



The use of next-generation sequencing in movement disorders

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New advances in genomic technology are being introduced at a greater speed and are revolutionizing the field of genetics for both complex and Mendelian diseases. For instance, during the past few years, genome-wide association studies (GWAS) have identified a large number of significant associations between genomic loci and movement disorders such as Parkinson's disease and progressive supranuclear palsy. GWAS are carried out through the use of high-throughput SNP genotyping arrays, which are also used to perform linkage analyses in families previously considered statistically underpowered for genetic analyses. In inherited movement disorders, using this latter technology, it has repeatedly been shown that mutations in a single gene can lead to different phenotypes, while the same clinical entity can be caused by mutations in different genes. This is being highlighted with the use of next-generation sequencing technologies and leads to the search for genes or genetic modifiers that contribute to the phenotypic expression of movement disorders. Establishing an accurate genome–epigenome–phenotype relationship is becoming a major challenge in the post-genomic research that should be facilitated through the implementation of both functional and cellular analyses. In this review, we summarize the latest genetic discoveries made by the use of NGS technologies and purpose future directions and challenges to truly understand the pathophysiology of MDs.

Keywords: next-generation sequencing, movement disorders, gene discovery, novel neurological phenotypes

INTRODUCTION

Movement disorders (MDs) are a group of diseases and syndromes affecting the ability to produce and control movement

Abbreviations: AD, autosomal dominant; AHDS, Allan–Herndon–Dudley syndrome; ALS, amyotrophic lateral sclerosis; AP4, adaptor protein complex 4; AR, autosomal recessive; AT, ataxia telangiectasia; BFIE, benign familial infantile epilepsy; ChAc, chorea-acanthocytosis; CMT, Charcot–Marie–Tooth; CMT1, Charcot–Marie–Tooth type 1; CMT2, Charcot–Marie–Tooth type 2; CP, cerebral palsy; DRD, dopa-responsive dystonia; EA, episodic ataxia; ES, exome sequencing; ET, essential tremor; FA, Friedreich's ataxia; FAHN, fatty acid hydroxylase-associated neurodegeneration; FALS, familial ALS; FTD, frontotemporal dementia; GWAS, genome-wide association studies; HD, Huntington's disease; HDL2, Huntington disease-like 2; HDLS, hereditary diffuse leukoencephalopathy with spheroids; HSN2C, hereditary sensory neuropathy type IIC; HSP, hereditary spastic paraplegia; IBMPFD, inclusion body myopathy, Paget disease, and frontotemporal dementia; ICCA, infantile convulsions and choreoathetosis syndrome; ID, intellectual disability; MDs, movement disorders; MJD, Machado–Joseph disease; MLS, X-linked McLeod syndrome; MSA, multiple system atrophies; MR, mental retardation; NA, neuroacanthocytosis; NGS, next-generation sequencing; NSID, non-syndromic ID; PD, Parkinson's disease; PED, paroxysmal exercise-induced dyskinesias; PGD, progressive generalized dystonia; PKAN, pantothenate kinase-associated neurodegeneration; PKC, paroxysmal kinesigenic choreoathetosis; PKD, paroxysmal kinesigenic dyskinesias; PMD, Pelizaeus–Merzbacher disease; PMLD, Pelizaeus–Merzbacher-like disease; PNKD, Paroxysmal non-kinesigenic dyskinesias; PSP, progressive supranuclear palsy; RLS, restless legs syndrome; SALS, sporadic ALS; SCA, spinocerebellar ataxia; SPG, spastic paraplegia; TR, targeted resequencing; TS–CTD, Tourette syndrome/chronic tic disorder; TS, Tourette's syndrome; WD, Wilson disease; WGS, whole-genome sequencing; XLD, X-linked dominant; XLR, X-linked recessive.

and are often accompanied by secondary clinical presentations such as seizures, cognitive deficits, autoimmune deficiencies, and psychiatric symptoms, among others, causing major difficulties in diagnosis and treatment. MDs comprise the following clinical conditions: ataxia, dystonia, essential tremor (ET), Huntington's disease (HD), multiple system atrophies (MSA), Parkinson's disease (PD), progressive supranuclear palsy (PSP), restless legs syndrome (RLS), tics, Tourette's syndrome (TS), and Wilson disease (WD). MDs are classified as monogenic (Mendelian) or multifactorial or polygenic (Complex). However, mutations in known MD genes account for only a small percentage of cases, indicating that more genes and higher-risk alleles await discovery (Kompolti and Verhagen, 2010).

Although linkage analysis along with candidate gene screening was traditionally the preferred method for gene discovery in inherited MDs (Paisán-Ruiz et al., 2004, 2005), these are not appropriate for families with largely reduced penetrance or reduced number of affected individuals. And even though there has been considerable success in identifying genetic risk factors for PD and PSP through the application of genome-wide association studies (GWAS; Simon-Sanchez et al., 2009; Hamza et al., 2010; Hoglinger et al., 2011), a detailed mapping through targeted resequencing (TR) is still required to further identify both high-risk alleles and haplotypes (Tucci et al., 2010; Freedman et al., 2011). By contrast, next-generation sequencing (NGS) technologies, such as exome sequencing (ES) and whole-genome sequencing (WGS), enable

respectively a complete scan resolution of the entire both exome and genome, allowing a rapid identification of disease-causing mutations and higher-risk alleles. This has already been evidenced in rare Mendelian diseases where large sample sizes are difficult to gather (Ng et al., 2009, 2010), and in families previously deemed statistically insufficient for positional cloning (Bilguvar et al., 2010; Marti-Masso et al., 2012). Likewise, *de novo* pathogenic mutations have recently been identified in autism spectrum disorders by performing trio-based ES in only 20 sporadic cases (O’Roak et al., 2011). In conclusion, NGS is an ideal approach to identify causal alleles for inherited MDs and its application will increase the candidate gene list associated with MDs, facilitating the subsequent diagnosis and understanding of the disease process (Singleton, 2011).

In this review, we first describe the phenotypic spectrum associated with MDs and second summarize the novel genetic findings achieved by the use of NGS in MDs. The genetic contribution of MDs is expanding by the discovery of novel genes and the association of novel neurological phenotypes to already known disease genes.

MOVEMENT DISORDER PHENOTYPES IN WHICH NGS HAS BEEN PERFORMED

Below the phenotypes and genetic backgrounds of some inherited MDs in which NGS technologies have been employed are described. Phenotypes are listed in alphabetical order.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that controls the voluntary muscle movement. Because it is sometimes accompanied by PD and related disorders and some MDs genes can also cause ALS (Bosco et al., 2011), we decided to include it here. ALS is characterized by upper and lower motor neuron dysfunction resulting in progressive paralysis generally followed by death due to respiratory failure (Johnston et al., 2006; Johnson et al., 2010). The majority of ALS is sporadic (~90%), and the clinical features of familial ALS (FALS) and sporadic ALS (SALS) are virtually indistinguishable, aside from a slightly earlier age at onset of FALS. Even though all FALS genes have also been implicated in SALS, these only account for a small proportion of cases, leaving much of the genetics of this disorder to be discovered (Andersen and Al-Chalabi, 2011). Some ALS-associated genes may also cause other disorders, such as frontotemporal dementia (FTD), cerebellar ataxia, motor neuropathies, hereditary spastic paraplegia (HSP), and Parkinsonism.

Ataxia describes a lack of muscle coordination during voluntary movements usually due to pathology in the cerebellum and its connections, such as spinocerebellar and pontocerebellar pathways. Although it is a neurological symptom, there are several inherited disorders that are due to this unsteady movement of gait and limbs, including Friedreich’s ataxia (FA), spinocerebellar ataxia (SCA), episodic ataxia (EA), ataxia telangiectasia (AT), and Machado–Joseph disease (MJD). Ataxias can present as sporadic or hereditary and are divided into five main categories: mitochondrial, metabolic, defective DNA repair, abnormal protein folding and degradation, and channelopathies. Based on neurological examination, ataxias can be broadly classified into pure cerebellar ataxias and those in which additional neurological deficits are also present.

Most of the ataxias are labeled with the term SCA followed by a number to denote the distinct locus. At present, there are over 30 SCA loci and at least 17 disease-related genes identified (Filla and De Michele, 2012; Subramony, 2012a,b).

Cerebral palsies (CPs) comprise a heterogeneous group of neurodevelopmental disorders characterized by motor and postural impairments (Pakula et al., 2009). CP is classified according to the movement disorder observed as spastic, ataxic, dystonic, or athetoid, and according to the limbs affected as monoplegic, hemiplegic, diplegic, or quadriplegic (Moreno-De-Luca et al., 2012). Furthermore, CP is often associated with other neurological complications such as intellectual disability (ID), psychosocial disorders, and seizure disorders, making diagnosis and management of symptoms difficult (Aisen et al., 2011).

Charcot–Marie–Tooth (CMT) disease is the most common inherited neurological disease characterized by distal muscle weakness and atrophy (Weedon et al., 2011), and sometimes it occurs with sensory loss, depressed tendon reflexes, and *pes cavus* (highly arched feet). There are two main forms of CMT: CMT1 or type 1 that causes demyelination and CMT2 or type 2 that affects nerve axons. CMT is quite genetically heterogeneous, with over 40 disease-associated loci identified, and presents with intra-familial phenotypic variability (Del Bo et al., 2006), making traditional screening techniques time consuming and genetic diagnosis difficult.

Dystonias comprise a clinically and genetically heterogeneous group of MDs characterized by involuntary sustained muscular contractions affecting one or more sites of the body that produce abnormal postures and repetitive movements. They are classified according their etiology as primary when dystonia is the sole manifestation or secondary when it is accompanied by other neurological conditions, and according to the affected muscle groups’ distribution as focal, segmental, multifocal, generalized, and hemidystonias. The most common type of primary dystonia is primary torsion dystonia, which is caused by mutations in either *DYT1* or *DYT6* genes (Ozelius et al., 2011). However, even though there are more than 20 loci associated with dystonia, most cases are idiopathic and all familial forms present with reduced penetrance, making traditional linkage analyses inaccurate (Fuchs and Ozelius, 2011).

Fatty acid hydroxylase-associated neurodegeneration (FAHN) is caused by a deficiency of fatty acid 2-hydroxylase (FA2H; Kruer et al., 2010). *FA2H* pathogenic mutations were first described in families with leukodystrophy, spastic paraplegia (SPG), and dystonia (Edvardson et al., 2008), but later in families with complex SPG (SPG35) and neurodegeneration with brain iron accumulation (NBIA; Dick et al., 2010; Kruer et al., 2010). NBIA is characterized by progressive extrapyramidal deterioration and high brain iron deposition, most consistently in the basal ganglia.

Leukoencephalopathies are white matter diseases, in which a movement dysfunction is often a symptom. Sensory, behavioral, and cognitive deficits are also common. For instance, hereditary diffuse leukoencephalopathy with spheroids (HDLS) is associated with variable behavioral, cognitive, and motor dysfunction (Rademakers et al., 2011). Clinically, it is difficult to

diagnose because it often presents with intra-familial heterogeneity and a firm diagnosis often occurs post-mortem (Baba et al., 2006). Pelizaeus–Merzbacher disease (PMD) is an X-linked hypomyelinating leukodystrophy, manifested as impaired motor development followed by ataxia, dystonia, dysarthria, and progressive spasticity (Vauers-Barriere et al., 2009).

Parkinson's disease is the third most common neurodegenerative disorder, behind Alzheimer's disease and ET, affecting approximately 1–2% of the population above the age of 65, and whose incidence increases steeply with age (Lang and Lozano, 1998). It is characterized by bradykinesia, resting tremor, muscular rigidity, and postural instability. Although approximately less than 20% of cases follow clear Mendelian inheritance and the majority of PD is sporadic (Lees et al., 2009), there are 16 PD loci reported and at least eight genes identified to date (Hardy et al., 2009).

Paroxysmal kinesigenic dyskinesias (PKD), also called paroxysmal kinesigenic choreoathetosis (PKC), is the most common paroxysmal movement disorder and is characterized by recurrent, brief attacks of dyskinesia that are induced by sudden voluntary movements. The attacks manifest in dystonia or choreoathetosis. There are two other types of paroxysmal dyskinesias: exercise-induced (PED) and non-kinesigenic (PNKD). PED is genetically heterogeneous and only a small percentage of familial and sporadic cases are explained by deficiency in the glucose transporter type 1 gene (*GLUT1*) whereas PNKD is mainly due to mutations in the myofibrillogenesis regulator 1 gene (*MR-1*; Bhatia, 2011). Most PKD cases follow an autosomal dominant (AD) inheritance pattern (65–72%). Benign familial infantile epilepsy (BFIE) clinically resembles PKD and thus both are often misdiagnosed. BFIE can be familial or sporadic and is characterized by brief, non-febrile convulsions starting in the first year of life (Rochette et al., 2008). The co-occurrence of BFIE and PKD within a single family gave rise to the distinct clinical entity called infantile convulsions and choreoathetosis (ICCA) syndrome.

Spastic paraplegias are a group of MDs characterized by progressive spasticity in the lower limbs. Clinically they are classified as pure when consisting mainly of spasticity, abnormal reflexes, and motor deficits, or complex when a wide range of neurological symptoms are also present (Salinas et al., 2008). Genetically, they can arise from mutations in at least 23 genes, with more still being discovered, as 48 SPG loci have already been reported. Spasticity is also a symptom often seen in many other neurological diseases, and mutations in some SPG genes are responsible for other neurodegenerative diseases such as atypical ALS and atypical Parkinsonism (Orlacchio et al., 2010; Paisan-Ruiz et al., 2010).

Tourette syndrome/chronic tic disorder (TS–CTD) is fairly common, affecting 1–10 per 1000 boys, with milder versions affecting up to 10% of children (Rampello et al., 2006). It is characterized by motor and vocal tics. Although multiple rare copy number variants within several genes have recently been found associated with TS (Sundaram et al., 2010), most of the genetic causes have yet to be determined, as candidate gene association and linkage studies have been inconsistent and irreproducible (Rampello et al., 2006).

As stated above and the literature illustrates, MDs are both genetically and phenotypically heterogeneous and thus NGS technologies are the preferred and more rapid method to elucidate their causal alleles.

NOVEL MOVEMENT DISORDER GENES IDENTIFIED THROUGH NGS

In the last 2 years, NGS technologies have seen great use in the field of movement disorder genetics in which eight novel genes have been elucidated and many other NGS-related manuscripts will probably come to light in the next couple of years. Novel genes have been identified for ALS, CMT type 2, PD, PKD, spinocerebellar ataxia, BFIE, ICCA syndrome, and TS–CTD (**Table 1A**).

In some studies linkage analyses were carried out prior to NGS approaches. For instance, several studies identified the chromosome 9p21 as a causal locus for both ALS and FTD (Le Ber et al., 2009; Van Es et al., 2009; Shatunov et al., 2010). Although a large Swedish family was previously reported as presenting with mainly dementia in the first to third generation and motor neuron disease and mild dementia in the fourth generation (Gunnarsson et al., 1991), not until lately has the genetic cause for this link been identified: a massively expanded hexanucleotide repeat (GGGGCC). This hexanucleotide repeat was found in a non-coding region of *C9orf72* located on chromosome 9p21 and is suggested to be the most common cause of both FALS and FTD identified to date (DeJesus-Hernandez et al., 2011; Renton et al., 2011). The *C9orf72*-associated phenotype has recently been defined as an early-onset, AD neurodegenerative disease presenting with cognitive and behavioral impairment, specific neuroimaging changes, and reduced survival (Byrne et al., 2012). Similarly, PKD families were previously linked to chromosome 16p.11–q12.1 by different groups (Tomita et al., 1999), but not until now, taking advantage of ES technologies, has the causal gene, *PRRT2*, been identified (Chen et al., 2011; Wang et al., 2011; Li et al., 2012). *PRRT2* mutations have additionally been reported in BFIE and ICCA families previously linked to chromosome 16p.11–q12.1 (Szepietowski et al., 1997; Caraballo et al., 2001; Heron et al., 2012), and in familial and sporadic cases with PKD, ICCA, PED, or PNKD-like disease (Liu et al., 2012), further confirming the *PRRT2*'s pathogenic role. *TGM6* genetic variability has likewise identified in spinocerebellar ataxia-35 (SCA35), which was mapped to chromosome 20p13–12.2 and is characterized by a slowly progressive and relatively pure form of adult-onset cerebellar ataxia affecting both upper and lower limbs (Wang et al., 2010). *TGM6*, encoding transglutaminase 6, is expressed in Purkinje cells (Hadjivassiliou et al., 2008) and anti-transglutaminase 6 antibodies have been proved to cause ataxia in mice (Boscolo et al., 2010).

In conclusion, the pathogenesis of *C9orf72*, *PRRT2*, and *TGM6* genes is fully disclosed by the linkage and disease-segregation data, the absence of pathogenic mutations in neurologically normal individuals, and their further replication in additional or animal studies.

But other studies performed ES directly or after exclusion of known genes. For instance, *DYNC1H1* (cytoplasmic dynein heavy chain 1) genetic variability, which was previously shown to cause sensory neuropathy with motor neuron loss in mice (Chen et al., 2007), has recently found responsible for AD CMT2 in humans (Weedon et al., 2011). In addition, a mutation in the vacuolar protein sorting 35 (*VPS35*), p.Asp620Asn, identified by two independent groups in PD patients (Vilarino-Guell et al., 2011; Zimprich et al., 2011), has both been replicated and failed to be replicated in recent studies (Sheerin et al., 2011; Guella et al.,

Table 1 | Next-generation sequencing in movement disorders.

Disease	Mode	Method	Gene	OMIM (#)	Nucleotide change	Protein change	Reference
A. NOVEL MD GENES IDENTIFIED THROUGH NGS							
Amyotrophic lateral sclerosis with frontotemporal dementia	AD	TR	<i>C9orf72</i>	614260	(GGGGCC) _n #	N/A	Renton et al. (2011), DeJesus-Hernandez et al. (2011)
Benign familial infantile epilepsy and infantile convulsions with choreoathetosis syndrome	AD	TR	<i>PRRT2</i>	614386	c.629_630insC	p.Ala211Serfs*14	Heron et al. (2012)
Charcot-Marie-Tooth disease type II	AD	Exome	<i>DYNC1H1</i>	600112	c.649_650insC	p.Arg217Profs*8	Weedon et al. (2011)
	AD	Exome TR		614386	c.879 + 1G > T c.879 + 5G > A c.950G > A c.917A > G c.649insC	N/A N/A p.Ser317Asn p.His306Arg p.Arg217Profs*8	Chen et al. (2011), Wang et al. (2011), Li et al. (2012)
Paroxysmal kinesigenic dyskinesia	AD	Exome TR	<i>PRRT2</i>	614386	c.487C > T	p.Gln163Stop	Wang et al. (2011)
Parkinson's disease	AD	Exome	<i>VPS35</i>	601501	c.369dupG	p.Ser124Valfs*10	Li et al. (2012)
Spinocerebellar ataxia	AD	Exome	<i>TGM6</i>	613900	c.1858G > A	p.Asp620Asn	Vilarino-Guell et al. (2011), Zimprich et al. (2011)
Tourette syndrome/chronic tic disorder	AD	Exome	<i>MRPL3</i>	607118	c.1550T > G	p.Leu517Tyr	Wang et al. (2010)
	AD	Exome	<i>DNAJC13</i> <i>OFCC1</i>	614334 614287	c.224G > A c.6169G > T c.385A > G	p.Ser75Asn p.Ala2057Ser p.Arg129Gly	Sundaram et al. (2011)

(Continued)

Table 1 | Continued.

Previously associated phenotype – novel associated phenotype	Mode	Method	Gene	OMIM (#)	Nucleotide change	Protein change	Reference
B. MOVEMENT DISORDERS GENES ASSOCIATED WITH MULTIPLE PHENOTYPES							
IBMPFD – amyotrophic lateral sclerosis	AD	Exome	VCP	601023	c.961G > A	p.Arg191Gln	Johnson et al. (2010)
Spastic paraplegia – fatty acid hydroxylase-associated neurodegeneration [§]	AR	Exome	FA2H	611026	c.707T > C	p.Phe236Ser	Pierson et al. (2011a)
Tumor development – hereditary diffuse leukoencephalopathy with spheroids	AD	Exome	CSF1R	164770	c.2624T > C	p.Met875Thr	Rademakers et al. (2011)
ID and autism – hereditary spastic paraplegia type 30/HSN2C [®] /NSID ^f	AR	Exome	KIF1A	601255	c.764C > T	p.Ala225Val	Erllich et al. (2011)
Spastic paraplegia/parkinsonism – juvenile amyotrophic lateral sclerosis	AR	Exome	SPG11	610844	c.5199delA	p.K1733NfsX105	Daoud et al. (2012)
X-linked MR/AHDS/PMID-like disease – Pelizaeus–Merzbacher disease	XLR	Exome	MCT8	300095	c.704_705delAT c.1102A > T	p.H235RfsX12 p.Arg368Stop	Tsurusaki et al. (2011)
Glutaric aciduria type I – progressive generalized dystonia	AR	Exome	GCDH	608801	c.1275G > A	p.Val400Met	Marti-Masso et al. (2012)
Spinocerebellar ataxia type 28 – spastic ataxia-neuropathy syndrome	AR	Exome	AFG3L2	604581	c.1847G > A	p.Tyr616Cys	Pierson et al. (2011b)
Spastic tetraplegia cerebral palsy with ID – spastic paraplegia type 47	AR	Exome	AP4B1	607245	c.664delC	p.Ile222fs	Bauer et al. (2012)
Spastic paraplegia with severe intellectual disability ^g	AR	Exome	AP4S1	607243	c.124C > T	p.Arg425Stop	Abou Jamra et al. (2011)
AD cerebral atrophy, macrocephaly, seizures, and developmental delay – spinocerebellar ataxia	AR	Exome	SYT14	610949	c.1451G > A	p.Gly484Asp	Doi et al. (2011)

A. Novel genes identified through NGS; B. MD genes associated with multiple phenotypes. Diseases, mode of inheritance, sequencing method, OMIM number, nucleotide and protein changes, and author references are shown. [®]Where n > 30 copies. AD, autosomal dominant; AR, autosomal recessive; IBMPFD, inclusion body myopathy; Peget disease, and frontotemporal dementia; MR, mental retardation; ID, intellectual disability; HSN2C, hereditary sensory neuropathy type IIC; NSID, non-syndromic ID; PMD, Pelizaeus–Merzbacher disease. [§]Although FA2H mutations were already associated with FAHN, this is the second report and confirms previous findings. [®]In this study, linkage analysis followed by candidate gene screening was performed. ^fIn this study, only candidate gene screening was performed. ^gPathogenic mutations in AP4S1 were first identified by Abou Jamra et al. (2011) but mutations in other subunits of AP4 were already associated with multiple neurological phenotypes.

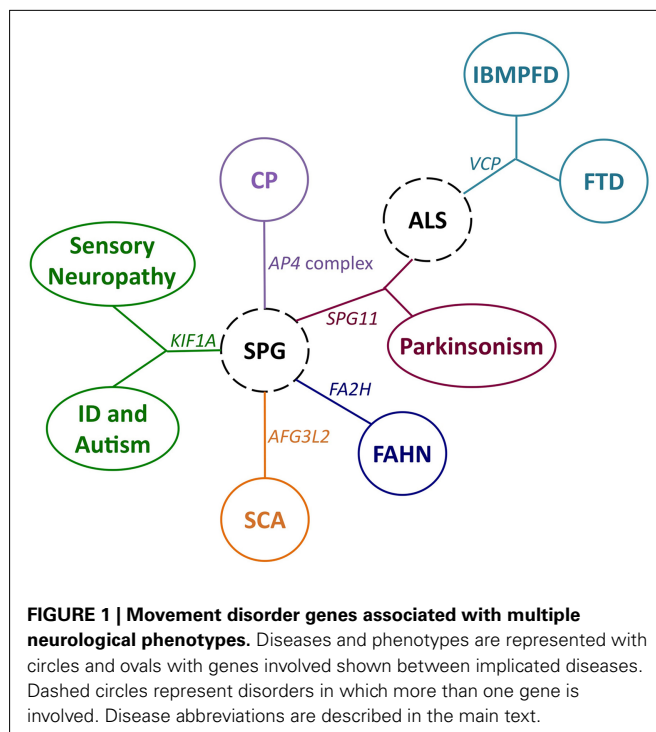
2012); and even though disease-segregating mutations in three genes, *MRPL3*, *DNAJC13*, and *OFCC1*, have recently identified in a three-generational TS-CTD pedigree (Sundaram et al., 2011), further studies are needed to corroborate this finding.

MOVEMENT DISORDER GENES ASSOCIATED WITH MULTIPLE PHENOTYPES

With the advent of NGS technologies not only have novel MDs genes been identified, but also 10 already-disease-associated genes have been found mutated in other diseases, expanding the phenotypic spectrum associated with a single gene (Table 1B). In most of these studies, SNPs-based arrays along with NGS were used to identify the genetic defects underlying disease. Examples are described below.

SPG11 mutation, although are known to be the most common causes of autosomal recessive (AR) HSP with thin corpus callosum (HSP-TCC; Hehr et al., 2007; Stevanin et al., 2007; Paisan-Ruiz et al., 2008a), has also been identified in AR both parkinsonism (Paisan-Ruiz et al., 2010) and juvenile ALS (ARJALS; Orlacchio et al., 2010). Through the use of ES, this latter association has recently been confirmed (Daoud et al., 2012) in a family consisting of two affected siblings, who one manifested with ALS and the other manifested with HSP-TCC, confirming the intra-familial phenotypic heterogeneity associated with *SPG11* mutation, which is also seen in recessively inherited parkinsonism (Anheim et al., 2009). In conclusion, *SPG11* genetic variability should be considered in SPG, ALS, and Parkinsonism, especially when they occur within the same family (Figure 1). Likewise, *FA2H* mutations were first known to cause complex forms of ARHSP (Edvardson et al., 2008; Dick et al., 2010) and later to cause NBIA, a syndrome that acquired the name of FAHN (Kruer et al., 2010). But recently, a compound heterozygous *FA2H* mutation has also been identified in a child with typical clinical features of NBIA and axonal sensory neuropathy, confirming previous findings and expanding the phenotypic spectrum associated with *FA2H* genetic variability, as axonal sensory neuropathy was not seen before in FAHN (Pierson et al., 2011b). *KIF1A*, already implicated in ID and autism (Galasso et al., 2008), has recently found mutated in hereditary sensory neuropathy type IIC (HSN2C; Riviere et al., 2011), non-syndromic ID (NSID; Hamdan et al., 2011), and HSPs (Erlich et al., 2011; Klebe et al., 2012). Due to their phenotypic heterogeneity, *KIF1A* mutations have been suggested to predict different phenotypes depending on their nature: nonsense mutations lead to a complete knockout of protein function and cause HSN2C while missense mutations in the kinesin motor domain lead to upper motor neuron dysfunction and cause SPG (Klebe et al., 2012).

Previously, mutations in two subunits, *AP4M1* and *AP4E1*, of the adaptor protein complex 4 (AP4) were found associated with AR spastic tetraplegia as well as cerebral palsy and microcephaly, respectively (Verkerk et al., 2009; Moreno-De-Luca et al., 2011). But recently, pathogenic mutations in three AP4 subunits, *AP4S1*, *AP4B1*, and *AP4E1*, have also been identified in consanguineous families presenting with early-onset complex SPG, severe ID, microcephaly, inability to walk, and epilepsy (Abou Jamra et al., 2011); *AP4B1* pathogenic mutations are also responsible for SPG type 47 (Bauer et al., 2012). Since patients carrying AP4



mutations share many clinical features, the existence of a complex AP4-deficiency syndrome, characterized by severe ID, growth retardation, stereotypic laughter, progressive spasticity, cerebral palsy, and inability to walk, has been suggested, further supporting the key role of AP4-mediated trafficking in brain development and functioning (Abou Jamra et al., 2011).

Mutations in *AFG3L2*, encoding a subunit of a mitochondrial *m*-AAA protease, were previously associated with spinocerebellar ataxia type 28 (SCA28; Di Bella et al., 2010), but recently, a *AFG3L2* mutation, p.Y616C, has also been identified in affected siblings presenting with early-onset SPG, progressive myoclonic epilepsy, and peripheral neuropathy (Pierson et al., 2011a), adding peripheral neuropathy to the *AFG3L2*-associated symptoms. Since *AFG3L2* could form a homo-oligomeric isoenzyme with itself or a hetero-oligomeric complex with paraplegin, whose mutations are associated with an adult form of SPG (Casari et al., 1998), the *AFG3L2* mutation, p.Y616C, has been suggested to specifically interrupt the formation of both the homo-oligomer and the hetero-oligomer with paraplegin, giving rise to a complex phenotype that combines symptoms of *SPG7* and *SCA28* along with mitochondrial symptoms like myoclonic epilepsy (Pierson et al., 2011a).

SYT14, previously found mutated in a 12-year-old girl with AD cerebral atrophy, macrocephaly, seizures, and developmental delay, in the form of a *de novo* balanced rearrangement [t(1;3)(q32.2;q25.2; Quintero-Rivera et al., 2007)], has lately been found mutated in AR forms of SCA (ARCA) and psychomotor retardation (Doi et al., 2011). Although both cases present with mental retardation and cerebellar atrophy, the ARCA phenotype differs in the mode of inheritance and presents with oculomotor apraxia, spasticity, peripheral neuropathy, retinal abnormality,

and psychomotor retardation, largely increasing the phenotypic spectrum associated with *SYT14* genetic variability.

Likewise, disease-segregating mutations in the valosin-containing protein, *VCP*, known to cause inclusion body myopathy, Paget disease, and FTD (IBMPFD), have recently been identified in FALS (Johnson et al., 2010), suggesting that the motor neuron degeneration seen in ALS patients should be included in the IBMPF-associated phenotype. Indeed, the presence of both Paget's disease and FTD was subsequently reported in two ALS families carrying *VCP* mutations (Johnson et al., 2010).

Mutations in the colony-stimulating factor 1 receptor, *CSF1R*, previously implicated in tumor development, including myeloid and hematological malignancies (Ridge et al., 1990), have recently been identified in patients with HDLS, who reported having no bone-structure abnormalities (Rademakers et al., 2011); this suggests that *CSF1R*, which regulates the survival, proliferation, differentiation, and function of microglia in the brain (Stanley et al., 1997), may also be implicated in motor dysfunction. Likewise, *SLC16A2* genetic variability, which was already implicated in X-linked mental retardation, Allan–Herndon–Dudley syndrome, and Pelizaeus–Merzbacher-like disease (Friesema et al., 2004; Dumitrescu et al., 2006; Frints et al., 2008; Vaurs-Barriere et al., 2009), has recently been associated with a X-linked form of leukoencephalopathy, clinically diagnosed as PMD (Tsurusaki et al., 2011). Although *SLC16A2* encodes a thyroid hormone transporter known as monocarboxylate transporter 8, MCT8, none of PMD patients carrying *SLC16A2* mutations reported thyroid dysfunction.

Lastly, mutations in *GCDH*, which encodes a glutaryl-CoA dehydrogenase, were known to cause glutaric aciduria type 1 (GA-1; Busquets et al., 2000), which is characterized by accumulation of glutaric acid (GA) and 3-hydroxyglutaric acid (3-OHGA) in brain and body fluids, leading to neurotoxicity, encephalopathy, macrocephaly, and eventually a dystonic–dyskinetic disorder (Jafari et al., 2011). However, a homozygous, disease-segregating *GCDH* mutation has recently been identified in two siblings who suffer from an AR progressive generalized dystonia (PGD; Marti-Masso et al., 2012) and whose urine samples showed excess of 3-OHGA. Since neither patient showed encephalopathy or macrocephaly, this finding associates *GCDH* deficiency with PGD, a phenotype not previously described in GA-1-associated *GCDH* deficiency.

DISCUSSION

Next-generation sequencing technologies enable a comprehensive analysis of the entire genome and exome and as such have dramatically progressed the field of biological and biomedical research, especially in Mendelian diseases. Nonetheless, these novel methodologies also have several limitations; for instance, although the target coverage is continually improving, a complete coverage will probably never be reached since specific genomic regions such as GC-rich areas and repetitive elements are difficult to amplify and large copy number variations are hard to detect. Despite this, here we report on several movements disorder studies in which NGS technologies have successfully been employed for disease-causing mutations' identification. Some of these findings have already been replicated. This is the case of *C9orf72* causing ALS

and *PRRT2* causing PKD, ICCA syndrome, paroxysmal exercise-induced dyskinesias, and paroxysmal non-kinesigenic dyskinesias. In both cases, linkage analysis was performed years before the gene identification but the causal gene did not come to light until the use of NGS technologies. As for *C9orf72*, since the genetic defect is an expanded hexanucleotide repeat located in a non-coding region, it would have been difficult to find through traditional gene screening techniques, in which only coding variants are usually examined. Two other novel MD genes identified, *TGM6* causing cerebellar ataxia and *DYNC1H1* causing CMT type 2, were previously shown to cause similar symptoms in mice, further confirming their pathogenicity. Novel genes have also been identified for PD and TS–CTD; but in contrast, due to the lack of both linkage and functional data, further molecular studies are required to further prove their pathogenicity.

These studies have demonstrated that ES is a terrific tool to molecularly diagnose genetically and clinically heterogeneous MDs in which a large number of genes should be screened and a wide range of clinical features is usually present. In addition, recent NGS studies have shown that a single gene may be involved in multiple clinical entities. Accordingly, genes causing complex SPG may also be responsible for ALS, cerebral palsy, FAHN, Parkinsonism, sensory neuropathy, and spinocerebellar ataxia phenotypes; and *VCP* mutations already associated with IBMPFD, may also be present in amyotrophic lateral sclerosis (Figure 1). These phenotypic heterogeneities associated with a single gene clearly lead us to seek the molecular events by which mutations in a single gene can result in multiple phenotypes. This may lie in the nature of the mutation, as suggested for *KIF1A* mutations (Klebe et al., 2012), or the protein domain that is affected (De Angelis et al., 1999). However, the fact that the same mutation may sometimes cause multiple phenotypes requires the search of additional factors implicated in the phenotypic expression of a disease, such as interacting genes and other genetic and environmental modifiers. To face this ambitious challenge, the characterization of each gene function through cellular and animal studies is crucial. Today, novel molecular targets and subsequent cellular mechanisms may be determined by the employment of high-throughput techniques using either small animals such as *Caenorhabditis elegans*, *Drosophila melanogaster*, and *Danio rerio*, or automated cell culturing. In addition, these throughput techniques are perfect tools for drug discovery (Giacomotto and Segalat, 2010; Jain et al., 2011). Taken together, these analyses will definitely reveal novel insights into the disease-associated pathogenesis, which in turn are essential for developing more effective treatments.

We conclude that NGS, particularly in conjunction with other methods like SNPs-based arrays, has the robust capability to identify disease-causing genes in a very limited time and to some extent to expand the phenotypic spectrum associated with a single gene, improving diagnosis and leading to the development of more effective treatments. As NGS costs decrease, target coverage increases, and filtering databases grow, a trend toward sequencing the entire genome will come next, requiring advances in the understanding of non-coding genetic events and in the identification of both genetic and environmental modifiers. Finally, our understanding of the genetic contribution to MDs will surely

increase in the coming years, but further functional and cellular analyses will be required for establishing the disease-associated mechanisms and building all molecular networks associated with MDs.

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