor alleles of rs1182, rs3842225 and rs2296793 [36]. No such association was revealed when each one of these three SNPs was examined separately [36]. Therefore, it is possible that SNPs within 3'-UTR of exon 5 represent an additional functional genetic locus of TOR1A, though it may be under synergic action with other TOR1A genetic variants.

Both variants emerged in our analysis may have some functional consequences. In particular, rs1182 is located in the UTR-3 that may affect transcription of TOR1A gene, whereas rs1801968 represents a missense mutation and is characterized as pathogenic in NCBI. In addition, an almost consistent effect across varied populations is also supportive of the significant role of both polymorphisms and by extension TOR1A gene. Moreover, the heterogeneity of effect size across studies it remained within acceptable limits (I<sup>2</sup>: 0–28%). However, it is not known whether these associations are causal without supportive functional analyses.

There are certain limitations in the present meta-analysis that must be acknowledged. [40]. Firstly, we included subjects regardless of the  $\Delta$ GAG mutation status, the diagnostic

methodology, the HWE values and the presence of positive family history or decent. We cannot also exclude a possible classification bias regarding the assignment of participants in dystonia phenotypes, as the majority of studies were performed before the dystonias' classification consensus update.

In conclusion, our meta-analysis revealed a possible influence of rs1182 TOR1A SNP on the risk of focal dystonia and of rs1801968 on the risk of writer's cramp. Further large-scale collaborative studies in different ethnic groups, with larger samples and with prospective and gene-environment interaction design are of great necessity in order to elucidate the role of TOR1A gene in focal dystonia. The investigation of additional genetic factors that predispose to dystonia may provide physicians with personalized tools for diagnosis, classification or treatment response.

## **Supporting Information**

**S1** Appendix. The complete search algorithm. (PDF)

**S2 Appendix. PRISMA 2009 Checklist.** (PDF)

**S3 Appendix. Results from Egger's test.** (PDF)

**S1** Table. Characteristics of the studies included in the meta-analysis. (DOCX)

**S2** Table. Characteristics of TOR1A SNPs that examined in the current meta-analysis. (DOCX)

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## **Author Contributions**

Conceptualization: VS ED GMH. Data curation: VS ED DR GMH. Formal analysis: VS ED DR GMH. Investigation: VS ED GMH. Methodology: VS ED GT GMH. Project administration: VS ED GMH. Resources: VS ED EET GT GD GMH. Software: VS ED DR KP GMH. Supervision: VS ED GMH. Validation: VS ED EET GT GD GMH. Visualization: VS ED DR MS SK KP GMH. Writing – original draft: VS ED EET GT GMH. Writing - review & editing: VS ED EET GT DR MS SK KP GD GMH.

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