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MR Imaging and Spectroscopy in Degenerative Ataxias: Towards Multi-modal, Multi-site, Multi-stage Monitoring of Neurodegeneration

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Abstract

Purpose of review—Degenerative ataxias are rare and currently untreatable movement disorders, primarily characterized by neurodegeneration in the cerebellum and brainstem. We highlight MRI studies with the most potential for utility in pending ataxia trials, and underscore advances in disease characterization and diagnostics in the field.

Recent findings—With availability of advanced MRI acquisition methods and specialized software dedicated to the analysis of MRI of the cerebellum, patterns of cerebellar atrophy in different degenerative ataxias are increasingly well-defined. The field further embraced rigorous multi-modal investigations to study network level microstructural and functional brain changes, and their neurochemical correlates. MRI and MRS were shown to be more sensitive to disease progression than clinical scales and to detect abnormalities in premanifest mutation-carriers.

Summary—MR techniques are increasingly well-placed for characterizing the expression and progression of degenerative ataxias. The most impactful work has arguably come through multi-institutional studies that monitor relatively large cohorts, multi-modal investigations that assess the sensitivity of different measures and their inter-relationships, and novel imaging approaches that are targeted to known pathophysiology (e.g., iron and spinal imaging in Friedreich ataxia). These multi-modal, multi-institutional studies are paving the way to clinical trial readiness and enhanced understanding of pathology in degenerative ataxias.

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Conflicts of interest

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Keywords

Friedreich ataxia; spinocerebellar ataxia; cerebellar multiple system atrophy; magnetic resonance imaging; cerebellum

INTRODUCTION

Ataxia refers to deficits in the coordination of movement and balance. While ataxia can present as a symptom of other neurological diseases and occur due to acquired causes (e.g. alcoholic cerebellar degeneration, vitamin deficiency), here we focus on hereditary and sporadic degenerative ataxias that are characterized by neurodegeneration in the cerebellum and its afferent and efferent connections, and frequently also in other brain regions [1] (Table 1). Conventional MR imaging is part of the diagnostic work-up in ataxias to confirm cerebellar atrophy (Figure 1). In addition, quantitative MR technologies have been used to evaluate structure, connectivity, function and biochemistry in ataxias for over two decades [2]. Rigorous quantitative MRI studies were in particular facilitated by the discovery of genetic mutations for many degenerative ataxias, which allowed studies of genetically defined cohorts. More recently, with exciting developments toward viable disease modifying therapies [3], a critical need for non-invasive, validated biomarkers of cerebral and cerebellar pathology has emerged to facilitate upcoming clinical trials. To present a meaningful picture of the recent progress in cerebellar ataxia imaging, we will highlight the important contributions from the last three years. Progress in this field has been particularly facilitated by the wider availability of high field MR scanners (3 tesla and above), development and dissemination of advanced MRI and MR spectroscopy (MRS) acquisition methods [4,5], and development of specialized software and templates dedicated to the analysis of MR images from the human cerebellum and brainstem [6,7].

AUTOSOMAL RECESSIVE ATAXIAS

Quantitative neuroimaging research in autosomal recessive ataxias has largely focused on Friedreich ataxia (FRDA), the most common ataxia (Table 1). Rarer disorders have most often been the subject of qualitative case reports, although several recent case-control studies are available. Overall, recent MRI studies have not only brought better delineation of atrophy patterns in autosomal recessive ataxias, but they have also increasingly moved beyond a myopic focus on cerebellar macrostructure. Studies characterizing network-level microstructural and functional brain changes, spinal morphology, as well as longitudinal studies of pathophysiology (e.g. iron accumulation) have been particularly impactful in understanding the evolution of these diseases. Efforts to define disease staging, to disambiguate developmental versus degenerative brain changes, and to uncover factors associated with inter-individual variability (i.e., age of onset) have also provided increasingly nuanced disease descriptions.

Friedreich Ataxia: Brain Morphometry

With the availability of cerebellum-focused image analysis tools, a pattern of grey matter atrophy weighted towards lobules IV to VI, and reductions in brainstem and cerebellar white

matter volume adjacent to the dentate nuclei and within the cerebellar peduncles, is now well-established [8–12] (Figure 2). Atrophy of the dentate nuclei was further supported using quantitative susceptibility mapping (QSM), alongside cross-sectional increases in iron concentration and longitudinal iron accumulation in these structures [13]. Outside of the cerebellum and brainstem, reports of more subtle anatomical changes remain mixed, with atrophy of the thalamus and cortical motor areas most consistently implicated and thought to reflect later-stage disease changes [9,10].

Friedreich Ataxia: Connectivity, Neurochemistry and Function

Robust microstructural white matter abnormalities were detected not only in the cerebellar peduncles and in the brainstem, but more subtle changes also extend to the cerebrum, most notably in corticospinal, callosal, and long-range association tracts [10–12,14] (Figure 2). Microstructural impairments appear to manifest over-and-above volumetric atrophy [11] and correlate with biochemical markers of neuronal loss (*N*-acetyl-aspartate-to-creatine ratio) [14]. The patterns of abnormalities reported across different neuroimaging indices point to the potential for both myelin-related and degeneration-related white-matter pathology in FRDA.

Whole-brain functional MRI (fMRI) studies in FRDA have also revealed evidence of network-level functional changes. Reduced cerebro-cerebellar and increased cerebro-cerebral connectivity were found using resting-state fMRI [15], and a recent task-based study of finger-tapping function provided evidence of cerebral compensation in parallel with cerebellar dysfunction [16]. These studies indicate the potential for adaptive mechanisms to play a role in disease mitigation or expression.

Friedreich Ataxia: Spine

While neuroimaging studies have conventionally focused on brain changes in FRDA, spinal cord atrophy is also a clearly established primary site of pathology in this disease. Recent MRI evaluations of spinal cord morphometry have identified flattening and reduced cross-sectional area across the full length of the spinal cord, most markedly in cervical regions [9,10]. Spinal cord changes are proposed to be early, progressive, and clinically relevant features of FRDA.

Other Autosomal Recessive Ataxias

Available literature in other, often very rare, autosomal recessive inherited ataxias has largely consisted of qualitative case reports or retrospective case series. Aggregated case reviews, which in some recent cases include many tens of subjects, have provided generalizable clinical insights into common radiological features evident in disorders such as ataxia telangiectasia (AT) [17], ataxia with oculomotor apraxia (AOA) [18], and autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) [19]. However, these reports are based on qualitative clinical judgement and are restricted to large morphological features (e.g., “cerebellar atrophy” or “vermal hypoplasia”).

Several quantitative case-control assessments of brain integrity have also been undertaken in rare recessive ataxias. Using a multi-modal imaging approach in children with AT, global

cerebellar volumetric and diffusion abnormalities were reported relative to healthy controls [20]. In the same study, the diffusion abnormalities correlated with spectroscopic indices of neuronal integrity and gliosis [20]. Similarly, although in a more limited sample of individuals with SYNE1 ataxia and matched controls, widespread grey and white matter impairments were identified throughout the brain [21].

AUTOSOMAL DOMINANT ATAXIAS

Autosomal dominantly inherited ataxias comprise spinocerebellar ataxias (SCAs) and episodic ataxias [1]. The majority of MRI literature available from the review period focusses on the most common SCAs, with only a few qualitative case reports available on MRI of episodic ataxias. Recent highlights in SCA imaging include the demonstration of the higher sensitivity of MRI and MRS to disease progression than clinical scales, detection of premanifest abnormalities in mutation-carriers, and developing a better understanding of the role of cerebellar degeneration in non-motor deficits using functional MR.

Spinocerebellar Ataxias: Morphometry

Genotype-specific atrophy patterns are increasingly well-mapped for the most common SCAs [22–26]. Atrophy is primarily found in the brainstem, cerebellum and basal ganglia in SCA1 and SCA3 [22,25] (Figure 2), the pons and cerebellum in SCA2 [24], and the cerebellum in SCA6 and SCA7 [22,26] (Figure 1). In addition, atrophy of the spinal cord is seen in SCA3 and cerebral atrophy is observed at late stages in this disease [25].

Such genotype-dependent volumetric measures were previously shown to correlate with the widely used and validated clinical scale, the Scale for the Assessment and Rating of Ataxia (SARA), and to be more sensitive to change than SARA [23]. This was confirmed by two other longitudinal studies in which volumetry outperformed clinical scores in the measurement of disease progression in SCA1, SCA2, SCA3 and SCA7 [27,28]. Together, these studies provide a strong rationale to supplement clinical outcome assessments with these objective, non-invasive MRI markers in clinical trials.

A large multisite study of individuals at risk of SCA has also shown brainstem and cerebellum atrophy prior to ataxia onset in SCA1 and SCA2 [29]. Similar results in preclinical and manifest SCA2 mutation carriers were recently obtained in a Cuban population [24]. Similarly, volume reductions were identified at the spinal cord, midbrain and substantia nigra at the preclinical stage in SCA3 [25].

Spinocerebellar Ataxias: Connectivity, Neurochemistry and Function

A number of reports prior to our review period had shown regional white matter abnormalities using diffusion tensor imaging (DTI) in the common SCAs [30,31]. Recent cross-sectional investigations further outlined differences in DTI metrics between patients with SCAs and controls in multiple brain regions, including the cerebellar peduncles and brainstem (pons) [25,27,32] (Figure 2). Most of these studies also showed correlations between DTI metrics and clinical severity in SCAs. Importantly, premanifest microstructural abnormalities were detected in the cerebellar and cerebral peduncles in SCA3 [25].

Similar to genotype-dependent morphometric findings, a recent MRS study showed genotype-dependent neurochemical abnormalities in common SCAs [33], which could be detected in presymptomatic mutation carriers up to 10 years prior to their estimated disease onset [33]. A longitudinal study in SCA1 also showed that both MRI volumetry and MRS were more sensitive to disease progression than SARA, and that MRS may have predictive value for disease progression [28]. In keeping with the move towards multimodal evaluations of disease, a novel statistical strategy to integrate multimodal biomarkers, including volumetry and MRS, was proposed to identify markers of disease progression in SCAs [34]. In addition to work directed towards biomarkers, an important contribution towards disease understanding was made when SCA7 was defined as a mitochondrial disease based in part on phosphorus (^{31}P) MRS data obtained during a visual task [35].

Among the few recent functional connectivity studies, a network-based statistical approach showed altered inter-nodal cerebellar-cerebrum connectivity in SCA2, providing clinical and neural clues about cognitive and motor dysfunction [36]. In SCA6, decreased resting-state functional connectivity in the attention network [37] and impaired functional activity in the sensorimotor cortex and supplementary motor area was observed [38].

X-LINKED ATAXIAS

Fragile X-associated tremor/ataxia syndrome (FXTAS) is the only X-linked ataxia for which quantitative neuroimaging has been reported. Here, midbrain, brainstem, and cerebellar atrophy was shown, with a large retrospective cross-sectional study also indicating that cerebellar and brainstem atrophy is progressive in both unaffected premutation carriers and those with frank illness [39,40]. Further investigations have supported the critical involvement of the cerebellar peduncles. White matter lesions in infratentorial regions correlate with motor and cognitive dysfunction [41], and diffusion-based microstructural indices of middle and inferior cerebellar peduncle integrity are associated with methylation levels in the causative *FMR1* gene and circulating FMR1 mRNA [42]. Longitudinal imaging also indicates that unaffected premutation carriers with smaller middle cerebellar peduncles may be at greater risk of transitioning to symptomatic states, perhaps reflecting a useful stratification biomarker [40].

SPORADIC DEGENERATIVE ATAXIAS

Sporadic degenerative ataxias comprise cerebellar multiple system atrophy (MSA-C) and the often more benign sporadic adult onset ataxia (SAOA) [1]. Recent MRI studies in sporadic ataxias focused on characterizing regional gray and white matter loss, as well as neurochemical and connectivity changes. A body of work has also attempted to use imaging to distinguish between MSA-C and SAOA, which may help with diagnosis early in the disease course.

Sporadic ataxias: Morphometry

Atrophy of the cerebellum and brainstem are common in both MSA-C and SAOA [43,44] (Figures 1, 2). This was recently further confirmed by a whole-brain morphometry study

showing gray matter volume loss specifically in the cerebellar areas subserving sensorimotor functions in both diseases [45].

MRI can also help to distinguish between MSA-C and SAOA. For example, while white matter loss in the cerebellum was prominent in both SAOA and MSA-C, brainstem white matter was found to be reduced only in MSA-C [45,46]. Structural MRI features, including pons and/or middle cerebellar peduncle (MCP) atrophy, are even included in the second consensus statement on the diagnosis of MSA [47]. Other MRI features, such as the “hot cross bun” sign, MCP hyperintensity, putaminal hypointensity and the hyperintense putaminal rim sign have also been described in MSA-C [48].

Sporadic ataxias: Connectivity, Neurochemistry and Function

Using diffusion MRI, prominent microstructural white matter involvement has been observed in MSA-C (Figure 2), but not in SAOA [45]. In MSA-C, DTI studies have further revealed a reduction of cerebellar fiber density, and impairment of frontal and occipital white matter connectivity [49]. In addition, microstructural alterations of the motor subnetworks in the diencephalon, thalamus and cerebellar regions were observed in MSA-C, which correlated negatively with clinical features including the Unified Multiple System Atrophy Rating Scale (UMSARS) and duration of illness [50]. One MRS study also demonstrated that brainstem volume and *N*-acetyl-aspartate-to-creatine ratio in the cerebellum reliably distinguished patients with MSA-C from those with SAOA [51].

Functional resting-state connectivity has revealed diminished functional connectivity in the cerebellum, dentate nucleus, pons, basal ganglia, default mode network, temporo-parietal regions and limbic system in patients with MSA-C compared with healthy controls, which was again associated with clinical performance [52,53]. Among the few functional studies in SAOA, abnormal intra-cerebellar functional connectivity patterns were reported in areas with gray matter loss relative to intact cerebellar regions, suggesting that atrophy occurs in those cerebellar regions characterized by abnormal connectivity measures [54].

CONCLUSIONS

Recent ataxia imaging has been marked by a move towards multi-modal MR imaging, both in service of furthering the understanding of progressive disease pathology, and in preparation for upcoming clinical trials in the most common degenerative ataxias, in particular FRDA and common SCAs. Importantly, a number of studies have demonstrated detection of CNS abnormalities prior to ataxia onset, which can be used for patient stratification in clinical trials. In addition, MR metrics most sensitive to disease progression can be used for treatment monitoring at both premanifest and manifest stages. Namely, atrophic changes may be slowed down or stopped upon treatment, while microstructural, functional and neurochemical abnormalities may be reversible since they mark changes prior to, and in many cases independent of, cell loss. To improve the robustness of disease characterizations, and prepare for these upcoming trials through validation of longitudinal MRI and MRS markers, several prospective multi-site studies have been initiated (Figure 3), such as EUROSCA (http://www.eurosca.org/), READISCA (https://readisca.org/), ESMI (http://www.ataxia-study-group.net/html/studies/esmi), and retrospective data pooling

platforms have been launched, such as ENIGMA-Ataxia (http://enigma.ini.usc.edu/ongoing/enigma-ataxia/). These efforts represent international collaborations, which are essential to gather sufficient trial-ready cohorts with these rare diseases, but also because of potential geographic differences in clinical characteristics of each disease entity. Similar multi-site, multi-modal, and longitudinal efforts are needed in recessive ataxias other than FRDA and in dominant ataxias other than the common SCAs. Harmonization of data collection methodologies is key for such multi-institutional efforts and is defined as a major goal for two recent initiatives, the SCA Global (http://ataxia-global-initiatives.net/sca-global/) and ARCA Global (http://ataxia-global-initiatives.net/arca-global/). Similar efforts are needed for sporadic ataxias, especially considering that MRI and MRS may have great utility in the clinic at early disease stages for diagnosis and prognosis in these conditions. Finally, while clinical case reports will continue to be a useful and necessary vehicle for characterizing very rare diseases, their utility would be greatly expanded through the use of quantitative measures where possible (e.g., Z-scores of cerebellar lobule volumes relative to a healthy control cohort).

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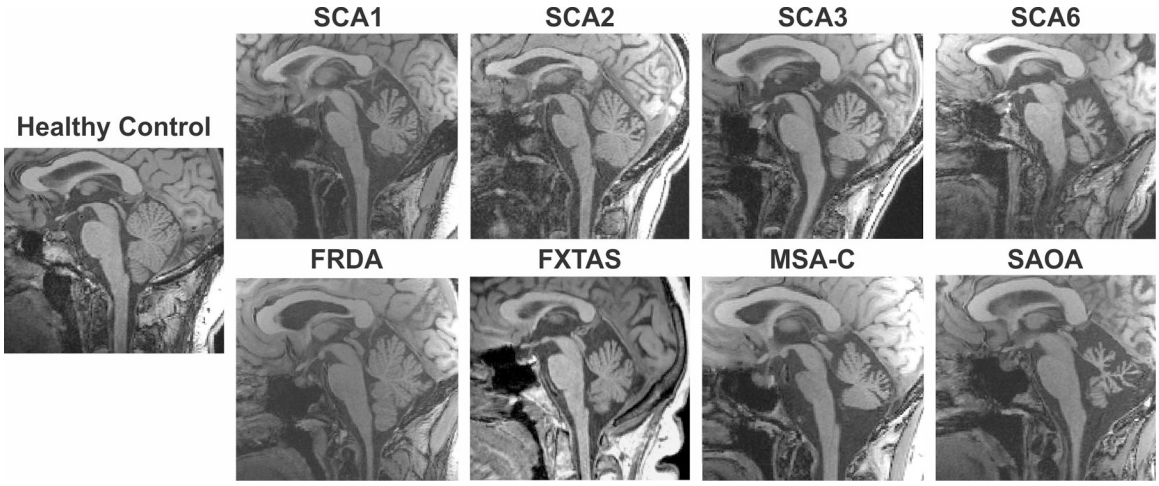
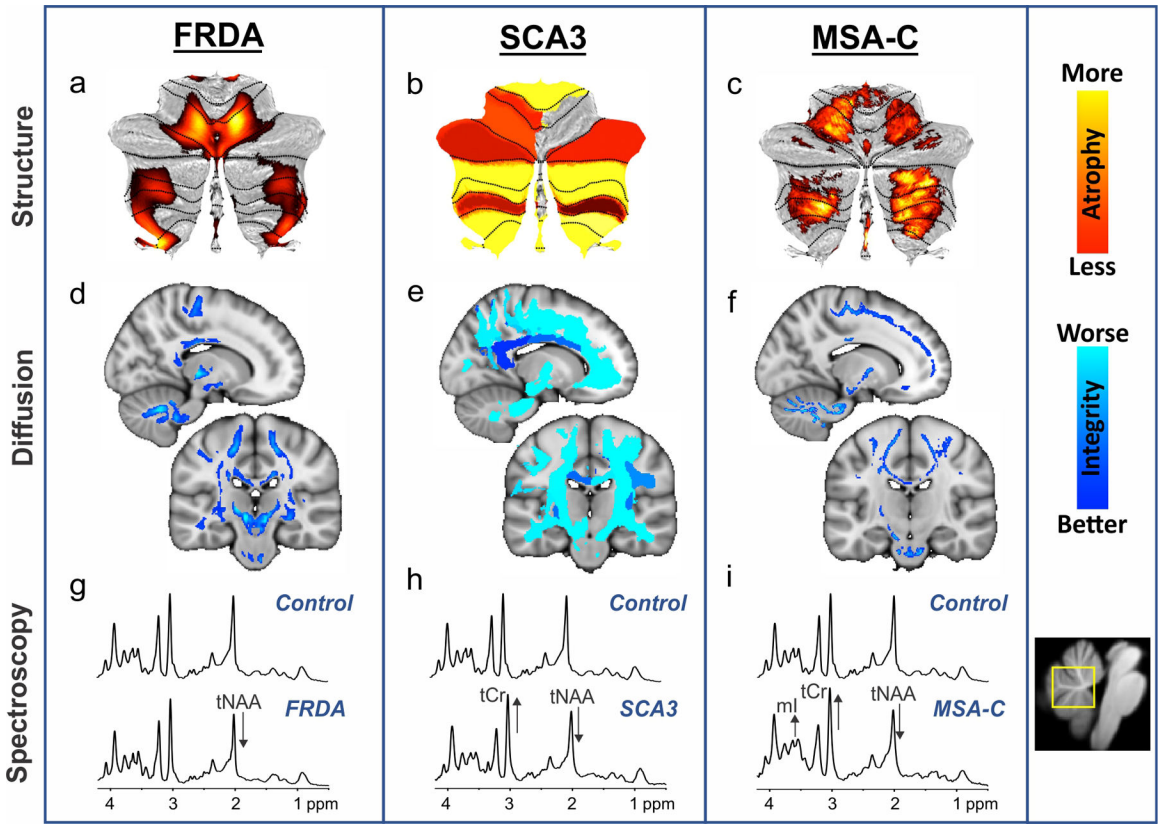
KEY POINTS

- Quantitative MR imaging in degenerative ataxias has moved towards multi-modal, multi-institutional studies with large cohorts, both to understand progressive disease pathology and to prepare for testing of disease-modifying therapies in the pipeline, in particular for Friedreich ataxia (FRDA) and spinocerebellar ataxias (SCAs).
- Similar efforts are needed in recessive ataxias other than FRDA, in dominant ataxias other than the common SCAs and in sporadic ataxias.
- Patterns of cerebellar atrophy in different degenerative ataxias are increasingly well-defined thanks to availability of advanced MRI acquisition methods and specialized software dedicated to the analysis of MRI of the cerebellum.
- Volumetric MRI and MR spectroscopy (MRS) are more sensitive to disease progression than validated clinical scales and cerebral and cerebellar abnormalities are detectable by structural and diffusion MRI and MRS at the premanifest stage in SCAs.



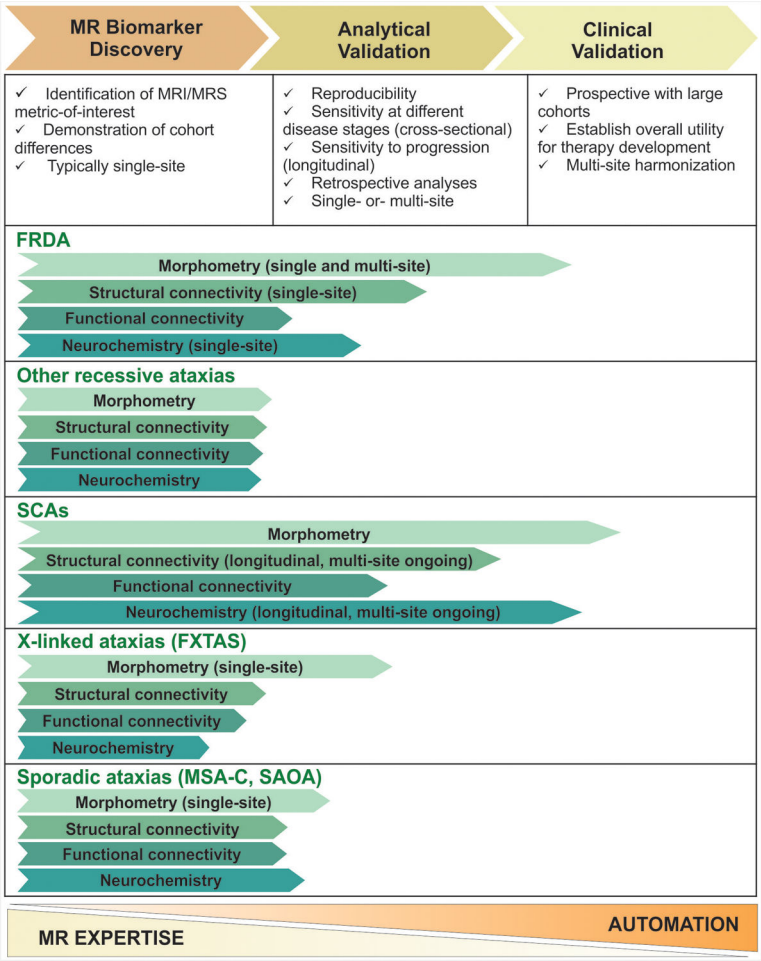
1. Typical MRI findings in the cerebellum and brainstem in degenerative ataxias.

Varying degrees of cerebellar and pontine atrophy are shown on T1-weighted mid-sagittal images. SCA: Spinocerebellar ataxia; FRDA: Friedreich ataxia; FXTAS: fragile X-associated tremor/ataxia syndrome; MSA-C: Cerebellar multiple system atrophy; SAOA: Sporadic adult onset ataxia.



2. Examples of the most common quantitative imaging approaches in the most prevalent degenerative ataxias among autosomal recessive, autosomal dominant and sporadic ataxias, namely Friedreich ataxia (FRDA), spinocerebellar ataxia type 3 (SCA3), and cerebellar multiple system atrophy (MSA-C).

Profiles of cerebellar atrophy from voxel-wise (a, c) and region-of-interest (b) analyses are displayed in hot colors (top). Fractional anisotropy findings from diffusion-weighted imaging, reflecting white matter microstructural integrity, are shown in cool colors (middle) from voxel-wise (d), region-of-interest (e), and tract-based spatial statistics (TBSS) (f) analyses. These images reflect different analysis approaches, but exemplify their common utility in defining key disease characteristics. The bottom panels (g-i) display neurochemical abnormalities in MR spectra obtained at 7T from a vermis voxel (shown in yellow on the right) in individuals with ataxia relative to a control spectrum. The alterations visible in the spectra are marked with arrows. tNAA: total *N*-acetylaspartate; tCr: total Creatine; mI: *myo*-Inositol. The panels in this figure are based on data from prior publications [11, 25, 33, 45] or unpublished data.



3. Pipeline for validating MR imaging biomarkers for use in clinical practice or clinical trials and the status of different MR modalities in the pipeline for different degenerative ataxia categories. Note that the final phase, regulatory approval ("Qualification") that follows the first three phases is not shown. The lengths of the arrows are meant to provide the reader an approximate idea of the place of the different markers in the pipeline relative to each other and relative to the phases defined on top. For example, prospective multi-site morphometry studies with large FRDA cohorts are in the planning stage, hence the arrow ends early in the third phase. Similarly, multi-site morphometry studies with relatively large SCA cohorts have been completed (e.g. EUROSCA), however sample sizes are still limited relative to natural history studies that have validated clinical scales. Typically, earlier stage biomarker discovery studies are conducted at sites with substantial MR expertise and as the identified biomarker moves through the pipeline, increased automation in data acquisition and analysis is necessary for clinical utility, as represented by the scale at the bottom.

Table 1.

Genetic, clinical, and imaging features in degenerative ataxias

Disease	Gene/Protein (locus)	Typical Age at Onset	Key-symptoms in addition to Cerebellar Ataxia	Morphometric Changes (MRI)	Neurochemistry (MRS), Function and Connectivity (fMRI, DWI)
AUTOSOMAL RECESSIVE ATAXIAS					
FRDA	FXN/frataxin (9q13)	Adolescence (around puberty)	Neuromuscular deformities, cardiac hypertrophy, abnormal eye movements	Spinal cord, brainstem, cerebellum; thalamus, and cortical motor areas (later stages)	↓tNAA*[1](/tCr)*[1]; ↑tCr*[1]; ↑mI*[1]; ↓cerebro-cerebellar and ↑cerebro-cerebral connectivity; cerebral compensation/ cerebellar dysfunction
AT	AT-mutated (ATM)/ATM protein (11q22–23)	Infancy - early childhood (2–4 years)	Oculomotor apraxia, cutaneous telangiectasias, dystonia chorea, immune-deficiency, malignancy	Cerebellum	↓tNAA/tCho*[1]; ↓tCho/tCr*[1]
AOA (1/2)	APTX/aprataxin (1) SETX/senataxin (2)	Early childhood (1), later childhood (2)	Oculomotor apraxia, movement disorders, pyramidal signs, intellectual disability	Cerebellum	(2): ↓tNAA*[1]; ↑mI*[1,*2]
ARSACS	SACS/sacsin (13q12.12)	Infancy (12 – 18 month)	Spasticity, peripheral neuropathy	Cerebellum, parietal lobe (bilateral); linear pontine hypointensities	NA
AUTOSOMAL DOMINANT ATAXIAS					
SCA1	ATXN1/ataxin-1 (6p22.3)	Early to mid-adulthood	Hypermetric saccades, pyramidal signs	Brainstem, cerebellum (preclinical), and basal ganglia	↓tNAA*[1,*2](/tCr)*[1]; ↓tCho/tCr*[1;] ↑tCr*[1]; ↑mI*[2]
SCA2	ATXN2/ataxin-2 (12q24.12)	Early child- to late adulthood	Slow saccades, peripheral neuropathy, motor neuron signs, autonomic dysfunction, cognitive impairment	Pons; cerebellum and brainstem (preclinical)	Altered inter-nodal cerebellar-cerebrum connectivity; ↓tNAA*[1,*2](/tCr)*[1]; ↓tCho*[2](/tCr)*[1]; ↑tCho*[1]; ↑mI*[1,*2](/tCr)*[1]; ↑tCr*[1]
SCA3 (Machado–Joseph disease)	ATXN3/ataxin-3 (14q32.12)	Childhood to mid-adulthood	Dystonia, sensory deficits, parkinsonism	Brainstem, cerebellum, basal ganglia; spinal cord, midbrain, substantia nigra (preclinical); cerebrum (later stages)	Microstructural abnormalities in cerebellar and cerebral peduncles (premanifest); ↓tNAA*[1,*2](/tCr)*[1]; ↓tCho/tCr*[1]; ↑tCr*[1]; ↑mI*[2]
SCA6	CACNA1A (19p13.2)	Early to late adulthood	Almost purely ataxic	Cerebellum	↓RS FC in attention network; impaired functional activity in SC and SMA; ↓tNAA*[1](/tCr)*[1]; ↑mI*[1]
SCA7	ATNX7/ataxin-7 (3p14.1)	Infancy to adulthood	Visual loss, mitochondrial dysfunction	Cerebellum, brainstem	↓tNAA*[1,*2](/tCr)*[1]; ↓Pi(/PCr) (^{31}P-MRS) in visual cortex during visual task
X-LINKED ATAXIAS					
FXTAS	FMR1	Late adulthood (> 50 years)	Intention tremor, dementia, and parkinsonism	Midbrain, brainstem, and cerebellum	NA
SPORADIC DEGENERATIVE ATAXIAS					
MSA-C	-	Adulthood	Autonomic dysfunction, dysarthria, oculomotor dysfunction, cognitive impairment	Cerebellum (GM+WM), brainstem (GM+WM), pons; “hot cross bun” sign, middle cerebellar peduncle hyperintensity, putaminal	↓tNAA*[1,*2](/tCr)*[1,*2]; ↑mI*[1,*2]; ↑tCr*[1]; microstructural white matter involvement (DTI); ↓cerebellar fiber density, and impairment of frontal and occipital white

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Disease	Gene/Protein (locus)	Typical Age at Onset	Key-symptoms in addition to Cerebellar Ataxia	Morphometric Changes (MRI)	Neurochemistry (MRS), Function and Connectivity (fMRI, DWI)
				hypointensity, and the hyperintense putaminal rim sign	matter connectivity (DTI); ↓connectivity of motor networks
SAOA	-	Adulthood	sporadic adult progressive cerebellar ataxia of unknown etiology	Cerebellum (GM+WM), brainstem (GM)	Abnormal intra-cerebellar FC

FRDA = Friedreich Ataxia; AT = Ataxia Telangiectasia; AOA = Ataxia with Oculomotor Apraxia; ARSACS = Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay; SCA = Spinocerebellar Ataxia; FXTAS = Fragile X-Associated Tremor/Ataxia Syndrome; MSA-C = Cerebellar Multiple System Atrophy; SAOA = Sporadic Adult Onset Ataxia; DTI = diffusion tensor imaging; tNAA = total *N*-acetylaspartate; tCr = total Creatine (creatine + phosphocreatine); tCho = total Choline; mI = *myo*-Inositol; $*^1$ = in cerebellum (vermis and/or cerebellar hemispheres); $*^2$ = in brainstem (pons); ↓ reduced compared to controls; ↑ increased compared to controls; RS = resting-state; FC = functional connectivity; SC = sensorimotor cortex; SMA = supplementary motor area; Pi/PCr = ratio of inorganic phosphate to phosphocreatine; ^{31}P-MRS = 31-phosphorus magnetic resonance spectroscopy. The listed findings are primarily based on review articles and meta-analyses; therefore, mostly metabolite ratios are displayed for MRS findings, and the respective metabolic reference is indicated in brackets, i.e. (/tCr). The respective “numerator” simultaneously represents the metabolite concentration from individual findings, i.e. tNAA in tNAA(/tCr). In those cases where individual metabolite concentrations are listed, only few findings are available, and meta-analyses are missing (i.e. AOA2) or findings are mixed (i.e. ↑mI in SCA6).

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