J Neurol (2015) 262:2382–2395
DOI 10.1007/s00415-015-7725-4

NEUROLOGICAL UPDATE

Genetic landscape remodelling in spinocerebellar ataxias: the influence of next-generation sequencing

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Received: 28 February 2015 / Revised: 25 March 2015 / Accepted: 26 March 2015 / Published online: 11 April 2015

Abstract Hereditary cerebellar ataxias (HCAs) are clinically and genetically heterogeneous neurodegenerative disorders, characterised by a cerebellar syndrome and other neurological or non-neurological signs. So far, more than 20 genes have been described in autosomal dominant HCA; in autosomal recessive HCA, even more genes are involved, in often more complex phenotypes. Because of that complexity, the genetic diagnosis of these diseases is often based on the next-generation sequencing techniques. In this review paper, we discuss the major contributions that they have made to the genetic landscape of HCAs. Numerous novel genes have been identified; still more have recently been implicated in HCAs in addition to being responsible for other diseases. The phenotypic spectrum associated with a single gene constantly gains in complexity. Novel types of mutations or transmissions in known genes are regularly being identified. All these factors make genotype–phenotype correlations particularly difficult. Some but not all of this variability can be explained by different pathophysiological consequences (loss of function, gain of function, variable levels of haploinsufficiency). This also raises the question of modifier genes. Finally, we highlight some functional pathways that increasingly appear important in HCAs.

Keywords Spinocerebellar ataxia · Next generation sequencing · Novel genes · Genotype-phenotype delineation · Pathways

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Introduction

Hereditary cerebellar ataxias (HCAs) are clinically and genetically heterogeneous neurodegenerative disorders. Clinically, they are characterised by a cerebellar syndrome, with dysarthria, gait or limb incoordination. Ocular movements are often altered. In many cases, other neurological or non-neurological systems are also affected as the disease progresses [1, 2]. Genetically, all modes of transmission have been described. In autosomal dominant (AD)-HCAs, called spinocerebellar ataxias (SCAs), trinucleotide CAG expansions are the most frequent mutations, followed by other non-coding expansions and conventional point mutations or rearrangements. More than 20 genes and 35 loci have been reported so far, but the genetic causes of AD-HCAs remain unknown in more than 40 % of cases [3]. The genetic landscape of autosomal recessive (AR)-HCAs is even more intricate, with numerous genes involved in complex syndromes [2], as in X-linked HCAs (*ABC7* [4], *SLC9A6* [5], *PRPS1* [6], *FMR1* [7]). This large genetic heterogeneity renders the genetic diagnosis of inherited HCAs difficult; in the last few years, much interest

has, therefore, been focused on next-generation sequencing, using either targeted sequencing (TS) [8] or whole-exome sequencing (WES). The latter has considerably changed the genetic landscape of HCAs, allowing many new genes to be discovered; but it has also brought challenges in terms of genotype–phenotype correlations, with a broadening of the phenotypes linked to mutations in a single gene, and the description of novel types of mutations, or transmission modes. In this review, we summarise the recent advances in the broad panorama of HCA genetics. We also stress some of the common pathways underlining these diseases that have gained in importance recently.

A bumper harvest of novel genes

Thanks to WES, there has been an explosion in the number of novel HCA-causative genes (Table 1). In AD-HCAs, new altered functions are highlighted, such as ribosomal translation in SCA26, due to mutations in *EEF2*, associated with late-onset pure cerebellar ataxia [9]. Loss-of-function mutations in *ELOVL5* (SCA38) were found in four independent pedigrees, and associated with low levels of serum arachidonic acid and docosahexaenoic acid [10]. Mutations in *TMEM240* (SCA21) [11] and *NOL3* [12] have been described in complex phenotypes. In AR-HCAs (SCAR16), *STUB1* mutations were described in three kindred with early-onset ataxia [13], and one family with ataxia and hypogonadism [14]. *STUB1* was subsequently implicated in later-onset ataxia, with associated pyramidal tract damage [15]. Another E3 ubiquitin ligase, *RNF216*, was involved in two families with AR-HCA, hypogonadism and dementia [16]. The prominence of the ubiquitin–proteasome pathway in HCAs [17] is supported by the involvement of *UCHL1* [18] and, putatively, *UBR4* (EA8) [19] (Table 1).

Spontaneous or knock-out mouse models have supported the pathogenicity of several new genes. Mutations were found in *WWOX* in two families with childhood-onset HCA, generalised tonic–clonic epilepsy and mental retardation (SCAR12); while the knock-out mice present spontaneous and audiogenic seizures as well as balance disturbances [20]. In a family with ataxia and sensorineural hearing loss, a homozygous mutation in *SLC9A1* was identified; in the spontaneous *swe* mutant mice, degeneration of deep cerebellar, vestibular and cochlear nuclei is reported [21]. In *GRID2*, loss-of-function mutations have been described in early-onset ataxia phenotypes with various accompanying symptoms, concordantly with *hotfoot* mice [22–24]. Missense mutations were described in AD congenital to late-onset HCA [25], as previously reported in *lurcher* mice [26].

The preponderance of mitochondrial dysfunction in HCAs was confirmed by homozygous *COX20* mutations identified in a family with congenital HCA and complex IV deficiency [27] and in a patient with dystonia–ataxia syndrome [28].

Finally, light has been shed on the vesicular compartment and, more specifically, the synaptic transmission, with mutations in *VAMP1* in AD spastic ataxia (SPAX1) [29], *SNAP25B* in AD-HCA with myasthenia and intellectual disability [30], and *SNX14* in AR-HCA [31].

The phenotypic apples and bananas of a single gene

Every geneticist knows that mutations in a single gene may be responsible for different diseases; the best-known example in SCAs is probably *CACNA1A/SCA6*, with mutations responsible for familial hemiplegic migraine type I, episodic ataxia type II (EA2) [32], and SCA6 [33]. The genotype–phenotype correlation is not perfect since CAG expansions are involved in EA2 [34], and, conversely, point mutations in SCA6 [35]. Recently, loss-of-function mutations in *KCND3*, previously implicated in cardiomyopathy (Brugada syndrome), were described in nine families with mild slowly progressive AD-HCA (SCA19 [36]/SCA22 [37]), confirming the involvement of ionotropic channels in HCAs. Along with the extensive use of WES for the genetic diagnostic came a broadening of the phenotypes linked to several genes, either through an enlargement of the clinical picture previously observed or a novel implication in a different disease. *ATM* mutations, responsible for ataxia–telangectasia, have been described in several families with atypical presentation, such as later age at onset, normal levels of alpha-foeto-protein, and a large range of movement disorders, including dystonia and tremor [38]. More dramatically, a *TGM6* mutation previously implicated in SCA35 has been shown to segregate with acute myeloid leukaemia [39].

Several observations have identified ceroid lipofuscinosis (CLN) genes, traditionally responsible for wider neurodegenerative phenotypes, as good candidates in adult-onset AR-HCA: *TPP1/CLN2* in SCAR7 [40], *CLN5* in adult-onset AR-HCA with cognitive decline [41], and *CTSD/CLN10* in AR-HCA with cognitive decline and retinitis pigmentosa [8].

As for why the phenotype linked to a single gene may vary, the answer is not always obvious. In some cases, different types of mutations (loss of function versus gain of function) may occur. In others, the degree of haploinsufficiency might explain some of the phenotypic variability. *PNPLA6*, previously known to cause complex hereditary spastic paraplegia (SPG39), was recently described as a cause of Boucher-Neuhäuser and Gordon-Holmes syndromes, as well as spastic ataxia [42], exhibiting a continuous spectrum of phenotypes including features amongst spasticity, ataxia, hypogonadism and chorioretinal dystrophy, none of them being mandatory (Fig. 1). Recently, it

Table 1 Summary of major clinical characteristics of novel HCA genes and genes newly implicated in HCA, described since 2012; for each clinical sign, figures in parentheses indicate the number of affected families, if not otherwise stated

Gene/locus	Mutational hotspot	#Pedigrees (more than 1 affected tested)	Cerebellar ataxia	Pyramidal signs	Cognitive impairment	Epilepsy	Other	Previous phenotype	Protein function	References
New genes										
AD										
EEF2/SCA26		1 (1)	Adult-onset, slowly progressive, pure ataxia	None	None	None	None	–	Protein translation (elongation factor)	[9]
ELOVL5/SCA38	Gly230Val (3/4)	4 (3)	Adult-onset, slowly progressive, pure, predominantly gait ataxia	NM	None	NM	Mild to moderate axonal neuropathy (1/4)	–	Lipid metabolism (elongase of very long chain fatty acids)	[10]
TMEM240/SCA21		8 (3)	Early-onset, very slowly progressive	None	Mild to severe mental retardation (5/8)	None	Behavioural disturbances (5/8)	–	Unknown	[11]
NOL3		1 (1)	Late mild gait and limb ataxia (4 patients/13)	None	None	None	Predominant familial cortical myoclonus, CA in some	–	Anti-apoptosis	[12]
VAMP1/SPAX1	Disruption of donor site (6/6)	7 (4)		All (7/7)	NM	NM	NM	–	Synaptic exocytosis	[29]
SNAP25B		1 (de novo)		NM	Intellectual disability	NM	Myasthenia, cortical hyperexcitability	–	Synaptic exocytosis	[30]
UBR4/EA8		1 (1)	Early-onset episodic ataxia/interictal impaired tandem gait	None		None	Migraine without aura in some		E3-ubiquitin ligase	[19]
AR										
STUB1		4 (2)	Young adult-onset, moderate to severe axial/limb ataxia	Increased DTR and positive Babinski (3/4)	Late cognitive impairment (1/4)	NM	Hypogonadotropic hypogonadism (1/4)	–	E3-ubiquitin ligase	[13, 14]
RNF216		2 (1)/3 het	Young adult-onset, progressive ataxia	NM	Dementia (5/5)	NM	Hypogonadotropic hypogonadism	–	E3-ubiquitin ligase	[16]
WWOX/SCAR12		2 (2)	Early-onset	Prominent (1/2)	Mental retardation (2/2)	Generalized tonico-clonic (2/2)	NM	–	Pro-apoptosis	[20]
SLC9A1		1 (1)	Early-onset	None	NM	None	Sensorineural hearing loss/delayed puberty in the male	–	Na^+/H^+ exchanger	[21]
GBA2/SPG46		8 (8)	Spastic ataxia	All	Mild intellectual disability (most)	NM	Cataract (all), sensorimotor neuropathy later on (2/4)		Lipid metabolism (beta-glucosidase, glucosylceramidase)	[91, 102]
CWF19L1		1 (1)	Congenital non progressive	NM	Mental retardation	NM			Unknown	[103]
COX20	Thr52Pro	2 (1)	Early-onset	Pyramidal signs (2/2)	None (1/2)	NM	Complex IV deficiency (2/2), dystonia (1/2), muscle hypotonia (1/2)	–	Complex IV formation	[27, 28]

Table 1 continued

Gene/locus	Mutational hotspot	#Pedigrees (more than 1 affected tested)	Cerebellar ataxia	Pyramidal signs	Cognitive impairment	Epilepsy	Other	Previous phenotype	Protein function	References
DNAJC3		11 (2)	Early-onset	Upper-motor-neuron damage	NM	NM	Diabetes mellitus, peripheral neuropathy, hearing loss	–	Immunoglobulin binding protein	[104]
AR and AD										
GRID2	Biallelic exon deletions/ Ala654Thr, Ala654Asp, Leu656Val	7 (2)	Congenital to late-onset	Increased DTR and Babinski (1/7)	Global developmental delay (3/7–AR), cognitive impairment (1/7–AD)	NM	Various ocular findings: tonic upgaze (2/7–AR), oculomotor apraxia (1/7–AR), retinal dystrophy (1/7–AR)	–	Ionotropic glutamate receptor	[22–25]
Phenotypic extension to CA										
AD										
KCND3/SCA19/ SCA22	345-390 (8/9)	9 (6)	Late-onset, slowly progressive	2/9	2/9	None	Hearing impairment (2/9)	Brugada syndrome	Ionotropic potassium channel	[36, 37]
DNMT1	570-606 (4/4)	4 (2)	Adult-onset	NM	Dementia (2/4)	NM	Narcolepsy–cataplexy (4/4), sensory neuronal deafness (4/4), optic atrophy (4/4)	Hereditary sensory neuropathy type 1E	DNA methyltransferase	[105]
ELOVL4/SCA34		1 (1)	SCA34/adult to late-onset, mild to moderate truncal/ limb ataxia	None	NM	NM	Erythrokeratodermia variabilis (1/1)	Stargardt disease	Lipid metabolism (elongase of very long chain fatty acids)	[94]
C9orf72	GGGGCC expansions	1 (1)	Adult-onset, axial ataxia with dysarthria	Late-onset	Not objectivized, but close assesment hard to achieve at the later stage of the disease	NM	Tachycardia, hyperventilation and stridor episodes/denervation in all extremities on EMG	ALS, FTD, FTD-ALS	Endosomal trafficking	[106]
CCDC88C/ SCA40		1 (1)	Adult-onset, severe	In some	NM	NM	NM	AR congenital hydrocephalus	Negative regulator of WNT signalling pathway	[107]
AR										
UCHL1		1 (1)	Early-onset	Spasticity	NM	NM	Optic nerve atrophy and blindness	PARK5 (AD)	Neuron-specific deubiquitin enzyme	[18]
TPP1/SCAR7		2 (1)	Childhood-onset, slowly progressive	Increased DTR, Babinski sign	None	NM	NM	Ceroid lipofuscinosis type 2	Lysosomal exopeptidase	[40]
CLN5		1 (1)	Adult-onset, progressive axial/ limb ataxia	Brisk DTR	Progressive cognitive decline	NM	Glaucoma	Ceroid lipofuscinosis type 5	Unknown	[41]
CTSD		1 (0)		NM	Cognitive decline	NM	Retinitis pigmentosa	Ceroid lipofuscinosis type 10	Lysosomal proteinase (cathepsin D)	[8]

Table 1 continued

Gene/locus	Mutational hotspot	#Pedigrees (more than 1 affected tested)	Cerebellar ataxia	Pyramidal signs	Cognitive impairment	Epilepsy	Other	Previous phenotype	Protein function	References
PNPLA6		6 (3)	Childhood to early adult-onset gait ataxia/Boucher Neuhauser, Gordon-Holmes syndromes, spastic ataxia	2/6	Mild cognitive impairment (2/6)	NM	Hypogonadotropic hypogonadism (5/6), chorioretinal dystrophy (4/6)	Complex HSP (SPG39)	Lipid metabolism (patatin-like phospholipase domain-containing protein)	[42, 43]
HSD17B4		3 (2)	Childhood-onset, slowly progressive	Mild signs (3/3)	Mild to severe (3/3)	NM	Sensorineural deafness (3/3), demyelinating neuropathy (3/3), hypergonadotropic hypogonadism (2/3) + azoospermia in male (1)	Severe D-bifunctional protein deficiency	Peroxisomal fatty acid beta-oxidation	[108–110]
X-linked										
GJB1		1 (1)	Childhood-onset	1/1	NM	NM	Sensorimotor neuropathy	Charcot-Marie-Tooth 1	Gap junction protein	[111]

AD autosomal dominant, *AR* autosomal recessive, *NM* not mentioned, *DTR* deep tendon reflexes, *ALS* amyotrophic lateral sclerosis, *FTD* fronto-temporal dementia

was identified in Oliver-McFarlane syndrome, which adds trichological and pituitary abnormalities to the previous spectrum. Clinical presentation was shown to correlate with the degree of enzyme malfunction, with no activity in the latter [43].

Numerous other examples of phenotypic broadening are summarised in Table 1 (*DNMT1*, *ELOVL4*/SCA34, *C9orf72*, *UCHL1*, *GBA2*/SPG46, *HSD17B4*, *SRD5A3*, *CCDC48C*/SCA40, *GJB1*).

Faced with this high clinical heterogeneity, many attempts have been made to identify a core phenotype linked to mutations in a given gene. ARCA3, caused by *ANO10* mutations, almost always presents as cerebellar atrophy with lack of neuropathy [44]. All *PLA2G6* carriers of biallelic mutations show a childhood-onset cerebellar atrophy preceding brain iron accumulation, with some correlation between the genotype and age at onset [45].

Novel types of mutations/transmission in previously described genes

On top of the description of novel genes and novel phenotypes for genes previously involved in human pathology, the new era of sequencing also reveals new types of mutations and transmission modes, for variants in previously described genes. This renders the functional interpretation of mutations particularly complex. In *ITPR1*/SCA15, most of the mutations reported up to 2012 were loss of function, with only one missense described [46]. Since 2012, three new missense variants, including one de novo, have been described [47, 48]. Notably, the variants described in [47] occur for congenital HCA, which is not the typical phenotype of SCA15. In SCA28, missense mutations were traditionally described in exon 15 and 16 of *AFG3L2* [49]. Recently, reports mentioned a deletion of exons 14–16 in two families with classical presentation [50], a deletion encompassing the entire gene in a patient with infancy-onset global developmental delay [51], and a frameshift mutation leading to a premature stop codon associated with late-onset HCA and cognitive decline [52]. *AFG3L2* was also recently involved in an AR syndrome comprised of spastic ataxia and neuropathy, SPAX5 [53]. *SPTBN2*, whose in-frame deletions and missense mutations account for AD-SCA5, was linked to AR ataxia and cognitive impairment, with homozygous loss-of-function mutations [54, 55].

Starting to uncover the genes underlying phenotypic heterogeneity

These elements of heterogeneity in the phenotype–genotype correlations raise the question of potential modifier genes. In SCAs with (CAG)*n*-repeats, the negative

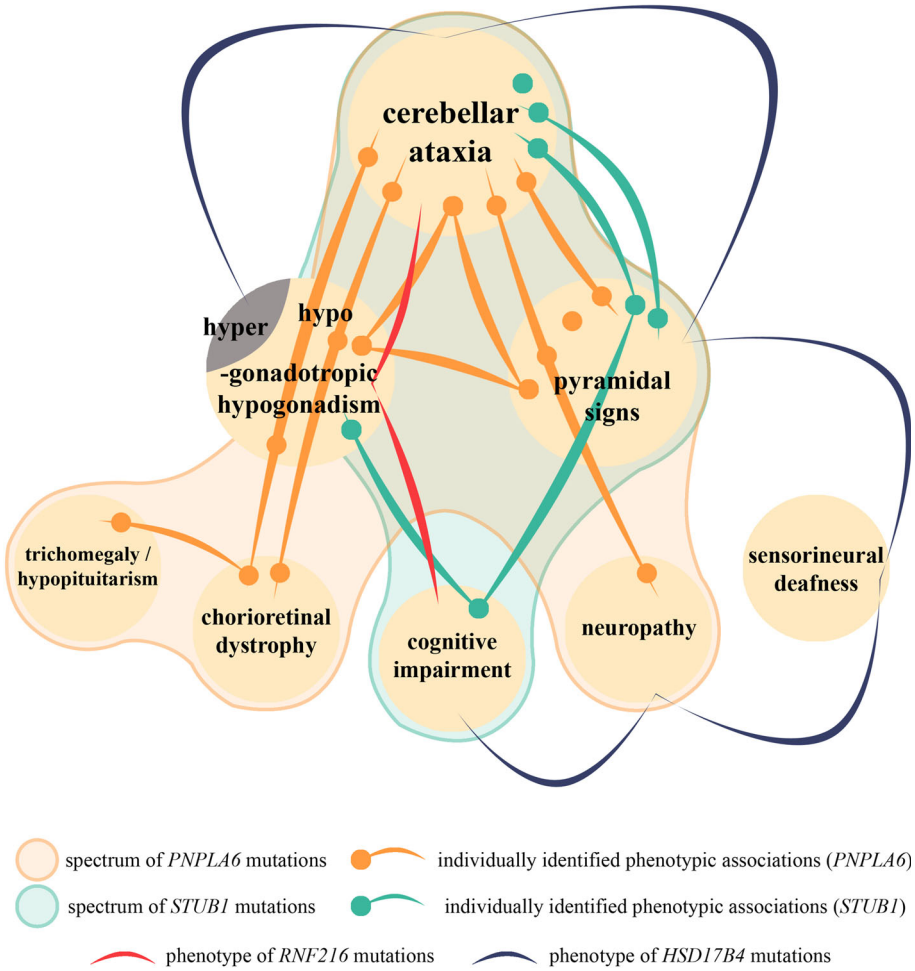

Fig. 1 Schematic representation of the phenotypic spectrum linked to newly described genes involved in ataxia plus hypogonadism. *RNF216* mutations are responsible for a uniform phenotype (*dark red*) with constant clinical signs [16]. Apart from severe D-bifunctional protein deficiency, the ataxia plus hypogonadism phenotype caused by *HSD17B4* mutations is also rather homogeneous (*dark blue*) [108–110]. In contrast, *PNPLA6* (*orange*) and *STUB1* (*light blue*) have been shown to induce variable phenotypes, with no or few mandatory signs [13–15, 42, 43]. This illustrates the complexity of genotype–phenotype correlations, accentuated with the next generation sequencing era

correlation between the size of the polyglutamine expansion and the age at onset [56] only accounts for 50–70 % of its variability. A large cohort study on 1255 affected patients allowed an assessment to be made of the influence on the age at onset of the length of the normal allele in trans (SCA1, 6, 7) and of other (CAG)*n*-containing genes [57]. Furthermore, intermediate-size CAG repeats in *ATXN2* were recently shown to be a risk factor in other neurodegenerative diseases, such as amyotrophic lateral sclerosis (ALS), frontotemporal dementia with ALS (>29 repeats [58]), and possibly in Parkinson's disease (>24 repeats [59]). Conventional mutations can also act as modifiers. In a family with optic atrophy plus syndrome and ataxia, a compound heterozygosity in *OPA1* was established, with a non-pathogenic per se coding variant, and a deep intronic mutation responsible for aberrant splicing and a premature stop codon [60].

These specific aspects, that bring Mendelian diseases beyond their traditional fields, are still not well understood, and much effort is, therefore, being devoted to them.

Common pathways emerging in HCAs

Genetic advances have allowed the identification of novel common pathways involved in HCAs. In AD-HCAs, transcription dysregulation, protein aggregation, RNA toxicity, ion channels' function, and mitochondrial pathways have recently been extensively reviewed [61]. Autophagy was also described as being important, in neurodegenerative diseases in general, and more specifically in SCA3 and SCA14 [61]. Recently, it has been proven to be impaired in SCA7 patients and knock-in mice [62]. The early autophagy-associated gene *ATG12* was shown to be upregulated in patients' peripheral blood mononuclear cells, correlating with the severity of disease, which might constitute a useful biomarker for therapeutic approaches. In AR-HCAs, multiple pathways have been implicated, including mitochondrial dysfunction, defects of lipoprotein assembly, deficiency of DNA repair, chaperone dysfunction [2], and ubiquitin–proteasome complex [17]. However, as new genes are described, the multiplicity of

pathways involved increases. Rather than discussing all the pathways involved in detail, we shall concentrate on the ones that stand out, either because of recent advances or because of recent implication in HCAs.

Channels are not only involved in episodic ataxias

Channels function has long been an on-going topic in the field of SCAs. The first channel to be implicated in the disease was *CACNA1A*, encoding the alpha-1a voltage-dependent calcium channel type P/Q, whose small polyglutamine expansions [33], but also point mutations [35], are responsible for SCA6. It was long debated whether the phenotype was due to a toxic effect of the polyglutamine stretch or to an altered channel activity [63, 64]. The pacemaking activity of Purkinje cells (PC) was shown to be irregular in a mouse with spontaneous *Cacna1a* mutation [65]. However, the link between irregular firing and symptoms severity is not linear [66]. A second cistron encoded by *CACNA1A* was recently described, with a transcription factor role on genes involved in neurite outgrowth of PC, which is altered with a 33 glutamine expansion [67]. The pathophysiology of SCA6 might, therefore, involve multiple pathways.

Other genes encoding channels have recently been involved in SCA pathology, namely *KCNC3*/SCA13 and *KCND3*/SCA19/SCA22, in which the pathogenicity result from loss of function. The first human mutations in *KCNC3* were associated with channel malfunction in *Xenopus* oocytes [68]. Recently, loss-of-function mechanisms were confirmed in mammalian cells, through reduced surface expression, shorter half-life [69], or Golgi retention and malformation for the p.R420H mutation [70]. The loss of function associated with *KCND3* mutations seems to occur through impaired membrane trafficking (p.F227del [37]) or endoplasmic reticulum retention (p.T352P, p.M373I, p.S390N [36]). While coexpressed with their regulatory beta subunit Kv channel-interacting protein 2, the membrane localization was restored for all but p.S390N mutant. However, patch-clamp studies proved that these complexes were either not or less functional than with the wild-type protein.

The product of *FGF14*, whose mutations cause SCA27 [71], was shown to interact with the pore-forming subunits of Na^+ channels [72]. In hippocampal neurons, the p.F145S mutant exerts a dominant negative effect on the wild-type protein interaction with the channel, decreasing the neurons' excitability [72], reminiscent of the attenuated spontaneous firing of $Fgf14^{-/-}$ PC [73]. In granule cells, both *FGF14* knock-down and overexpression of the mutant protein were recently shown to reduce Ca^{2+} currents, alter vesicular recycling, and, consequently, lower excitatory post-synaptic currents to the PC [74].

In the family of ligand-gated ion channels, only *ITPR1*/SCA15 has so far been implicated in humans [61]. Of interest is the recent involvement of *GRID2* biallelic loss-of-function mutations in AR-HCAs [22–24]. In mouse, the *Lurcher* gain-of-function point mutation in *Grid2* is responsible for a spontaneous cation leak, inducing PC death [26]; the same mutation, and others nearby, were found in patients with a semi-dominant inheritance pattern of either late-onset or congenital HCA [25].

More on mitochondrial dysfunction

Mitochondrial dysfunction has long been implicated in HCAs, with involvement of mutations in mitochondrial DNA, deficiency of coenzyme Q10 production, bioenergetic alterations (*POLG, C10orf2*), dysregulation of mitochondrial fusion–fission balance, and apoptosis (*MFN2, OPA1, SACS, PPP2R2B*/SCA12) [61]. Recent developments in the field include the growing list of genes inducing mitochondrial complex deficiency and cerebellar involvement (*TTC19* and complex III [75]; *COX20* and complex IV [27, 28]). Also of interest is the growing importance of protein quality control, with accumulating evidence of functional effects of *AFG3L2* alterations (SCA28), and cerebellar symptoms in *SPG7* patients. The mitochondrial inner membrane protein encoded by *AFG3L2* belongs to the family of m-AAA proteases, either in homo-oligomeric or in hetero-oligomeric complexes with paraplegin, encoded by *SPG7* [76]. Knock-out of *Afg3l2* induces mitochondrial network fragmentation and reduced mitochondrial uptake of Ca^{++} in mouse embryonic fibroblasts [77]. In PC, early abnormal mitochondrial dynamics, respiratory dysfunction and neurodegeneration are imputed to decreased mitochondrial protein synthesis [78]. Depletion in *Afg3l2* is also responsible for mitochondria anterograde transport defect [79]. In patients with *SPG7* mutations, whose clinical picture includes cerebellar ataxia, skeletal muscle cells showed multiple mitochondrial DNA deletions and respiratory chain deficiencies in complexes I, III and IV [80]. In three patients with heterozygous *SPG7* mutations, cerebellar signs and atrophy were described in the absence of spasticity [81].

Glutamate transmission

Glutamate transmission is also of increasing importance in HCAs. Involvement of *GRID2,* encoding the glutamate receptor ∂2 protein (GluRD2), which belongs to the family of ionotropic glutamate receptors, has already been mentioned above. *STUB1*-encoded protein has been shown, in combination with Fbx2, to promote the ubiquitination and

subsequent degradation of the NR2A subunit of *N*-methyl-D-aspartate receptors [82], an ability that was impaired in the mutant proteins [13]. *SPTBN2* protein product, whose mutations account for SCA5, stabilises the glutamate transporter EAAT4 at the cell membrane [83]; in SCA5 cerebellum extracts, EAAT4 levels were decreased, as was previously reported in SCA23 [84], and in SCA1 transgenic mouse [85]. GluRD2 membrane levels were also lower than in controls [83]. Recently, metabotropic glutamate receptor 1α (mGluR1α) was shown to have reduced localization at dendritic spines and decreased function in a SCA5 mouse model [86]. GluRD2, mGluR1 and PKCγ, whose mutations are responsible for SCA14, were all shown to interact in regulating synaptic transmission in PC [87].

Lipids biosynthesis as a growing pathway in HCAs

Lipids biosynthesis is a newly recognised pathway of importance in HCA pathology. It has previously been implicated in hereditary spastic paraplegia, with the description of mutations in *CYP7B1*/SPG5A, *FA2H*/SPG35, *DDHD2*/SPG54, *DDHD1*/SPG28 [88], *CYP2U1*/SPG56 [89], *B4GALNT1*/SPG26 [90], and *GBA2*/SPG46 [91]. Nonsense *GBA2* mutations were shown responsible for a spastic ataxia phenotype, arguing for a loss-of-function mechanism, inducing glucosylceramide accumulation in the ER in brain and testis of *Gba2*-KO mice [92]. *PNPLA6*, which encodes a bifunctional enzyme with a role in fatty acids and glycerophosphocholine synthesis, and in 2-arachidonoyl lysophosphatidylinositol catalyzation, has been mentioned above [42, 93]. Mutations in *PLA2G6*, encoding phospholipase A2, account for a large phenotypic spectrum, but childhood-onset cerebellar ataxia is a core element [45]. Finally, *ELOVL4* and *ELOVL5*, which code for elongases of very long chain fatty acids were, respectively, implicated in SCA34 and SCA38 [10, 94].

Aggregation processes strike again

Protein aggregation is a long-known hallmark of multiple neurodegenerative diseases, though its role in degeneration is still debated. In polyglutamine expansions, aggregates are mostly found in the nucleus [61]. Alongside these well-described inclusions, amyloidogenic processes, which are traditionally associated with Alzheimer's disease, are increasingly being implicated in cerebellar malfunction. Stop mutations in *ITM2B* have long been recognised to account for British and Danish familial dementias, through the accumulation of a newly synthesised amyloidogenic protein [95, 96]. The phenotype, however, is not circumscribed to CA, but also includes dementia and spastic paraplegia. More strikingly, PKCγ was recently established as an amyloidogenic protein. SCA14-linked mutations seem to accelerate the amyloid-like fibril formation [97].

Implications in clinical practice

As previously mentioned, the extreme intricacy in HCAs genetics makes it practically impossible to Sanger sequence all implicated genes one by one. Nowadays, the prominent technique for molecular diagnosis would either be TS [8] or WES [98], which allow massive parallel sequencing of many or all of the HCA-implicated genes. TS provides optimised coverage of targeted regions, and is still more cost-effective than WES. On the other hand, as new genes are described on a constant basis, the list of sequenced ones becomes obsolete even before the sequencing run is launched. Whole-genome sequencing technically overcomes pitfalls of both techniques, with more harmonious coverage, higher rate of mutation detection, and non-exonic DNA sequencing, allowing molecular diagnosis in previously unsolved case [99]; however, costs in sequencing and bioinformatics processing still postpone its wide-scale use in diagnosis. In all cases, as the phenotypic spectrum associated with a specific gene broadens, and new types of mutations or transmission modes are described, an open mind should be kept in deciphering the pathogenicity of newly found mutations. However, caution should be taken as not all mutations are disease-causing. Converging evidences of the mutation causality, including database frequency, conservation or pathogenicity scores, and segregation within the family, are necessary, but not always sufficient, to establish a diagnosis. Functional testing of every variant is not yet conceivable in clinical practice. As to overcome the lack of convincing clues, efforts might be invested to set up publicly available locus-specific databases [100, 101]. Even if challenged, genotype–phenotype correlations are still a major element in the causality sentence for a given variant.

Conclusion

The heterogeneous genetic landscape of HCAs raises challenges regarding the molecular diagnosis. Not all genes are known as yet, and new ones are constantly being discovered, either as novel genes involved in human diseases or known genes newly implicated in HCAs. Moreover, the phenotypic spectrum of known genes is widely extending along with the use of next-generation sequencing as a diagnostic tool. Novel types of mutations or transmission modes for well-described genes are discovered. The golden age of strict genotype–phenotype correlations seems to have receded with the advent of new technologies.

However, caution must be exercised when seeking to interpret new variants in known genes, especially when they are associated with new phenotypes, as many are not disease-causing. Efforts should be directed towards describing the core phenotypes for each gene, but in many cases, none of the clinical signs is mandatory. Therefore, the trend for genetic diagnosis in clinical practice is to use TS or WES.

In the latter case, the interpretation of results can also be challenging. In this respect, the classification of genes amongst the common networks is crucial to identify causative genes in undiagnosed patients. However, in the absence of sufficient arguments to validate new genes (lack of other affected cases to enable an analysis of co-segregation, absence of additional families), the proof of involvement is often difficult to achieve. Conversely, the description of multiple genes in a common pathway is essential for the pathophysiological understanding of HCAs, and for the future development of common therapeutic targets. We must stress the importance of genetic followed by functional studies (cell biology, biochemistry, animal models, etc.) to validate new genes, elucidate the mechanisms underlying HCAs and decipher new treatment approaches.

Acknowledgments This work was funded by the French "Agence Nationale de la Recherche" (to GS), the Verum Foundation (to AB and GS), the European Union (OMICs grant under the 7th Framework programme, to AB; the E-Rare programme, to GS), the Fondation Roger de Spoelberch (to AB) and the "Investissements d'avenir" programme (ANR-10-AIHU-06, to AB and GS). MC is the recipient of an "Aspirant" PhD fellowship from the Fonds de la Recherche Scientifique (F.R.S.-FNRS, Belgium).

Conflicts of interest The authors report no conflict of interest.

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