The genetics of spinocerebellar ataxia and dystonia

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Using the shared genetics of dystonia and ataxia to unravel their pathogenesis

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Abstract

In this review we explore the similarities between spinocerebellar ataxias and dystonias, and suggest potentially shared molecular pathways using a gene co-expression network approach. The spinocerebellar ataxias are a group of neurodegenerative disorders characterized by coordination problems caused mainly by atrophy of the cerebellum. The dystonias are another group of neurological movement disorders linked to basal ganglia dysfunction, although evidence is now pointing to cerebellar involvement as well. Our gene co-expression network approach identified 99 shared genes and showed the involvement of two major pathways: synaptic transmission and neurodevelopment. These pathways overlapped in the two disorders, with a large role for GABAergic signaling in both. The overlapping pathways may provide novel targets for disease therapies. We need to prioritize variants obtained by whole exome sequencing in the genes associated with these pathways in the search for new pathogenic variants, which can then be used to help in the genetic counseling of patients and their families.

Keywords

Spinocerebellar ataxia; dystonia; gene network; synaptic transmission; neurodevelopment; neurodegeneration; molecular pathways; pathophysiology

Introduction

The cerebellar ataxias are a heterogeneous group of movement disorders characterized by degeneration of Purkinje cells (PCs) and atrophy of the cerebellum. Motor symptoms include loss of balance and coordination, unstable gait, dysarthria and abnormal eye movements. Cerebellar ataxias can be primary (genetic), congenital (brain malformations) or acquired (e.g. after stroke). The spinocerebellar ataxias (SCAs), the genetically dominant forms of cerebellar ataxia, have an estimated prevalence of 1-3 per 100,000 in Europe with onset usually occurring in adulthood.[1] Dystonia is a neurological movement disorder characterized by involuntary muscle contractions that cause abnormal twisting movements and postures. It has many clinical manifestations, ranging from isolated and focal to generalized dystonia, or dystonia in combination with other neurological symptoms such as myoclonus or ataxia. The list of diseases that can cause or present with dystonia is extensive.[2]

Many patients show a combination of cerebellar ataxia and dystonia. Dystonia is frequently seen in SCA2 (14%), SCA3 (24%) and SCA17 (53%), and regularly seen in SCA types 1, 6, 12, 14, 15/16 and 20, in ataxia telangiectasia, in Friedreich's ataxia, and in ataxia with oculomotor apraxia.[3–5] Kuoppamaki and Van de Warrenburg reported eleven patients in total who showed early onset, primarily cervical, dystonia in combination with slowly progressive cerebellar ataxia. All had tested negative for the most common SCA types, although some patients had a positive family history, and all the patients showed cerebellar atrophy.[6,7]

Taken into account the clinical and etiological heterogeneity, the exact pathophysiological mechanisms of SCA and dystonia are not exactly clear. For SCA, several etiological roles have been identified that lead to neurotransmission deficits and result in PC death, including transcriptional dysregulation, autophagy, mitochondrial defects and alterations in calcium homeostasis.[8] In dystonia, the basal ganglia have classically been attributed a key role. However, recent theories support a pathophysiological model in which dystonia is seen as a network disorder involving several brain regions, including the sensorimotor cortex, brainstem, thalamus and cerebellum.[4,5] Nevertheless, it remains uncertain whether dysfunction of a single brain area, combined dysfunction of multiple areas, or abnormal communication between several brain areas leads to dystonia. Dystonia is regarded as a disorder of motor control[9] involving the cerebellum[10] and the basal ganglia, which are interconnected (Figure 1). The cerebellum also plays a role in cerebellar ataxias. In this review, we therefore focus on the potentially shared pathophysiology of the cerebellum in SCA and dystonia.

Evidence for overlap in pathology between ataxia and dystonia

Evidence from clinical studies

Evidence of cerebellar involvement in dystonia comes from several lines of research. By the beginning of the 20th century it had already been recognized that tumors in the posterior fossa could result in the abnormal postures of the head that we would now classify as dystonia.[11–14] These clinical findings were replicated in a larger cohort of 25 cervical dystonia patients, in which almost half of the patients had a lesion in the brainstem or cerebellum, whereas lesions in the basal ganglia were seen in only a quarter of them.[15] Batla et al. showed cerebellar abnormalities in 26 out of 188 (14%) cervical dystonia patients.[16] For secondary blepharospasm, a focal form of dystonia, lesions were found mostly in the thalamus, with the remainder equally split between basal ganglia and cerebellum.[17] Other cases reported oromandibular dystonia and blepharospasm after cerebellar infarction,[18–20] hemidystonia caused by vertebral artery occlusion,[21] and focal limb dystonia after isolated cerebellar tuberculoma.[22]

Only small case series have been reported for neuropathological changes in dystonia, specifically in isolated cervical dystonia. A recent review showed that no pathological abnormalities were found in almost all reported cases that had a high probability of suffering from cervical dystonia.[23] These case studies have, however, several shortcomings. The major limitation is that most were focused on specific brain regions that did not include the cerebellum or the brainstem. The authors also found that the cerebellums of the cervical dystonia patients had significantly lower PC density compared to healthy controls.[23,24] This implies a role for the cerebellum in dystonia, and it is further worth noting that loss of PCs is also associated with other neurodegenerative disorders, such as SCA.

Evidence from imaging studies

In addition to alterations in the sensorimotor cortices and the basal ganglia, structural abnormalities in the cerebellum or cerebellar projections have been found in several types of dystonia. Diffusion tensor imaging was used to assess microstructural white matter integrity in different non-hereditary isolated dystonias and demonstrated alterations varying from the white matter tracts underlying several cortical areas[25,26] to connections to the cerebellar lobules and peduncles.[27–32] See reviews by Neychev et al. and Zoons et al.[4,33] for a complete overview of the evidence for the role of the cerebellum based on imaging studies. More recent findings come from studies of several groups of hereditary dystonia. In DYT1, DYT6 and DYT11 patients, microstructural abnormalities were found close to the superior cerebellar peduncle.[34–36] A reduction in structural connectivity of the cerebellothalamic pathway in DYT1 and DYT6 patients was also seen by tractography.[37]

Metabolic imaging using [18F]-fluorodeoxyglucose-PET also shows involvement of the cerebellum in dystonia. The most reported pattern of altered metabolic activity involves the basal ganglia, pre-motor and motor areas, and the cerebellum, and is present in both hereditary as well as non-hereditary isolated dystonia.[38] More recently, Niethammer et al. described a motor-related activation pattern characterized by cerebello-thalamo-cortical motor circuits, that is increased in both hereditary and non-hereditary dystonia and even in non-manifesting carriers of DYT1 and DYT6.[28] Furthermore, the results of the eight voxel-based morphometry studies published to date have been inconsistent. An *increase* in gray matter volume of several parts of the cerebellum was seen in various types of isolated focal dystonia,[29,30,39–41] while a *decrease* in gray matter volume was shown in other studies.[30,42,43]

Lastly, cerebellar abnormalities have been frequently reported in a number of studies using fMRI. In addition to alterations in sensorimotor cortical areas and the basal ganglia, altered task-related activity (e.g. finger tapping, writing or speaking) was found in several cerebellar areas, including the cerebellar nuclei, posterior vermis, and paramedian cerebellar hemisphere. Again, however, the effects were inconsistent across and between different types of isolated dystonia.[44–51]

Evidence from electrophysiological studies

In the past few years, electrophysiological studies on dystonia have identified three common themes that explain its pathophysiology: loss of inhibition, maladaptive plasticity and defective sensorimotor integration.[9] Classically in isolated dystonia, there is a reduction in cortical inhibition (i.e. an increase in motor-evoked potentials and a reduction of the short intracortical inhibition using transcranial magnetic stimulation). However, in some types of dystonia (e.g. myoclonus dystonia), a contrasting pattern is seen that resembles the excitability profile of cerebellar pathology.[52,53] Maladaptive plasticity, a second common theme, has been demonstrated in several types of dystonia.[54] It is known, for instance, that beyond the basal ganglia, the cerebellum also plays a role in plasticity and motor learning.[55] Eye blink classical conditioning (EBCC) is a paradigm for associative motor learning that has been shown to be highly dependent on cerebellar functioning without basal ganglia involvement.[56,57] Teo and co-authors demonstrated significant abnormal EBCC in isolated dystonia patients,[58] which could be normalized by continuous theta burst stimulation; this suggests a secondary role for the cerebellum.[59] A study on sensorimotor adaptation using a motor learning paradigm that relies on both the cerebellum and the sensorimotor network (split-belt paradigm) demonstrated abnormalities in patients with blepharospasm and writer's cramp.[60] Defective sensorimotor adaptation was also seen in writer's cramp patients performing a visuomotor adaptation task, suggesting that the cerebellum had lost its ability to modulate sensorimotor plasticity of the motor cortex.[61] In contrast to these findings,

normal sensorimotor adaptation was seen in cervical dystonia patients.[60,62] Experiments with a therapeutic focus also demonstrated cerebellar involvement in dystonia. In focal hand dystonia patients, cerebellar transcranial direct current stimulation improved handwriting and cyclic drawing kinematics, most likely by reducing cerebellar-brain inhibition.[63] In cervical dystonia patients, two weeks of cerebellar stimulation resulted in a small but significant, clinical improvement of approximately 15% measured by the Toronto Western Spasmodic Torticollis Rating Scale.[64]

While these effects of non-invasive stimulation have been modest or transient so far, they show that manipulating cerebellar physiology can influence the severity of dystonia. More direct manipulations of the cerebellum, analogous to pallidotomy or deep brain stimulation of the basal ganglia, may be required to produce robust and lasting effects. Cerebellar dentatectomy[65] and direct electrical stimulation of the cerebellum[66] were once routinely applied as treatments for dystonia, but these procedures were abandoned because the benefits were unpredictable. However, the indication for these procedures was "hypertonia" or "cerebral palsy", which could reflect any combination of dystonia, spasticity and/or rigidity, and this grouping together of many disorders with potentially different causes may have been responsible for the unpredictable outcomes. Now that the various types of hypertonia are better distinguished, more recent studies have begun to discriminate between the beneficial effects of dentatectomy[67] and cerebellar stimulation,[68] although further studies are still needed.

Evidence from animal models

In line with the evidence from patients who show both dystonia and cerebellar ataxia, several animal models confirm the role of the cerebellum in the etiology of dystonia. Ataxia and dystonia were identified in a mouse model (leaner) with a spontaneous missense mutation in the splice donor consensus sequence, at the 5' end of the affected intron in *Cacna1a,* which encodes the voltage-gated calcium channel $Ca_v2.1$.[69–71] This phenotype is associated with abnormal physiological activity and slow degeneration of cerebellar Purkinje neurons.[70,72–77] Mutations in *CACNA1A* have been linked to a range of movement disorders including SCA6 and benign paroxysmal torticollis of infancy.[78,79] Notably, in the leaner mouse model, the dystonia abated while the ataxia worsened as PCs were lost over time.[80] This finding is evidence for the hypothesis that PC-dysfunction leads to dystonia, whereas PC-loss causes ataxia. Additionally, *Cacna1a* null mice also exhibited dystonia and highly selective cerebellar degeneration, further confirming a key role for PC functioning in a shared pathology of dystonia and ataxia.[69] Additionally, a mouse model for rapid-onset dystonia-Parkinsonism (RDP), which mimicked the effect of mutations in the α3 isoform of the Na(+)/K(+)-ATPase (sodium pump), exhibited ataxia quickly followed by a dystonic phenotype upon blockage of α3-sodium pumps with ouabain.[81] Fremont et al. showed that restricted cerebellar perfusion with ouabain

is sufficient to induce dystonia, and *in vivo* recordings from these dystonic mice showed persistent high-frequency-burst firing of PCs.[82] Moreover, selective knock down of the α3-sodium pump in the substantia nigra resulted in a Parkinsonism phenotype, while knockdown in other basal ganglia regions had no apparent effect. Cerebellum-specific knockdown of the α3-sodium pump recapitulated the phenotype of the RDP mouse, which was again associated with altered intrinsic pacemaking of PCs, but it had no effect on the firing rate of neurons from the deep cerebellar nuclei (DCN) (see Figure 1 for projections between brain regions).[83] However, DCN neurons fired irregularly in dystonic animals compared to controls, a difference most likely caused by aberrant PC input to the DCN.[83] Furthermore, a disynaptic connection between the cerebellum and the basal ganglia via the thalamic intralaminar nuclei, was shown to underlie the dystonic phenotype of the RDP mouse, as lesions of the centrolateral nucleus alleviated the dystonia.[84]

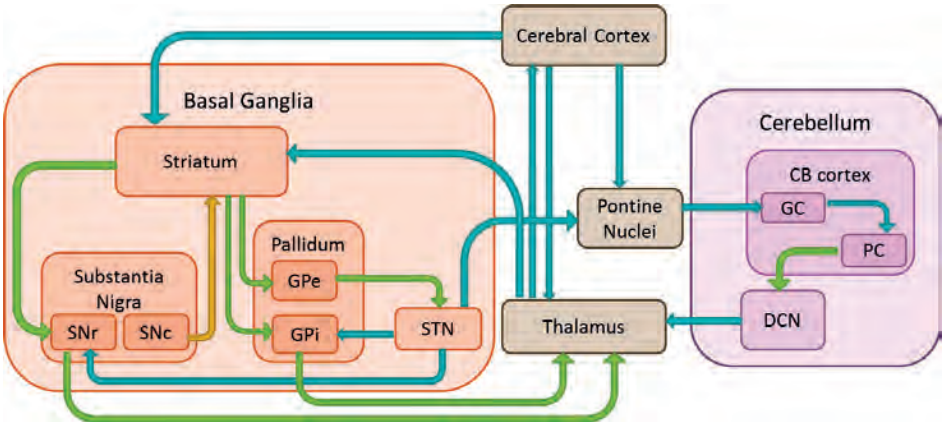

Figure 1. Schematic representation of connections between basal ganglia and cerebellum
Blue arrows represent excitatory glutamatergic projections. Green arrows represent inhibitory GABAergic projections. Yellow arrow represents dopaminergic projections. CB = cerebellum; GC = granule cells; PC = Purkinje cells; DCN = deep cerebellar nuclei; STN = subthalamic nucleus; SNr = substantia nigra pars reticulata; SNc = substantia nigra pars compacta; GPe = globus pallidus externus; GPi = globus pallidus internus.

In another model, Atcay$^{ji\text{-}hes}$ mice, which show very low levels of the caytaxin protein, action-induced stiff dystonic legs can be turned into broad-based ataxic gait by partial cerebellectomy or lesions of the DCN.[85] In contrast, homozygous missense mutations in *ATCAY*, the human orthologue of Atcay, cause autosomal recessive Cayman ataxia but not dystonia.[86] The dystonic phenotype in mice is most likely the consequence of increased repetitive firing of DCN neurons caused by absence of inhibitory repetitive firing of PCs. Thus, it is the combination of aberrant firing patterns of PCs and DCN neu-

rons that likely exaggerates the hyperexcitability of the DCN neurons above a threshold sufficient to directly activate muscle groups resulting in dystonia and ataxia.

Finally, knockout of *fgf14,* the human disease gene underlying SCA27, resulted in ataxia and a paroxysmal hyperkinetic movement disorder mimicking a form of dystonia.[87] With the notion that fgf14 was most abundantly expressed in cerebellar granule cells of the cerebellum, PC dysfunction rather than a direct PC deficit seems to cause the ataxia and dystonia-like phenotype.

Overall, these studies show a clear role for the cerebellum in the etiology of dystonia. We therefore hypothesize that shared genetic pathways might underlie the pathogenesis of dystonia and SCA, and that the cerebellum plays a major role in both disorders. To further elucidate this hypothesis, we first explore the current knowledge about the genetic background of both groups of disorders.

Genetics of dystonia and SCA

The introduction of high-throughput next generation sequencing (NGS), which rapidly detects all protein-coding variants, has led to the discovery of multiple disease genes for SCA (Table 1) and dystonia (Table 2). Exome sequencing has become common practice for gene identification of Mendelian forms of dystonia and SCA. To date, 16 genes have been identified using exome sequencing, including the recently discovered mutations in *COL6A3*[88] and *TRPC3*.[89] However, linkage analysis is still commonly used to pinpoint the region of interest and to filter exome sequencing results. Exome sequencing has its limitations, and an alternative method would be genome sequencing of the complete genome (coding and non-coding parts). However, genome sequencing remains relatively expensive and produces a very long list of putative candidates with undefined pathogenicity, many of which will be located in non-coding regions, making pathogenicity very difficult to establish. Furthermore, many diagnostic requests come from independently referred patients (singletons) who lack the additional affected family members necessary for co-segregation analysis. In reality, conventional genetic testing is usually only performed for the most common SCA and dystonia types, leaving a large group of patients genetically undiagnosed.

Despite the many disease genes that have been identified, our knowledge of the underlying biological pathways and pathogenesis of dystonia and ataxia is still limited. The main biological pathway linked to dystonia before the introduction of NGS was dopamine synthesis, which was implicated via mutations in *GCH1* and *TH,* which encode GTP cyclohydrolase 1 and tyrosine hydroxylase, respectively.[90,91] This finding was reinforced by the observation that these patients are levodopa (L-DOPA) responsive.[92]

Table 1. Known SCA genes

SCA type	OMIM Number	Locus	Gene Name	Mutation type	References
SCA1	164400	6p22.3	*ATXN1*	CAG repeat	[240]
SCA2	183090	12q24.13	*ATXN2*	CAG repeat	[241,242]
SCA3	109150	14p32.12	*ATXN3*	CAG repeat	[243,244]
SCA5	600224	11q13.2	*SPTBN2*	Deletion, MM	[218,245]
SCA6	183086	19p13.13	*CACNA1A*	CAG repeat	[78]
SCA7	164500	3p14.1	*ATXN7*	CAG repeat	[246]
SCA8	608768	13q21	*ATXN8OS*	CTG repeat (non-coding)	[247]
SCA10	603516	22q13.31	*ATXN10*	ATTCT repeat	[248–250]
SCA11	604432	15q15.2	*TTBK2*	Deletion	[251]
SCA12	604326	5q32	*PPP2R2B*	CAG repeat (non-coding)	[252]
SCA13	605259	19q13.33	*KCNC3*	MM	[102,253]
SCA14	605361	19q13.42	*PRKCG*	MM	[254]
SCA15	606658	3p26.1	*ITPR1*	Deletion	[255,256]
SCA16	606658	3p26.1	*ITPR1*	Deletion	[255,256]
SCA17	607136	6q27	*TBP*	CAG repeat	[257]
SCA19/22	607346	1p13.2	*KCND3*	MM	[103,104,258,259]
SCA20	608687	11q12	*DAGLA*	12 genes duplication	[260,261]
SCA21	607454	1p36.33	*TMEM240*	MM	[262]
SCA23	610245	20p13	*PDYN*	MM, frameshift	[116,263]
SCA26	609306	19p13.3	*EEF2*	MM	[264,265]
SCA27	609307	13q13.1	*FGF14*	MM	[266]
SCA28	610246	18p11.21	*AFG3L2*	MM	[267,268]
SCA29	117360	3p26.1	*ITPR1*	MM	[106,269]
SCA31	117210	16q22	*BEAN*	TGGAA repeat (non-coding)	[270,271]
SCA34	133190	6q14	*ELOVL4*	MM	[272]
SCA35	613908	20p13	*TGM6*	MM	[273]
SCA36	614153	20p13	*NOP56*	non-coding repeat	[274]
SCA38	615957	6p12	*ELOVL5*	MM	[275]
SCA40	616053	14q32.12	*CCDC88C*	MM	[276]
SCA41	616410	4q27	*TRPC3*	MM	[89]
SCA42	616795	17q21.33	*CACNA1G*	MM	[100]

MM= missense mutation

However, the majority of dystonia patients do not respond to L-DOPA treatment, indicating that there are other biological pathways involved. At first, no main biological pathway was recognized for SCA, as the functions of *ATXN1* and *ATXN3* had not then been determined. Now, however, the main pathway involved has been identified as altered synaptic transmission due to mutations in *KCNC3, KCND3, CACNA1A, ITPR1, TRPC3* and *PDYN*. These encode various ion channels, receptors and a neuropeptide precursor,

affecting potassium (*KCNC3* and *KCND3*), calcium (*CACNA1A, ITPR1* and *TRPC3*) and opioid receptor signaling (*PDYN*). See reviews of the genetics of dystonia and SCA by Matilla-Dueñas, Storey and Phil, Balint and Bhatia, and Xiao et al.[93–96] for further details.

Table 2. Known dystonia genes

Dystonia type	OMIM Number	Locus	Gene Name	Inheritance pattern	References
DYT1	128100	9q34.11	*TOR1A*	AD	277,278
DYT2	224500	1p35.1	*HPCA*	AR	279
DYT3	314250	Xq13.1	*TAF1*	XLR	280,281
DYT4	128101	19p13.3	*TUBB4A*	AD	282
DYT5	128230	14q22.2	*GCH1*	AD	90,283
DYT6	602629	8p11.21	*THAP1*	AD	284–286
DYT8	118800	2q35	*PNKD*	AD	287,288
DYT9	601042	1p34.2	*SLC2A1*	AD	289,290
DYT10	128200	16p11.2	*PRRT2*	AD	291–293
DYT11	159900	7q21.3	*SGCE*	AD	294,295
DYT12	128235	19q13.2	*ATP1A3*	AD	296,297
DYT16	612067	2q31.2	*PRKRA*	AR	298
DYT18	61216	1p34.2	*SLC2A1*	AR	299
DYT23	614860	9q34.3	*CACNA1B*	AD	99
DYT24	615034	11p14.2	*ANO3*	AD	233
DYT25	615073	18p11	*GNAL*	AD	178
DYT26	616398	22q12.3	*KCTD17*	AD	300
DYT27	616411	2q37.3	*COL6A3*	AR	88
	612716	2q13.2	*SPR*	AR	301
	605407	11p.15.5	*TH*	AR	91
		9q34.11	*CIZ1*	AD	302

AD = Autosomal dominant; AR = Autosomal recessive; XLR = X-linked recessive.

Investigating the shared genetic background

For this review we brought together dystonia and SCA genes to identify the shared genetic components and expose possible common underlying biological pathways. Our focus lies on dominantly inherited SCAs and dystonias and we have therefore used 16 autosomal dominant dystonia genes and 28 SCA genes, including polyQ-SCA genes, as input seeds for further analysis (Table 1 and Table 2).To gain insight into the common biological pathways we used GeneNetwork (http://129.125.135.180:8080/GeneNetwork/cytoscape.html), a co-expression tool based on approximately 80,000 microarrays from Gene Expression Omnibus,[97] and PANTHER software to analyze gene ontologies.[98] Based on the assumption that co-expressed genes are more likely to be involved in

similar biological pathways, this guilt-by-association approach enabled us to assess which genes generally tend to be activated simultaneously, and are thus under similar transcriptional regulation with known autosomal dominant dystonia and ataxia genes. By applying independent GeneNetwork analyses for both known autosomal dominant dystonia and ataxia genes (Supp. Figures 1 and 2) and with manual assessment of the overlap in genes between these gene networks, we identified 99 genes shared by the two disorders (Figure 2). No data was filtered out of the analysis. In contrast, when we

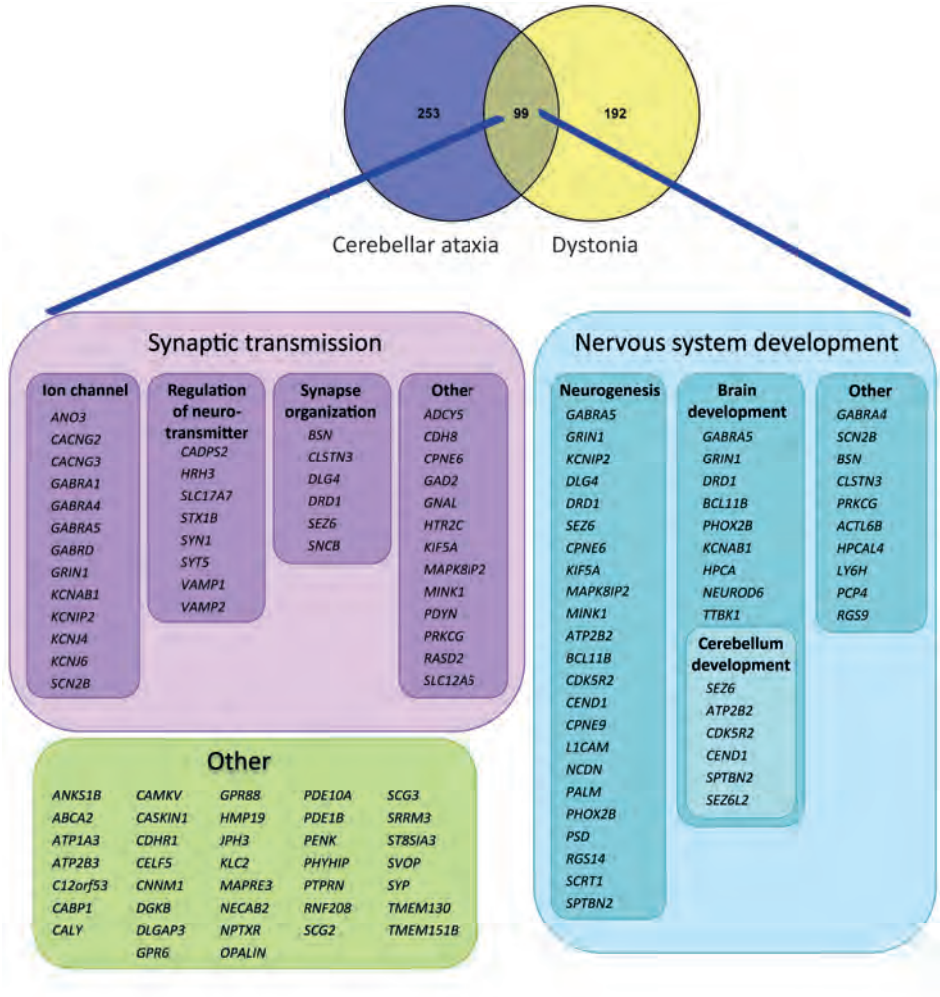

Figure 2. Shared genes between SCA and dystonia
We found 99 genes are shared between the SCA and dystonia gene co-expression networks. Two main pathways were identified that involved synaptic transmission (39 genes) and nervous system development (38 genes).

compared either the dystonia gene network or the ataxia gene network with a "control" gene network based on 26 known autosomal dominant Charcot-Marie-Tooth (CMT) genes, we did not find any significant overlap (p = 0.2153 for CMT/SCA and p =0.1222 for CMT/Dystonia), thereby validating our approach. Additionally, six of the 99 genes shared between dystonia and SCA were known dystonia or ataxia genes (*ATP1A3, ANO3, GNAL, SPTBN2, PRKCG,* and *PDYN*) and their presence further validates our hypothesis that shared co-expression networks likely point towards shared pathogenesis. Using PANTHER, we were able to categorize most of the 99 shared genes into two major neurological pathways: synaptic transmission and nervous system development (Figure 2). We observed a 14-fold enrichment (P = 8.39E-31) for genes playing a role in synaptic transmission (39/99 genes; see Figure 2) and a 3.8-fold enrichment (P= 8.96E-10) for genes involved in nervous system development (38/99 genes). However, not all genes fit into these two categories (see Figure 2), indicating that there are other biological pathways/mechanisms playing a role in the molecular pathology of ataxia and dystonia. In the next section, we focus on these two major neurological pathways and highlight their role in disease pathogenesis.

Genes involved in synaptic transmission

Ion channels

We observed that 40 of the shared genes identified by our network approach were involved in synaptic transmission, a finding that was validated by recent studies showing that both dystonia and ataxia are characterized by altered excitability of neurons.[99–101] One-third of the shared genes identified as involved in synaptic transmission encode ion channel subunits that regulate neuronal potassium, calcium or chloride signaling. Notably, 13.1% of the shared genes encode ion channels compared to 2% of all genes in the complete exome (P < 0.0001), further emphasizing the importance of ion channels in the etiology ataxia and dystonia. In contrast, no ion channels were present among the genes that were shared between CMT and SCA and between CMT and dystonia (data not shown).

The role of ion channels in the pathophysiology of both dystonia and SCA is underscored by the identification of human mutations leading to these diseases in *CACNA1B* (DYT23; voltage-gated calcium channel Cav2.2), *KCNC3* (SCA13; voltage-gated potassium channel Kv3.3), *KCND3* (SCA19; voltage-gated potassium channel Kv4.3), *CACNA1A* (SCA6; voltage-gated calcium channel Cav2.1), *CACNA1G* (SCA42; voltage-gated calcium channel Cav3.1), *ITPR1* (SCA15/16; Type 1 Inositol 1,4,5-Trisphosphate Receptor) and *TRPC3* (SCA41; Transient Receptor Potential Cation Channel, Subfamily C, Member 3).[78,89,99,102–106] Additionally, various ion channel mutations in mouse models lead

to dystonia and/or ataxia including *cacna1a* knockout and *cacna1a* mutants, such as leaner mouse with generalized dystonia/ataxia, tottering mouse displaying ataxia plus paroxysmal generalized dystonia and rocker mouse exhibiting ataxia with paroxysmal focal dystonia. In contrast, lethargic *cacna1b* mutant mouse models appear to have ataxia with paroxysmal exertional dystonia.[107,108] A putative role for calcium channels in human dystonia was proposed based on the fact that mice treated with an L-type calcium channel agonist developed a phenotype resembling generalized dystonia.[109] Furthermore, in addition to ataxia, posture dystonia was observed in the opisthotonos mouse, which carries a spontaneous mutation in *itpr1* (*ITPR1* is the human SCA15/16 gene) that codes for the type 1 inositol 1,4,5-trisphosphate receptor, which is involved in calcium release from the endoplasmatic reticulum.[110] While many ion channels are associated with various forms of epilepsy, this topic lies outside the scope of this review and will not be described in further detail here. In the following paragraphs, we discuss the evidence for a role of the shared ion channel genes in the pathogenesis of dystonia and ataxia based on both human and mouse data and according to the pathway in which these genes function.

The shared genes shown to be involved in potassium signaling are *KCHIP2* (Kv channel interacting protein 2), *KCNAB1* (regulatory beta subunit Kvβ1), and *KCNJ4* and *KCNJ6* (inwardly rectifying potassium channels Kir2.3 and Kir3.2/GIRK2, respectively). *KCHIP2* has been implicated in the pathogenesis of SCA19[111] and mutations in *KCNA1* encoding Kv1.1, the alpha subunit of Kvβ1, cause episodic ataxia (EA1) in humans.[112] In mouse striatum, Kir2.3 is specifically located in matrix compartments, which may primarily influence motor circuits within basal ganglia, suggesting it has a role in dystonia.[113] A homozygous point mutation in the pore region of *Girk2* (Gly156Ser) causes the weaver phenotype in mice, which is characterized by cerebellar granule cell death, dopaminergic neuronal cell death in substantia nigra, severe ataxia and spontaneous seizures. In contrast, heterozygous mutant mice showed a thinner granule cell layer and a disorganized PC layer, but no motor phenotype.[114] Furthermore, GIRK2 modulates the degree of opioid inhibition upon opioid receptor activation,[115] a pathway known to be affected in SCA23.[116] GIRK2 has also been shown to be a key determinant of the sensitivity of dopaminergic neurons of the ventral tegmental area to the motor-stimulatory effects of opioids.[115] However, its effect in dopaminergic neurons of the substantia nigra is not yet known.

There is increasing evidence that GABAergic signaling is altered in various movement disorders, including dystonia, ataxia, epilepsy and tremor.[117] The shared GABA type A receptor subunits *GABRA1, GABRA4, GABRA5* and *GABRD* identified in our network are ligand-gated chloride channels responsible for the inhibitory effects mediated by the neurotransmitter GABA (γ-aminobutyric acid) in the brain. Multiple cerebellar neurons

use GABA as their output neurotransmitter, including GABAergic inhibitory projection neurons and small GABAergic interneurons in the cerebellar nuclei and Purkinje, Golgi, Lugaro, stellate, basket and candelabrum cells in the cerebellar cortex.[118] Additionally, GABAergic projections are present in basal ganglia arising from striatum, globus pallidus and substantia nigra reticula (Figure 1).[119] Loss of inhibition is thought to be a crucial causal component in the pathogenesis of dystonia,[120] and alterations in $GABA_A$ receptors may affect inhibition of action potential firing, thus contributing to disease.[121] Differential expression of $GABA_A$ receptors was observed in a SCA6 mouse model caused by mutations in *Cacna1a*.[122] In contrast, mice with PC-specific knockdown of *Vgat,* which encodes a vesicular GABA transporter, showed an ataxic phenotype that did not coincide with visible brain malformations at 40 weeks of age. This suggests that GABA release is important for PC functioning, and alterations in PC-specific GABA release cause ataxia.[123]

Shared genes *CACNG2* and *CACNG3,* which encode voltage-dependent calcium channels γ-subunits 2 and 3, play a role in regulation of glutamate signaling by their function as transmembrane AMPA receptor (AMPAR) regulatory proteins (TARPs). The AMPAR-TARP complexes are involved in long-term potentiation and long-term depression, and therefore play a role in memory and motor learning, which has been implicated in various mouse ataxia models.[124–126] Stargazer mice show distinctive head-tossing and ataxic gait caused by mutant *CACNG2* (TARP-γ2, stargazin).[127] In zebrafish, Cacng2a was shown to be required for trafficking of the AMPAR to the membrane that mediates normal AMPAR functioning.[128] The role of glutamate in the pathogenesis of both dystonia and ataxia is further highlighted by a shared gene, *GRIN1,* which encodes the *N*-methyl-D-aspartate (NMDA)-type glutamate receptor subunit, GluN1. GLuN1 can interact with the dopamine receptor D1R[129], and mutations in this gene are likely to affect both NMDA and dopamine signaling, causing non-syndromic intellectual disability and epileptic encephalopathy, encephalopathy with infantile-onset epilepsy, and hyperkinetic and stereotyped movement disorders.[130,131] Glutamate excitotoxicity has been postulated as a possible disease mechanism for various neurodegenerative disorders, including SCA.[132] The GRIN1 interaction with DR1 suggests that putative mutations in *GRIN1* or alterations in *GRIN1* expression may lead to aberrant dopamine signaling and subsequently to dystonia.[133]

Sodium signaling, amongst others mediated by the shared gene *SCN2B* that encodes the auxiliary β2-subunit of voltage-gated sodium channels, has only recently been implicated in dystonia. A spontaneous mouse mutant carrying a mutation in *scna8* developed a chronic movement disorder with early onset tremor and adult onset dystonia.[134] Given that Nav1.6 (encoded by *scna8*) is important for the initiation of action potentials, loss of Nav1.6 function might affect the repetitive firing of PCs. Thus, genes

encoding components of sodium signaling could be considered as candidate genes for human movement disorders, including dystonia.

Regulation of neurotransmitters

Our search also identified a group of shared genes involved in the regulation of neurotransmitters, and a clear role for neurotransmitter regulation can be seen in the pathogenesis of dopamine-responsive dystonias. Most of the shared genes are associated with neurotransmitter-containing vesicles and thus play a role in the release of neurotransmitters and control synaptic transmission. Interestingly, the majority of these genes are involved in glutamatergic and GABAergic signaling. Shared genes *SYT5* (synaptotagmin V) and *CADPS2* (Ca^{2+}-dependent activator protein for secretion) are both linked to dense-core vesicles. Syt5 is involved in Ca^{2+}-dependent exocytosis in mouse brain,[135] and *cadps2* is involved in secretion of vesicles containing brain-derived neurotrophic factor (BDNF) and neurotrophin-3 (NT-3) that play a pivotal role in neuronal differentiation and survival.[136] BDNF goes on to induce presynaptic glutamate release, increase NMDA-receptor density and increase the dendritic complexity of the GABAergic neurons.[137,138] Furthermore, *cadps2* knockout mice showed deficits in cerebellar development accompanied by aberrant motor coordination and eye movement.[136] Solute carrier family 17, member 7, encoded by shared gene *SLC17A7 (VGLUT1),* is a vesicular glutamate transporter necessary for filling glutamate vesicles that thereby influences synaptic transmission efficiency.[139] VGLUT1-deficient mice appeared normal until postnatal week two, after which they started to lag in development and differ in movement and behavior, with death occurring between postnatal week P18 and P21.[140]

Among the shared genes identified in our search, there are also components of the SNARE-complex involved in exocytosis of neurotransmitter vesicles. We identified *STX1B* (syntaxin-1B) and vesicle-associated membrane proteins (*VAMP1*/synaptobrevin1 and *VAMP2*/synaptobrevin2) in our network. Decreased spontaneous GABAergic transmission frequencies were detected in STX1B knockout cerebellar cultures,[141] whereas mutations in *VAMP1* have been identified as causing dominant hereditary spastic ataxia (SPAX1).[142] Moreover, VAMP1-deficient mice (lethal-wasting (*lew*)) showed premature death at P15 and were found to have neurological deficits, including profound motor impairments that were most likely caused by reduced functioning of neuromuscular junctions.[143,144] VAMP2-deficient mice demonstrated a critical role for VAMP2 in Ca^{2+}-dependent vesicle exocytosis[145] and in postsynaptic insertion of GluA1-containing AMPA receptors into the synaptic plasma membrane.[146] However, an association with a human disorder has yet to be found. Another shared gene is *SYN1* (synapsin I), which encodes a synaptic-vesicle-associated phosphoprotein involved in organization of the vesicles at the presynaptic terminal and in axonal development.[147,148]

The only gene in this shared group not specifically linked to vesicles is histamine receptor H3 (*H3R*), which is selectively expressed in brain[149] and present on presynaptic terminals, where it acts as an autoreceptor inhibiting histamine production and release. H3R is also present on postsynaptic nerve terminals where it functions as a heteroreceptor that inhibits the release of other neurotransmitters such as norepinephrine, serotonin, GABA, acetylcholine, glutamate and dopamine.[150] While no mutations in *H3R* have been reported, *hrh3*-knockout mice showed reduced locomotor activity, indicating that *H3R* is a plausible candidate gene for movement disorders.[151,152]

Synapse organization

The third group of shared genes that emerged from our network analysis plays a role in the organization of synapses and encodes scaffolding proteins necessary for proper synapse formation and vesicular structures. On the postsynaptic site, we identified *DLG4* (Disc large 4, or postsynaptic density protein 95; *PSD95*) and *CLSTN3* (calsyntenin-3/alcadein-β) as shared genes between ataxia and dystonia. *DLG4* is involved in clustering of NMDA-receptors, potassium channels and interacting proteins,[153] some of which some, e.g. *KCNC3, KCND3,* and *KCTD17,* are already linked to ataxia or dystonia. Additionally, a *DLG4* knockout mouse model showed enhanced long-term potentiation accompanied by impairments in spatial learning, but no motor phenotype.[154] *CLSTN3* is a cadherin protein that forms a functional complex with α-neurexin and is mainly involved in regulating inhibitory synaptic functions including GABAergic signaling.[155–157] We also identified dopamine receptor D1 (*DRD1*) in the network, which is a G-protein-coupled receptor for the neurotransmitter dopamine that also regulates NMDA receptor functions.[158] Variants in D1R have been associated to tardive-like dystonia[159] and D1R-knockout mice showed reduced dynorphin expression in the striatum and increased locomotor activity.[160] However, loss of dopaminergic neurons does not necessarily lead to Parkinsonism in SCA2 and SCA3 patients.[161] Moreover, *SEZ6* (seizure-related 6 homolog) and *SNCB* (β-synuclein) were identified in our search, and the exact functions of these genes are still unclear. However, sez-6 knockout mice do display altered dendritic branching, a smaller number of excitatory synapses and defects in excitatory synaptic transmission leading to reduced motor coordination.[162,163] Bassoon, a presynaptic scaffold protein encoded by *BSN,* is primarily involved in ribbon synapses in retina and cochlear hair cells, and thus shows no direct link to movement disorders.[164]

Other shared genes involved in synaptic transmission

We identified 13 other shared genes involved in synaptic transmission that did not match the GO-terms *ion channel*, *neurotransmitter regulation* or *synapse organization*. A number of these genes are involved in intracellular signal transduction. *PRKCG*, for example, encodes the neuron-specific protein kinase C gamma that mediates neu-

ronal signal transduction. *PRKCG* is the causative gene for SCA14, in which dystonic phenotypes, including writer's cramp, myoclonus and focal dystonia are regularly reported.[165–168] We also identified *MAPK8IP2* (mitogen-activated protein kinase 8-interacting protein 2/JNK-interacting protein 2 (JIP2)), a synaptic scaffolding protein involved in the JNK-signaling cascade.[169] Jip2 knockout mice showed sensorimotor deficits and impaired social interaction due to changes in the morphology of dendritic arbors of PCs associating with aberrant NMDA- and AMPA-receptor-mediated glutamatergic signaling.[170] Notably, Jip1/Jip2 double knockouts were severely ataxic,[171] demonstrating a role for JIP2 in the underlying pathology of cerebellar ataxias.

Two other shared genes are directly implicated in dystonia: *ADCY5* encoding adenylyl cyclase 5[172] and *GNAL* encoding stimulatory G-protein α-subunit Gαorf. [173] Mutations in *ADCY5* have been found to cause familial dyskinesia with facial myokymia (FDFM)[174,175] and (benign) chorea with dystonia,[176,177] while mutations in *GNAL* underlie adult-onset cervical and segmental dystonia (DYT25).[178] Additionally, *RASD2* (RASD family, member 2/tumor endothelial marker 2 (TEM2)/Ras homolog enriched in striatum (RHES)) encodes a small GTPase that plays a role in dopaminergic signaling[179,180] and enhances L-dopa induced dyskinesia via activation of mTOR,[181] giving it a putative role in dystonia.

Three other shared genes, *SLC12A5, HTR2C* and *KIF5A,* are involved in regulation of receptor functioning, thereby mediating post-synaptic neurotransmission. *SLC12A5* (solute carrier family 12, member 5/potassium-chloride cotransporter 2 (KCC2)) encodes a neuron-specific ion transporter that is the main extruder of the intracellular chloride used to create the chloride gradient necessary for GABA- and glycine-receptor functioning, and which ultimately promotes post-synaptic inhibition.[182,183] *KIF5A* encodes a neuron-specific kinesin heavy chain protein involved in microtubule-based cargo transport of, among others, the $GABA_A$-receptor.[184,185]

For the remainder of the genes in this group, brain functions are not yet completely established, but some, including *GAD2, PDYN, MINK1* and *CPNE6,* seem to link to GABA neurotransmitter synthesis and synaptic plasticity.[186–189] Of this list, only *PDYN,* the precursor for the neuropeptides α-neoendorphin, dynorphin A (Dyn A) and dynorphin B (Dyn B), is directly linked to ataxia. Notably, dynorphins are involved in pain sensing, addiction and depression via opioid signaling,[190] while mutations in *PDYN* have been shown to cause SCA23 and suggestively affect glutamate signaling.[116] Lastly, *CDH8* mediates Ca^{2+}-dependent cell-cell adhesion involved in presynaptic organization and synaptic remodeling.[191] *Cdh8* knockdown in rat primary neurons led to aberrant dendritic arborization and decreased self-avoidance of dendritic branches.[192]

Genes involved in neurodevelopment

Beyond the large group of genes involved in synaptic transmission, we identified many shared genes involved in development of the nervous system. Indeed, many disorders that combine dystonia with other neurological features are developmental.[2] Neurodevelopmental abnormalities have already been linked to DYT1 dystonia and include alterations in the cerebello-thalamo-cortical pathways.[193] Recently, cerebellar neurogenesis was found to be compromised in mouse models of DYT1 dystonia,[194] demonstrating that loss of Tor1A induces important developmental alterations in the cerebellum, and thereby contributing to the development of dystonia in *DYT1* mutation carriers. To date, no clear evidence has been reported for alterations in brain development in the pathology of dominant hereditary ataxias. However, developmental delay has been reported for SCA27, SCA2, SCA5 and SCA13.[102,195–197] In SCA13, differences in axonal pathfinding were observed in zebrafish motor neurons expressing mutant F448L-KCNC3,[198]which is also indicative of aberrant neurogenesis. More evidence that abnormalities in cerebellum development and deficits in axon elongation may give rise to ataxia came from a mice lacking neuron navigator 2 (Nav2).[199] These mice exhibited a small cerebellum at E17.5 and ataxia at age 5 months due to aberrant migration of post-mitotic granule cells. Given that all these examples showed a young age of onset or juvenile ataxia, in contrast to the late age of onset found in the majority of SCAs, it seems difficult to reconcile them with playing a role in neurodevelopment in disorders with a late age of onset. However, some preliminary evidence has been reported for a role of neurodevelopment in Alzheimer's disease and Parkinson's disease.[200–202] Therefore, we will now address the overlapping ataxia-dystonia network genes in the context of their putative role in the central nervous system (CNS) development, including neurogenesis and brain/cerebellum development.

Neurogenesis

The shared genes involved in this group are implicated in axon path finding, regulation of dendrite/axon extension, or dendrite morphogenesis. Many of these genes (*GABRA5*, *GRIN1*, *SEZ6, ATP2B2*, *BCL11B*, *CDK5R2*, *CEND1* and *SPTBN2*) were also listed in the group for brain/cerebellum development and these will be discussed in the next section. Additionally, some genes that are involved in neurogenesis and/or neurodevelopment (*GABRA5, GRIN1, SEZ6, KCNIP2*, *DLG4 (PSD-95), CPNE6*, *KIF5A*, *MAPK8IP2* and *MINK1)* are also involved in synaptic transmission and have already been discussed in the *Synaptic transmission* section.

Of the genes involved in neurogenesis, Copine1, which is encoded by *CPNE9,* regulates neurite outgrowth and differentiation of hippocampal progenitor cells.[203] In contrast, *LCAM1* and *NCDN,* which encode cell adhesion molecule L1 and neurochondrin,

respectively, modify neurite growth either in cerebellar neurons[204] or PC12 cells.[205] The paired-like homeobox domain protein Phox2b is a key determinant of neuronal identity, as it is required for the initial phase in neuronal differentiation, giving rise to noradrenergic neurons that may be involved in the pathology of dystonia.[206,207] For *PSD*, *RSG14* and *SCRT1,* not much is known about their role in neurogenesis. However, the relation of *PSD* to *DLG4* (see section on *Synaptic transmission*), and the fact that *RSG14* and *SCRT1* are highly expressed during early postnatal development,[208,209] suggest a role for these genes in brain development.

Brain/cerebellum development

Data highlighting GABAergic signaling as a shared pathway in movement disorders including dystonia, ataxia, epilepsy and tremor, was mentioned in the *Synaptic transmission* section, but GABAergic signaling also plays a role in brain development. Cerebellar maturation was reported to depend on modulation of the pool of GABAergic interneurons via exogenous Sonic hedgehog.[210] For example, direct neuronal migrations of cortical interneurons expressing $GABA_B$ receptors are regulated by Gai-Go-coupled receptor signaling in which the G-protein-regulator of neurite outgrowth 1, encoded by shared gene *GRIN1,* seemingly participates.[211,212] *In situ* data showed that GRIN1 was expressed on a migrating subpopulation of neurons from the caudal rhombic lip to the precerebellar nuclei of the brainstem, and moderate GRIN1 expression was seen in the cerebellum, suggesting it has a role in cerebellum development.[212,213] *NEUROD6*, a member of the basic helix-loop-helix transcription factors is involved in neuronal differentiation of GABAergic and glycinergic interneurons.[214]

The role of the plasma membrane Ca^{2+}-Pump 2 encoded by shared gene *ATP2B2* in cerebellar development was established by studies of cerebellar organotypic slice cultures. Here, inhibition of the Ca^{2+}-pump resulted in a reduction of the PC dendritic tree, confirming the importance of calcium signaling in controlling dendritic growth.[215] Mutations in *ATP2B3,* which is also expressed in the cerebellum, led to X-linked congenital cerebellar ataxia,[216] further emphasizing the importance of these pumps in the pathology of cerebellar ataxias. Additionally, cell-type-restricted and time-dependent expression of the neuron-specific calcium-binding protein hippocalcin, which is encoded by shared gene *HPCA* and underlies DYT2, was observed in the developing brain; this suggests that hippocalcin plays a role in neuronal differentiation in the early stages of development.[217] Furthermore, mutations in overlapping gene *SPTBN2* cause SCA5,[218] and mutant B-III-spectrin led to mislocalization and dysfunction of mGluR1α at dendritic spines.[126] These findings further connect glutamatergic dysfunction and aberrant calcium homeostasis to brain/cerebellar development. Potassium signaling may also play a role in the proper development of the CNS, as differential regulation of

distinct potassium channel beta subunits, including Kvbeta 1 (*KCNAB1*), was observed to mediate neuronal survival and maturation.[219]

Neuronal-specific gene Cell Cycle Exit And Neuronal Differentiation 1 (CEND1) is required for normal cerebellar development. Mice lacking Cend1 showed impaired cerebellar development and motor dysfunction due to an increased proliferation of granule cell precursors, delayed granule cell migration, and alterations in PC differentiation.[220] In contrast, *CDK5R2*, which encodes the neuronal-specific activator of CDK5 kinase, indirectly regulates dendrite development and axon guidance by regulating gene expression and phosphorylation of key targets such as Connexin 43 and PIPKI gamma 90 during brain development.[221–223] However, no direct role for Tau Tubulin Kinase 1, TTBK1, in brain development has yet been reported.

Other genes not tagged as involved in neurogenesis or brain cerebellum development

In this last group, ten genes were identified that did not fit the GO terms *neurogenesis* and/or *brain-cerebellum development*. We have already discussed *GABRA4*, *SCN2B*, *BSN* and *PRKCG,* which have been previously linked to synaptic transmission, but apparently they also play a role in CNS development. Of the remaining genes, not much is known about their respective functions or role in brain development. However, calcium signaling again plays a role, as *CLSTN3*, *HPCAL4*, *PCP4* and *Ly6h* are all seemingly involved in mediating intracellular calcium homeostasis.[156,224,225]

Shared gene *ACTL6B* is part of a neuronal-specific chromatin-remodeling complex that mediates long-term memory formation via the coordinated regulation of gene expression.[226] This complex also contains the rBAF factor that regulates the expression of genes involved in the dendritic development required for synaptic plasticity and memory. Deficits in plasticity were also already reported in DYT1 dystonia mice and various ataxia mouse models.[125,227–229]

Shared gene *RGS9,* which encodes a regulator of G-protein signaling, was found to have a restricted expression in the basal ganglia and suggestively plays a role in local signaling pathways that include mu-opioid receptor signaling.[230,231] Aberrant opioid signaling was reported in a hamster model of paroxysmal dystonia[232], and mutations in the precursor protein of the opioid dynorphin peptides, prodynorphin, cause SCA23.[116] However, no clear evidence has been published with regard to its postulated role in CNS development. Further studies are required to establish a role for these shared genes in neurodevelopment.

Discussion

By combining gene co-expression networks for dystonia and SCA, we have identified a set of 99 shared genes that may play a role in the pathogenesis of both disorders. These results further validate the clinical observations of co-morbidity of ataxia and dystonia and show a role for the cerebellum in dystonia. Additionally, a "control" network based on known CMT genes showed no significant overlap with dystonia or SCA gene network, confirming that dystonia and SCA are biologically closer related. The key shared molecular pathways between ataxia and dystonia were synaptic transmission and neurodevelopment, with the involvement of synaptic transmission in both disorders well recognized, as mutations in many ion channels have already been shown to cause these diseases.[78,99,100,102–104,233] On the other hand, molecular pathways related to neurodevelopment had not been as clearly linked to ataxia and dystonia, although a recent review mentioned neurodevelopment as a common theme in dystonia,[234] and developmental defects have been described in DYT1[193] and developmental delay is known in SCA27, SCA13, SCA5 and SCA2.[102,195–197] Moreover, genes involved in neurodevelopment may not exert their function solely during development of the CNS because they also appear to play a role in Alzheimer's disease and Parkinson's disease,[200–202] thus providing a link between development and degeneration. Identifying common pathways may aid the development of therapies because restoring a pathway will help patients with different genetic backgrounds.

Within both major pathways, the importance of glutamatergic-, and especially GABAergic signaling was strikingly demonstrated by the identification of four GABA receptor genes in the overlapping gene set. While mutations in these genes are not currently known to cause SCA or dystonia, they have been linked to epilepsy,[121,235,236] making them potential candidate genes for movement disorders. Furthermore, we also identified a number of genes that indirectly affect GABAergic signaling, including *CADPS2, STX1B, H3R, SLC12A5, KIF5A, GAD2* and *GRIN1*. We therefore suggest prioritizing genes involved in GABAergic signaling in genetic studies of SCA and dystonia patients, as these genes are likely candidate genes in genetically unexplained cases. This is particularly important because GABAergic signaling can be targeted by drugs; this is a treatment approach used in multiple neuropsychiatric disorders[237] that has also been proven to relieve rotenone-induced Parkinsonism-like symptoms.[238]

There were 37 genes that did not fit within the GO-terms *synaptic transmission* or n*ervous system development*. This does not, however, mean that these genes are not involved in these pathways, but rather that their functions may be unknown or that they might have more than one function, in both cases this would contribute to their lack of representation in the GO annotations. Alternately, the existence of this group of genes may indicate the involvement of other molecular pathways, in addition to the

two major ones we have described here. Other pathways have certainly been described as triggering SCA and/or dystonia pathology and include transcriptional dysregulation, mitochondrial defects, autophagy, dopaminergic signaling, ER stress and alterations in calcium homeostasis.[8,239]

Further unraveling of the common pathways in SCA and dystonia will improve our understanding of disease pathologies and may open the way to novel therapies by identifying new drug targets. Furthermore, our sophisticated network approach strongly suggests that the molecular pathways of ataxia and dystonia are indeed closely related. Both should be tested for simultaneously in genetic diagnostics work on ataxia and dystonia patients. As up to 100 genes need to be screened, this will be easier to achieve with the implementation of disease-focused gene panels or dedicated exome strategies. Genes that have been identified in the gene set that overlaps between ataxia and dystonia should be prioritized when searching for disease gene mutations in patients without a genetic diagnosis, because variants in these genes are more likely to be involved in their disease pathology. Overall, this gene co-expression network provides useful insights into the possible shared molecular mechanisms of ataxia and dystonia and it will lead to a better understanding of their pathogenesis.

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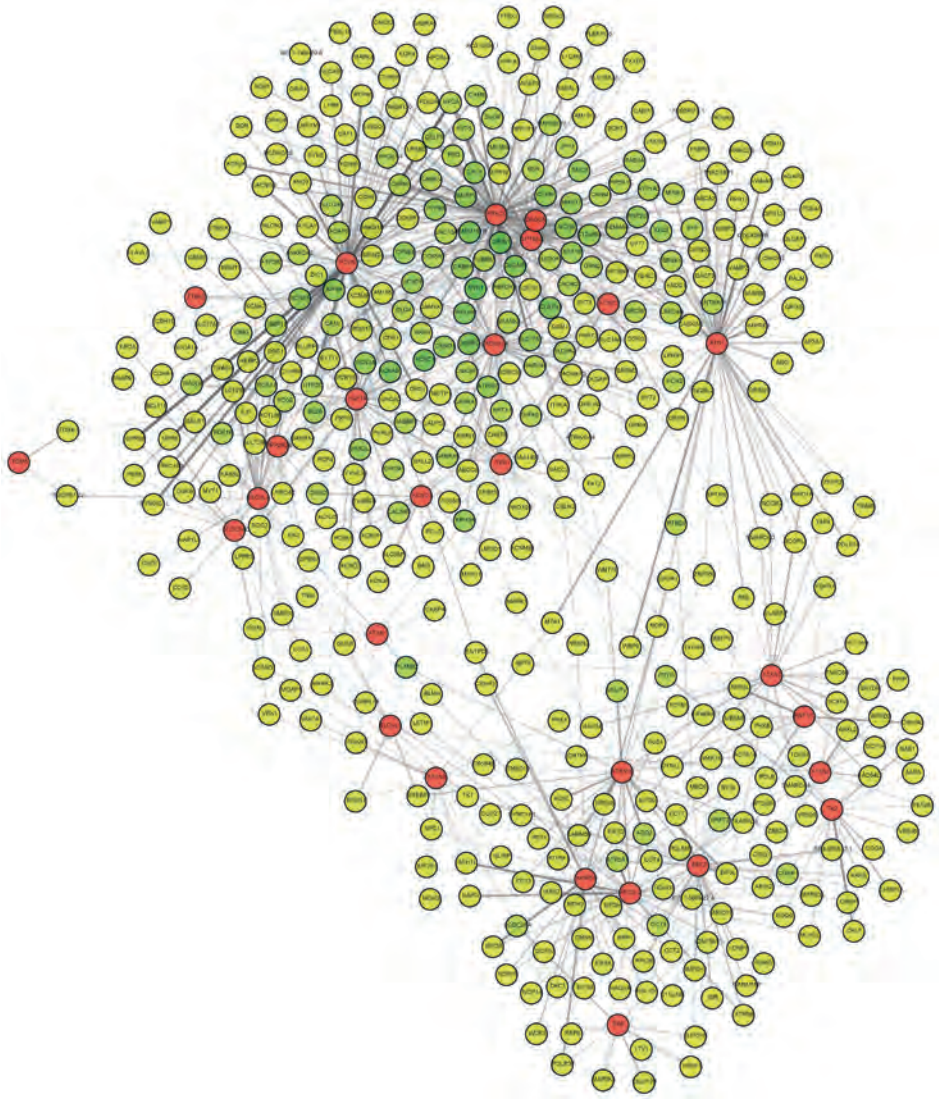
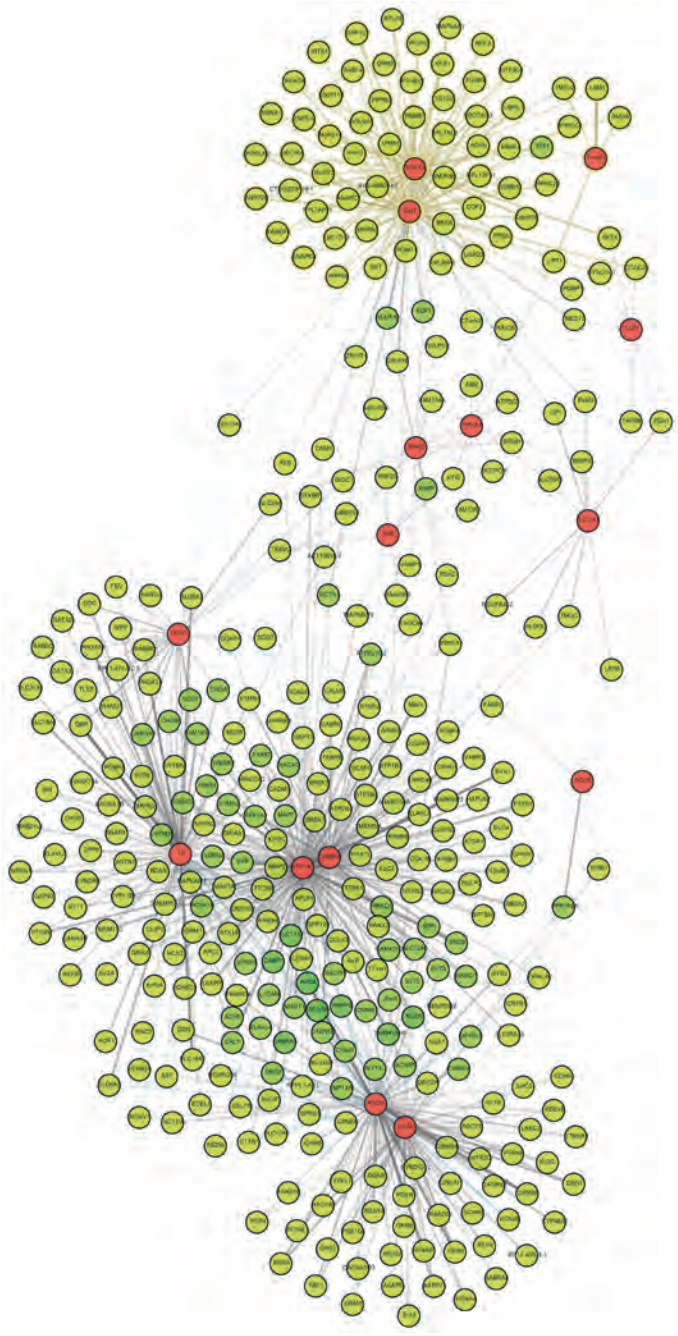


Supplementary Figure 1. Gene co-expression network based on known SCA genes
Red dots are the input genes (known SCA genes). Yellow to green dots represent co-expressed genes, darker colored dots have more connections. The thickness of the line indicates the strength of co-expression.



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