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REVIEW

Spinocerebellar ataxia type 23 (SCA23): a review

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Abstract

Spinocerebellar ataxias (SCAs), formerly known as autosomal dominant cerebellar ataxias (ADCAs), are a group of hereditary heterogeneous neurodegenerative diseases. Gait, progressive ataxia, dysarthria, and eye movement disorder are common symptoms of spinocerebellar ataxias. Other symptoms include peripheral neuropathy, cognitive impairment, psychosis, and seizures. Patients may lose their lives due to out of coordinated respiration and/or swallowing. Neurological signs cover pyramidal or extrapyramidal signs, spasm, ophthalmoplegia, hyperactive deep tendon reflexes, and so on. Different subtypes of SCAs present various clinical features. Spinocerebellar ataxia type 23 (SCA23), one subtype of the SCA family, is characterized by mutant prodynorphin (PDYN) gene. Based on literatures, this review details a series of SCA23, to improve a whole understanding of clinicians and point out the potential research direction of this dysfunction, including a history, pathophysiological mechanism, diagnosis and differential diagnosis, epigenetics, penetrance and prevalence, genetic counseling, treatment and prognosis.

Keywords Spinocerebellar ataxia type 23 · Prodynorphin · Clinical symptoms · Pathophysiological mechanisms · Epigenetics · Spinocerebellar ataxias

Introduction

Spinocerebellar ataxias (SCAs) are a set of degenerative and progressive diseases, and there are two major classification methods. The first one is Harding classification according to clinical manifestation, which comprises three types, ADCA I, II, III. ADCA I contains a series of syndromes, that is, ataxia with ophthalmoplegia, dementia, extrapyramidal motor signs, optic atrophy and muscular atrophy; ADCA II is a kind of progressive ataxia accompanied by retinal degeneration; ADCA III means "pure" cerebellar ataxia. Spinocerebellar ataxia type 23 (SCA23), a subtype of SCAs, belongs to ADCA III in Harding classification [1]. Helping doctors narrow the clinical scope and developing strategies for genetic and molecular detection, this classification is still playing a crucial role in clinical work. Likewise, another classification, according to the mechanism of disease, classify SCAs into three subtypes, respectively, Subtype I, II, III. Subtype I, mainly polyglutamine SCAs related to CAG repeat expansion mutations, is caused by dynamic repeat expansion mutations in the coding region of genes [2]; Subtype II refers to non-coding region SCAs encoded by repeat expansion mutations. Subtype III, which SCA23 belongs to, means SCAs for deletion, insertion, missense, nonsense or frameshift mutation of a specific gene [3]. So far, classical genetic studies have revealed 47 different chromosomal locations of SCAs and identified 40 pathogenic genes [4–9]. Among the various genes, prodynorphin (PDYN) gene is the pathogenic gene relevant to SCA23. Lacking of overall analysis and comparison, studies in SCA23, to date, mainly focus on the single or multiple mutants identified, which are scattered and independent. With available detection and increased diagnosis due to recent advances in next-generation sequencing, comprehensive understanding of SCA23 is necessary. There are still numerous challenges for us in SCA23, such as the expansion of mutant database, the relationship between genotype and phenotype, as well as the specific treatment. In other words, it shows several research projects waiting for us to explore. In this manuscript, we aim to review the existing studies and potential future research directions of SCA23, furthermore,

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to improve acknowledgment of this disorder in clinicians and researchers.

History of SCA23

In 2004, Verbeek et al. reported a Dutch three generations pedigree of SCA, whose pathogenic gene was located on the 20p13-p12.3 chromosome by gene linkage analysis. HUGO Nomenclature Committee designated the locus as SCA23 [10]. In 2010, Bakalkin et al. identified PDYN (GenBank ID: NM024411.3) as the pathogenic gene of SCA23, and also verified the function of the mutant gene [11]. After that, research on SCA23 and PDYN has been further studied.

Clinical symptoms and signs of SCA23

The major symptoms of SCA23 are gait ataxia, limb ataxia, dysarthria, tendon hyperreflexia, dysfunction of muscular apparatus. Other features are listed in Table 1 [10–14]. According to the statistics, the mean onset-age of SCA23 is 43.75 ± 15.04 years (range from 10 to 73). Head MRI and neuropathology present no significant difference from other SCA subtypes, and the mean duration of clinical symptoms is 14.76 ± 12.60 years (range from 1 to 47 years). Depending on the data, the average rate of SCA23-development seems to be relatively slow. Most of the initial symptom that attracted the attention of patients is gait ataxia, followed by dysarthria. Prodromal symptoms include cognitive impairment (such as memory loss or mental retardation), or dizziness and epilepsy. Because of the limited number of reported cases, it is not clear whether these prodromal symptoms are associated with SCA23 disease itself. Similarly, no obvious characteristic symptoms of SCA23 have been discovered.

Neuroimaging of SCA23

Neuroimaging examinations appear abnormal manifestations earlier than clinical symptoms, which are helpful in the diagnosis of the disease. Semi-quantitative or quantitative MRI, SPECT and PET data can describe the structure, microstructure and functional changes of the cerebellum, brain stem, brain and spinal cord, and can also be used as effective physiological and pathological markers. Simultaneously, they are more sensitive than clinical features in tracking the progression of neurodegeneration [15]. In addition, imaging techniques play a significant role in the differential diagnosis of diseases [16, 17].

The most common sign of MRI in patients with SCA23 is brain atrophy (moderate-severe cerebellum, cerebellar vermis, middle cerebellar peduncle, cerebral cortex, corpus callosum) with or without brainstem atrophy, besides, "hot cross bun" (HCB) sign, in a few cases, can be seen in the brainstem. Followed common sign is white matter lesions (frontal and parietal lobes, periventricular). Additionally, a few patients show basal ganglia anomaly including

Table 1 Clinical symptoms and signs of SCA23

Symptoms or signs	The percentage	Mutations
Gait ataxia	87.00%	p. L211S, p. R212W, p. R215C, p. R318S, p. C22Y, p. L85L, p. R206H, p. R206C, p.G227D, p. W220GfsX33, p. R215H, p. R213H
Dysarthria	69.57%	p. L211S, p. R212W, p. R215C, p. R318S, p.C22Y, p. R206H, p. W220GfsX33, p. R215H, p. R213H
Increased tendon reflexes	65.22%	p. R318S, p. C22Y, p. L85L, p. R206H, p. R206C, p. G227D, p. W220GfsX33, p. R215H, p. R213H
Limb ataxia	43.48%	p. L211S, p. R212W, p. R215C, p. R318S, p. C22Y, p. L85L
Oculomotor impairment or Saccade slowing	43.48%	p. L211S, p. R215C, p. R318S, p. C22Y, p. R206H, p. R206L, p. R215H
Babinski's sign	30.43%	p. L211S, p. R318S, p. L85L, p. G227D, p. W220GfsX33
Tremor (limbs or head)	30.43%	p. R215C, p. R206C, p. W220GfsX33, p. R215H, p. R213H
Polyneuropathy	26.09%	p. L211S, p. R212W, p. R215C, p. R318S
Urinary disorders (urgency of urination, Incontinence)	8.70%	p. R206C, p. W220GfsX33
Parkinson-like features	8.70%	p. L211S, p. R215H
Occasional dizziness	4.35%	p. L85L
Cognitive impairment	4.35%	p. R206H
Abnormal behavior	4.35%	p. R206H
Psychiatric symptoms	4.35%	p. R206H
seizures	4.35%	p. C22Y

hyperintense lateral putaminal rim and atrophy outside the globus pallidus, while a few present normal MRI. Compared with other subtypes of SCA, there are no meaningful differences and no characteristic signs in SCA23. Various MRI manifestations of the patients may be relevant to the type of mutation, the development-stage of SCAs and the age of patients, and also the interference of the underlying diseases.

In summary, neuroimaging examination is essential in the diagnosis and differential diagnosis. The imaging findings of patients with SCA23 are not distinctly different from other types of SCAs, which have yet to be further studied.

Gene detection of SCA23

Gene detection is the golden standard of SCAs. Next generation of sequencing (NGS) improves the accuracy, speed and throughput of sequencing. In addition, the cost is lower [18]. NGS allows the use of three main methods for gene testing: (a) Target re-sequencing panels (TRPs); (b) Exon sequencing (ES); (c) Whole-genome sequencing (WGS). The sequence of molecular genetic tests and the interpretation of the results are complex and may require the support of experienced laboratories, clinical geneticists and genetic consultants [4]. With the detection of the variant genes, it is necessary to improve the genetic examination of the patient's related family members to further analyze whether there are co-segregation of mutation and phenotype. In addition, functional analysis is indispensable for newly discovered SCA mutants. Clinical significance of the mutations can be identified according to the American College of Medical Genetics (ACMG) standards and guidelines [19].

The differential diagnosis of SCA23

SCA23 is diagnosed based on a comprehensive assessment of clinical features, physical examination, complementary tests (especially gene detection), and family history. In addition, differential diagnosis is critical to neurodegenerative disease, and it is necessary to exclude treatable and/or structural cerebellar ataxia. Complete neuroimaging and routine laboratory tests required for differential diagnosis should be guided by medical history and physical examination, while blind screening is not recommended for increased cost of patients. Differential diagnosis about SCA23 is very extensive, including drugs or toxic effect, lack of nutrition, endocrine disease, infection and infection after state, structural abnormalities, paraneoplastic syndrome and certain neurodegenerative diseases caused by secondary ataxia, and also the identification of primary ataxia between each subtype [20–25].

Pathology of SCA23

There are few pathological studies on SCA23. The pathology of a deceased SCA23 patient studied by Verbeek et al. showed that the brain weight is less than a normal brain. The macroscopic manifestation is moderate-to-severe brain atrophy, while the microscope assumes that the loss of neurons in the Purkinje cell layer, especially in the dentate nucleus and inferior olive, is accompanied by the loss of variable glia and myelin in the surrounding white matter. No significant neuronal loss is observed in substantia nigra and locus ceruleus in the pontine nucleus. Lewy bodies are occasionally found in substantia nigra, and a few neurons contain obvious intranuclear inclusions-Marinesco bodies (non-specific ubiquitin inclusions in substantia nigra neurons). Other "neurodegenerative deposits" are rarely found by immunohistochemical staining. In tau staining, some astrocytes around the central nucleus, dentate nucleus and substantia nigra are positive [10].

Relationship between genotype and phenotype

Previously reported cases of SCA23 show that patients with mutant genes behave more or fewer syndromes, but the following phenomena are thought-provoking. Different missense variations are translated into specific amino acids, but the same manifestations are seen in diverse patients; Patients who carry the same mutation, have their own specific phenotypes including various clinical symptoms, age of onset and severity of disease (e.g., p. R215C, p. R215H, p. R318S); Some patients' relatives show related symptoms, but the genetic test results are negative (e.g., p. R206H); in 2004, there was an asymptomatic gene carrier in the autosomal dominant family of mutant p. R318S; although there is a base variation, the amino acid does not change after translation, while the patient still shows manifestations of SCA (e.g., p. L85L). In addition, the syndromes of different subtypes of SCAs are identical, and the view that particular mutations lead to the same phenotype strongly suggests that the common biological pathway is the basis of separate SCA types. At present, it is not clear about such polymorphism in the gene. Wille-Bille et al. studies have shown that prenatal alcohol exposure can affect the expression of PDYN by regulating epigenetic parameters such as mRNA and methylation, and then influence the phenotype of offspring rats, which leads us to speculate that the expression of PDYN may be related to the epigenetic mechanism, but further research is needed.

Mechanism of epigenetics in genotype and phenotype

The body is under a complex metabolic mechanism, which is closely applicable to such aspects as genes, internal and external environment. Not entirely determined by the DNA, the phenotype of an individual essentially decided by both genetic and non-genetic factors, in which epigenetics plays an indispensable role in the action mechanism of non-genetic factors [26]; besides, it is closely linked to the development of the nervous system [27]. Epigenetics refers to the change in gene expression level stemmed out of non-gene sequence changes, which is used to describe the differences between genotypes and phenotypes during individual development [28, 29]. DNA methylation, histone modification and non-coding RNA make up the three major epigenetic events [30]. Additionally, epigenetic reprogramming and the relationship between epigenetics and environment have been also ranked as the pioneering research areas [31].

DNA methylation can silence genes through CpG Island (CGI) by obstructing gene expression. Bazov et al. reckoned that the regulation of PDYN gene expression features relationship with CGI [32]. Acetylation, phosphorylation, methylation, ubiquitin and other ways can help modify histone, which meanwhile modify the interaction with DNA, change the chromatin configuration and regulate gene transcription [33, 34]. Non-coding RNA, such as short RNA molecule miRNAs, mature miRNAs can be bound to the 3 untranslated regions of the target mRNA, thus resulting in degradation or inhibition of protein translation [35]. The reprogram of epigenetics is achieved in the duration of gametogenesis and embryo-fetal development, which helps shape an epigenetic system different from that of their parents and regulate gene expression [31]. In addition, environmental factors also exert effects upon epigenetics by impacting intermediates or substances required in the body's metabolic response, including specific enzymes, *S*-adenosine methylene, etc.; or by effecting signal receptors involved in the reaction, such as G-protein-coupled receptor (GPCR); or by destroying the cellular structural continuum from the extracellular matrix, plasma membrane to chromatin [36, 37]. In addition to the above-mentioned related mechanisms, diet, a touted environmental factor, can also modify the epigenetics in virtue of regulating the intestinal microflora [38, 39]. Epigenetic modification is featured by its reversibility, which can not only activate genes [40] but also silence genes [41], taken into account in the phenotype that a certain appearance can be acquired and inherited. Additionally, it can also disappear soon after the attainment (Fig. 1). Epigenetics does not constitute a negation of Mendelian genetics, but an expansion and perfection beneficial to unlock the genetic code.

Existence pattern of mutations

Based on previous reports, SCA23 mutations show familial autosomal dominant inheritance or sporadic existence.

Penetrance of SCA23

As reported, carries with mutations in the Big dynorphin all show explicit symptoms, although the symptoms are various. In contrast, other regional variations are uncertain, despite most are symptomatic. Notedly, mutant p. R318S contains an asymptomatic carrier reported in 2004 [10]. Additionally, genetic anticipation maybe consists in SCA23 just as Satoh et al. described [42]. Therefore, whether there exists tolerance or the phenomenon of decreased penetrance in different mutants still needs further exploration to verify.

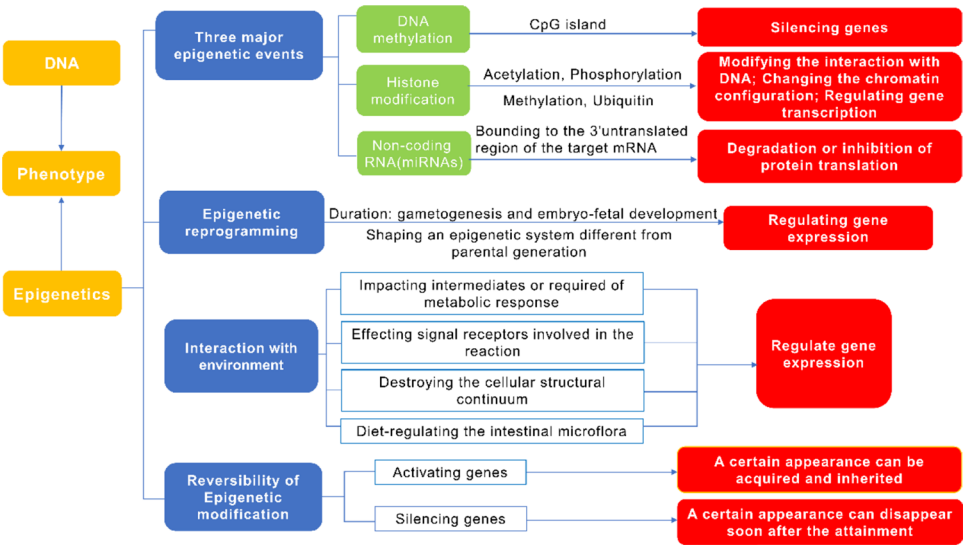

Fig. 1 Functions of epigenetics in phenotypes. DNA determines the specific sequences, while epigenetics can affect genes expression through a variety of mechanisms

Table 2 The prevalence of SCA23 in several countries

State	Ataxia-group	Control group	Frequency (%)	References
Dutch	1100	500	4/1100 ≈ 0.36	[11]
UK	852	570	3/852 ≈ 0.36	[12]
Central Europe	104	0	0/104 ≈ 0.00	[44]
Chinese Han	305	500	0/305 ≈ 0.00	[13]
French	371	400	4/371 ≈ 1.08	[14]
USA	119	0	1/119 ≈ 0.84	[45]

Prevalence of SCA23

The global prevalence of SCAs is 3/100,000 [43]. People are genetically screened for SCA23 and PDYN in over one country, and study groups are ataxia populations. The frequency of mutations investigated is set out in Table 2. These studies can just give a general picture of the frequency of mutant PDYN in the ataxia group, not prevalence in the population, but it is commendable that SCA23 is a rare type of SCAs in many countries. The prevalence of ADCAS is estimated to be about 1–5:100,000, and the rare SCA in it is less than 1%, further showing that the incidence of SCA23 is 1–5: 10 million people [4].

Existing mutations of SCA23

Based on literatures, 16 mutations (p. L211S, p. R212W, p. R215C, p. R318S, p. C22Y, p. R25Q, p. G159D, p. L85L, p. R206H, p. R206C, p. G227D, p. W220GfsX33, p. R215H, p. R213H, p. H200H, p. M146L) have been reported in PDYN, including 15 missense mutations and 1 deletion mutation. According to the ACMG standards and guidelines, variants of PDYN can be classified into five levels, that is, "pathogenic", "likely pathogenic", "uncertain significance", "likely benign", and "benign" (Table 3). As shown in the Table 3, four variants (p. L211S [11], p. R212W [11], p. R215C [11], p. W220GfsX33 [14]) are classified as "pathogenic", five variants (p. R318S [11], p. R206H [14], p. R215H [42], p. G227D [14]) "likely pathogenic", five variants (p. C22Y [12], p. R25Q [12], p. G159D [12], p. L85L [13], p. R206C [14], p. R213H [46]) "uncertain significance", two variants (p. M146L [45]) "likely benign", and 1 variant (p. H200H [45]) "benign". Furthermore, eight variants are considered being directly or indirectly related to dynorphin A (Dyn A), and five variants are considered being related to dynorphin B (Dyn B). Three variants, besides, tend to have familial genetic co-segregation, which are characterized by autosomal dominant inheritance. One variant contains a

Table 3 Clinical significance and pathophysiological mechanism (s) of PDYN variants reported in SCA23

Clinical significance	Pathophysiological mechanism (s)	Variant (s)
Pathogenic	Dyn A related	p. L211S, p. R212W, p. R215C, p. W220GfsX33
	Dyn B related	p. R212W, p. R215C*, p. W220GfsX33
	Others	p. L211S, p. R215C,
Likely pathogenic	Dyn A related	p. R318S, p. R206H, p. R215H*, p. R213H
	Dyn B related	p. R318S*, p. G227D
	Others	p. R318S, p. G227D
Uncertain significance	–	p. C22Y, p. R25Q, p. G159D, p. L85L, p. R206C
Likely benign	–	p. M146L
Benign	–	p. H200H

*Means a variant existing co-segregation with disease in multiple affected family members

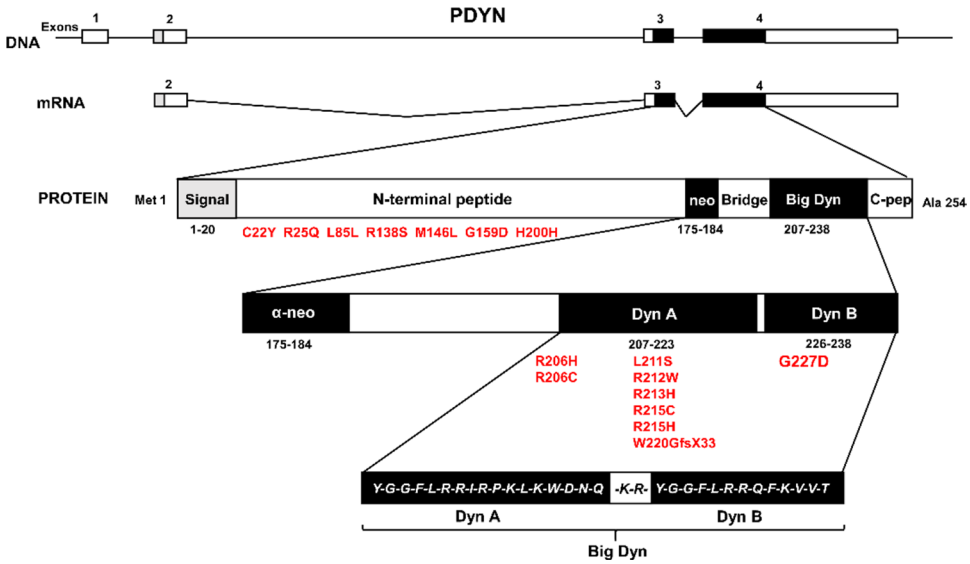

Fig. 2 Schematic diagram of PDYN structure and locus of reported mutants

homozygous missense mutation (p. R215H). Notably, the ataxic symptoms the patient presented are more severe than heterozygous patients, as well as little younger onset-age. These studies show that Dyn A and Dyn B are the most pathological neuropeptides, which strongly indicates that the Big Dyn is an active mutant region of SCA23.

Pathophysiological mechanisms of SCA23

Neuropeptides are a grand family of signaling molecules that regulate a variety of physiological functions and behaviors by mediating and regulating neuronal communication processes acting on cell surface receptors [47, 48]. Acting on the kappa, mu and delta opioid receptors, PDYN, a precursor protein of opioid neuropeptide, expresses in specific neural circuits in the basal ganglia, frontal lobe, hippocampus,

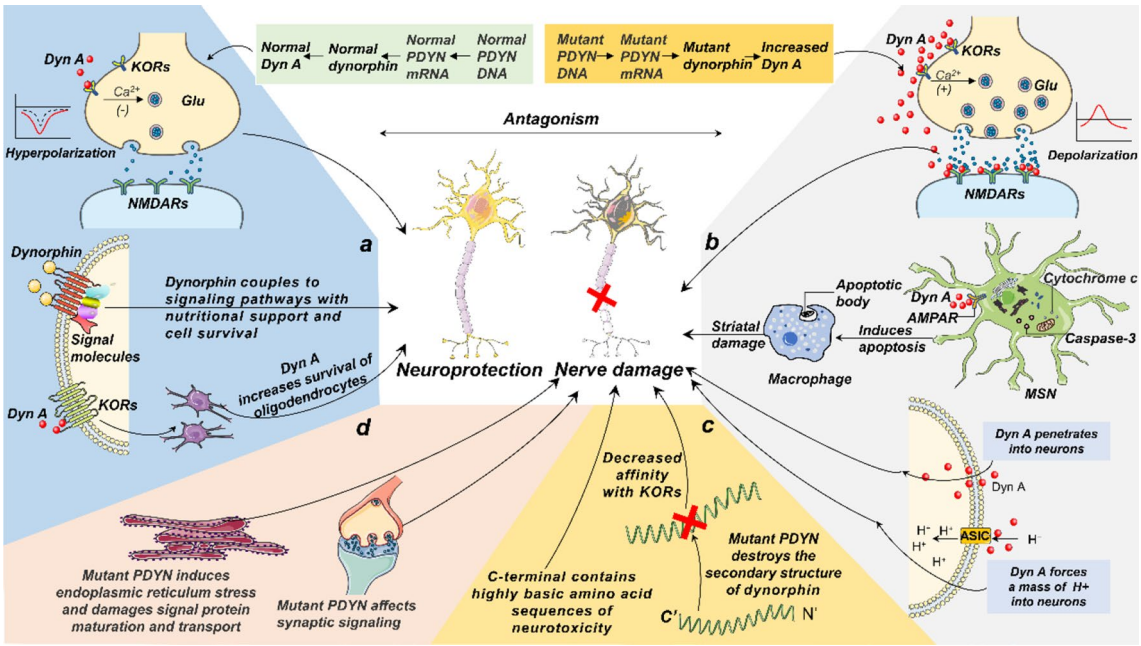

Fig. 3 Pathophysiological mechanisms of SCA23. **a** Mechanisms of non-opioid pathogenicity; **b** mechanisms of non-opioid pathogenicity; **c** mechanisms of secondary structural changes of peptides; **d** mechanisms of dynorphin as signal molecules regulating various physiological and pathological processes. Normal PDYN gene can express a moderate amount of dynorphin dominant by an opioid receptor protective mechanism. While elevated Dyn A is produced by mutate PDYN, thus nerve damage mechanisms playing a major role

and other brain regions [49–52]. The structure of PDYN includes α-neoendorphin (α-neo) and Big dynorphin, while Big dynorphin comprises dynorphin A (Dyn A) and dynorphin B (Dyn B) (Fig. 2).[53]. With a high affinity for kappa opioid receptor (KORs) rather than other opioid receptors (ORs), Dyn A plays a vital role in the pathogenesis [54]. Genetics, pharmacological and clinical trials have shown that dynorphin is associated with reward and emotion control, learning and memory, stress response, pain, drug use and alcohol abuse [54–56]. PDYN and its primary peptide products are mainly in Purkinje cells (PCs) of the cerebellum, besides, there are a mass of PCs and atrophic dendritic loss in SCA23 [11]. The following mechanisms may account for the pathogenesis (Fig. 3).

Mechanisms of opioid receptor actions

Dynorphin can play a neuroprotective role when normal PDYN gene expresses moderate amount [57, 58]. Furthermore, Dyn A couples and activates KORs, and then the membrane is hyperpolarized with increased excitability threshold by regulating, reducing calcium influx, to improve nerve damage and antagonize dynorphin non-opioid neurotoxicity [59, 60]. ORs, additionally, can be coupled to signal pathways with nutritional support and cell survival to serve a neuroprotective function [61]. The coupling of Dyn A and KORs can increase the survival of oligodendrocytes [62]. Opioid receptor neuroprotective action, negligible, is exerted under a mild amount of dynorphin expressed by normal PDYN gene. Instead, mutant PDYN gene results in elevated expression of dynorphin, especially the level of Dyn A, which initiates the powerful non-opioid mechanism of dynorphin dominate [11]. Neuroprotective functions of ORs are far from antagonistic to its pathogenic function under abnormal circumstances [47]. Ultimately, various pathological changes and neurodegeneration are induced by mutant PDYN, including neurological dysfunction and cell death [11, 63, 64].

Mechanisms of non-opioid pathogenicity

Non-opioid functions are primarily characterized by neuroexcitatory toxicity, which is mainly relevant to directly or indirectly interaction between dynorphin and glutamate receptors [65]. On one hand, binding to KORs, Dyn A acts on N-methyl-D-aspartate (NMDA) receptors indirectly through the cellular pathway by increasing the content of neurotoxic glutamate. On the other hand, Dyn A can be directly coupled with NMDA, such as connecting with the redox regulatory site conformation, improving the affinity with NMDA receptors, and then plays a non-opioid pathogenic role [47, 65, 66]. Mutants can lead to markedly elevated expression of Dyn A [14], via the combination with NMDA, playing a dominant role in non-opioid pathogenesis and exerting excitatory neurotoxicity. There are several pieces of evidence to substantiate this view. (i) Intrathecal injection of Dyn A in mice can lead to increasing non-opioid excitatory activity through the N-methyl-D-aspartate (NMDA) receptor mechanism, resulting in hyperalgesia, paralysis and neuronal loss [67, 68]. (ii) Using mice model to further verify the function of mutant PDYN, Smeets et al. found that the level of Dyn A mutant is significantly increased, which coincided with transcriptional maladjusted ionic and metabolic glutamate receptors as well as glutamate transporters, and also changed the excitability of neurons, resulting in climbing fiber retraction and Purkinje cell loss [68]. (iii) The cerebellar autopsy tissues of one mutant PDYN (P. R138S) showed significant changes in the expression of key components of the opioid system and glutamic acid system [11]. (iv) Jezierska et al. analyzed the peptide production of PDYN in mutant individuals, indicating that SCA23 mutation can enhance the opioid function of dynorphin, or may have a dominant-negative effect on inducing neurodegeneration of non-opioid drugs [14]. (v) In addition, the elevated level of Dyn A is related to the pathology of Alzheimer's disease [69], which further demonstrates the neuroexcitatory toxicity of dynorphin in neurodegenerative diseases.

In addition to the neurotoxicity caused by interaction with glutamate receptors, there are several other non-opioid toxic mechanisms listed below. Dyn A can bind to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors of striatal medium spiny neurons (MSNs) and produce neurotoxic effects on striatum neurons by activating and regulating of apoptosis mechanism in cytochrome C and caspase-3 [47]. Furthermore, the C-terminal region of dynorphin contains highly basic amino acid sequences of neurotoxicity [70]. Besides, Dyn A can also serve neurotoxic functions via acid-sensing ion channels (ASICs). When dynorphin exists, it can impede the formation of acid ion homeostasis in the internal environment as well as cells, thus inducing neuronal damage [71]. Additionally, the interaction between peptide and plasma membrane is also involved [72–74]. For example, peptides are transferred into the cells and/or form membrane pores that allow calcium ions to flow into the cells [74, 75]. Calcium influx and membrane depolarization may cause excitotoxic reactions, neuronal dysfunction and atrophy. Madani et al. showed that pathogenic mutant Dyn A can cause changes in the membrane of the human brain neurodegeneration model, in which the formation of transient pores in the phospholipid membrane is the main reason for its neurotoxicity [73]. The non-opioid excitatory effects of mutant peptides accumulated over the years may lead to general pathological changes [68].

In summary, non-opioid functions of dynorphin play a crucial role in the pathogenesis of the disease.

Mechanisms of secondary structural changes of peptides

Smeets et al. showed that mutations of SCA23 in the Dyn A coding region destroy the secondary structure of the peptide, resulting in a decrease in the affinity between the α-helix of N-terminal and KORs. Consequently, activation of KORs is inhibited, which weakens the protective functions of ORs. Besides, the altered secondary structure can lead to the increase of peptide stability of Dyn A, thus induces neurological dysfunction and neurodegeneration [76].

Mechanisms of dynorphin as signal molecules regulating various physiological and pathological processes

Dynorphin is a type of signal molecules that regulate physiological and pathological processes. The synthesis of mutant dynorphin may affect the secretory pathways, synaptic transmission, and induce endoplasmic reticulum stress, while damage the maturation and transport of signal proteins [11, 14].

Hereditary heterozygous spinocerebellar ataxia is marked by cerebellar atrophy and PCs' degeneration. PCs are the sole output neuron in the cerebellar cortex, while damage to PCs can lead to motor dysfunction [77].

Summary of common mechanisms

In summary, pathological processes have developed on account of various long-term accumulated mechanisms caused by mutant PDYN gene, ultimately leading to degeneration. The phenomenon that different mutation mechanisms in separate genes lead to the same disease phenotype strongly indicates that the common biological pathway is the basis of the pathogenesis of SCAs. These common mechanisms include, but are not limited to, misfolding and aggregation of proteins, acquisition of toxic RNA functions, transcriptional disorders, and changes in glutamate and calcium signals that affect synaptic transmission [78–81].

Treatment of SCA23

At present, there is no known effective and specific therapy that can change the condition progression of SCA23. Therefore, the treatment conforms to the principle of SCAs generalization. Supportive care including gait disorders and speech therapy for dysarthria is essential. Using mechanical aid, such as crutches, walkers or wheelchairs, to maintain walking safety and freedom of movement for as long as possible is beneficial to alleviate the syndromes of the disease. Other symptoms such as insomnia, diplopia, spasm and urgent micturition or frequent micturition should be treated accordingly to promote the quality of life [20]. Depression is a potentially treatable and relatively common symptom that should be evaluated and actively considered when it exists [82]. Even if the management of the above symptoms can help improve function and overall condition of life, but it is not a fundamental treatment.

Precision therapy is the focus-treatment of SCAs diseases, mainly using two strategies. The first one is to use gene targeting strategies (RNA interference and antisense oligonucleotide) to silence mutant genes, so as to prevent the expression of mutant proteins. The other strategy is to identify and target disease aggregation mechanisms across SCAs as the basis for treatment. In other words, a variety of pathogenic processes, such as a disorder of homeostasis, RNA toxicity, abnormal synaptic signals, regulation of intracellular calcium, the excitability of Purkinje-neuron-membrane, and so on, are used as targets for SCAs therapy [83]. Therapeutic studies based on these two strategies have emerged. Scoles et al. believed that antisense oligonucleotide may be effective in the management of SCAs [84, 85]. Thomas et al. reasoned out that the application of RNA targeting therapy for neurodegenerative diseases has a noble prospect [86]. Kampinga et al. supposed that the approach of heat shock protein as a mark provides a prospect and hope for a successful project to overcome neurodegenerative disorders [87]. Serrano et al. pointed out that changing methylation patterns, modifying histone or drugs that can affect the metabolism of microRNAs (miRNAs) are potential treatments for SCA [88]. Shuvaev et al. found that baclofen can improve ataxia in SCA1 mice, and baclofen may be beneficial to other types of ataxia [89]. Nishizawa et al. conducted phase III trials on the drug treatment of sufferers with spinocerebellar degeneration (SCD). The experimental data showed that Lovarelin, a thyrotropin-releasing hormone analogue, is a potentially efficient choice to treat cerebellar ataxia in patients with major cerebellar manifestations of SCD. And the more serious the symptom is, the more noticeable the effect is [90]. Rodíguez-Labrada et al. proposed that cerebellar low frequency repetitive transcranial magnetic stimulation (rTMS) can improve some motor symptoms of the disease [91]. Tsai et al. suggested that intravenous injection of allogeneic bone marrow mesenchymal stem cells seems to be well tolerated. So far, precision analysis strategy of SCA23 still needs further study [92].

Table 4 Reported mutations of PDYN

Mutation	c. 632 T > C (p.L211S)	c. 634C > T (p.R212W)	c. 643C > T (p.R215C)	c. 643C > T (p.R215C)	c. 65G > A (p.C22Y)
Age of onset (years)	73	54	53	43	22
Gender	Male	Female	Female	Male	Male
Genetic mode	Sporadic	Sporadic	AD	AD	n.a
Segregated with the disease	–	–	+	+	–
Gait ataxia	+	+	n.a	+	+
Limb ataxia	+	+	+	+	+
Dysarthria	±	+	+	+	+
Oculomotor impairment	+	–	+	n.a	+
Other	Parkinson-like features; polyneuropathy and pyramidal signs in the legs	A progressive mixed axonal polyneuropathy	Postural arm tremor and a tremor of head; proximal paresis of the legs with mild signs of sensory neuropathy	Tremor of the head and arms	Slightly brisk reflexes
MRI	n.a	Generalized cerebral cortical and subcortical atrophy agenesis of the corpus callosum	Slowly progressive frontoparietal white matter abnormalities	Discrete peri-ventricular white matter lesions	Cerebellar atrophy and left hippocampal sclerosis
Mechanism	Markedly elevated Dyn A levels; probable increase PDYN phosphorylation levels by generating potential phosphorylation sites	Decreased Dyn B levels. markedly elevated Dyn A levels; increase neurotoxicity through Dyn A mutant	Markedly elevated Dyn A levels. increase neurotoxicity through Dyn A mutant; decreased Leu-enkephalin Arg levels; decreased Dyn B levels	Markedly elevated Dyn A levels; increase neurotoxicity through Dyn A mutant; decreased the levels of Leu-enkephalin-Arg. Decreased Dyn B levels	n.a
Pathology	n.a	n.a	n.a	n.a	n.a
References	[11]	[11]	[11]	[11]	[12]
Mutation	c.74G > A (p.R25Q)	c.374G > A (p.G159D)	c. 255G > A (p.L85L)	Normal	Normal
Age of onset (years)	n.a	n.a	53	28	45
Gender	n.a	n.a	Male	Male	Female
Genetic mode	n.a	n.a	n.a	n.a	n.a
Segregated with the disease	n.a	n.a	–	The brother of p. L85L	The mother of p. L85L
Gait ataxia	n.a	n.a	+	+	+
Limb ataxia	n.a	n.a	+	n.a	n.a
Dysarthria	n.a	n.a	–	+	+
Oculomotor impairment	n.a	n.a	–	–	–
Other	Rare, neutral polymorphisms	Rare, neutral polymorphisms	Occasional dizziness tendon hyperreflexia and was positive for Romberg's sign and Babinski's sign; a synonymous single nucleotide polymorphism	Psychiatric symptoms and neuroleptic treatment since age 22; attention difficulties; irritability, alcohol abuse	Mild intellectual deficiency since childhood

Table 4 (continued)

Mutation	c.74G > A (p.R25Q)	c.374G > A (p.G159D)	c. 255G > A (p.L85L)	Normal	Normal
MRI	n.a	n.a	Moderate atrophy in the cerebellum	Cerebellar vermis atrophy	Cerebellar vermis atrophy
Mechanism	n.a	n.a	n.a	n.a	n.a
Pathology	n.a	n.a	n.a	n.a	n.a
References	[12]	[12]	[13]	[13]	[13]
Mutation	c. 616C > T (p.R206C)	c.680G > A (p.G227D)	c.617G > A (p.R206H)	c. 658-659delGT (p. W220GfsX33)	p. R138S
Age of onset (years)	50	54	15	45	53
Gender	n.a	n.a	n.a	n.a	Female
Genetic mode	n.a	n.a	n.a	n.a	AD
Segregated with the disease	n.a	n.a	–	n.a	+
Gait ataxia	+	+	+	+	+
Limb ataxia	n.a	n.a	n.a	n.a	+
Dysarthria	+	–	+	+	–
Oculomotor impairment	+	–	+	–	+
Other	Tremor, incontinence, generalized increased reflexes	Moderate spastic gait, generalized increased reflexes; indifferent Babinski sign	Mild intellectual deficiency at age 4; abnormal behavior, psychiatric symptoms at age 28; attention and memory deficit at age 32; bilateral sensory deafness, generalized increased reflexes	Generalized increased reflexes, extensor Babinski's sign, urgency of urination, cataract, head tremor	Disturbed distal vibration and position sense; increased tendon reflexes
MRI	n.a	Cerebellar and brainstem atrophy	Cerebellar vermis atrophy	Normal	n.a
Mechanism	Modify the processing site just upstream of Dyn A at arginine 206 and no significant changes were detected for p.R206C. PDYN might have functional consequences for the precursor for example by impairing trafficking rather than changing the peptide levels	Markedly elevated Dyn B and Leuenkephalin-Arg levels	Markedly elevated Dyn A levels; modify the processing site just upstream of Dyn A at arginine 206 might have functional consequences for the precursor for example by impairing trafficking rather than changing the peptide levels	In addition, the two-base pair deletion causes a frame-shift that introduces a premature stop codon, affecting the last four amino acids of Dyn A and leads to total loss of the Dyn B sequence	n.a
Pathology	n.a	n.a	n.a	n.a	n.a
References	[14]	[14]	[13]	[14]	[10]
Mutation	p. R138S	p. R138S	p. R138S	p. R138S	p. R138S
Age of onset (years)	56	51	43	49	n.a

Table 4 (continued)

Mutation	p. R138S	p. R138S	p. R138S	p. R138S	p. R138S
Gender	Male	Male	Male	Male	n.a
Genetic mode	AD	AD	AD	AD	n.a
Segregated with the disease	+	+	+	+	–
Gait ataxia	+	+	+	–	–
Limb ataxia	+	+	+	n.a	–
Dysarthria	+	+	+	–	–
Oculomotor impairment	+	–	+	n.a	–
Other	Disturbed distal vibration and position sense; increased tendon reflexes, Babinski's sign	Ocular dysmetria	Disturbed distal vibration and position sense; increased tendon reflexes, Babinski's sign	Increased tendon reflexes	An asymptomatic carrier
MRI	n.a	n.a	Severe cerebellar atrophy, normal brain stem structures and basal ganglia; no cerebral cortical atrophy, and multiple small subcortical white matter lesions in the cerebral hemispheres that resembled vascular disease	n.a	n.a
Mechanism	n.a	n.a	n.a	n.a	n.a
Pathology	n.a	n.a	n.a	n.a	n.a
References	[10]	[10]	[10]	[10]	[10]
Mutation	p. R138S	c.664G > A (p.R215H)	c.664G > A (p.R215H)	c.664G > A (p.R215H)	c.664G > A (p.R215H)
Age of onset (years)	n.a	45	40	n.a	36
Gender	Female	Male	Male	Female	Male
Genetic mode	AD	AD	AD	AD	AD
Segregated with the disease	+	+	+	+	+
Gait ataxia	n.a	+	+	+	+
Limb ataxia	n.a	n.a	n.a	n.a	n.a
Dysarthria	n.a	+	–	–	+
Oculomotor impairment	n.a	+	n.a	–	–
Other	Died at the age of 80 years	Parkinsonism: bradykinesia, small steps, and frozen, gait; increased deep tendon reflex in upper and lower extremities	Cerebellar tremor; increased deep tendon reflex in lower extremities	n.a	Increased deep tendon reflex in lower extremities; a homozygote patient
MRI	n.a	Mild atrophy of both cerebellar hemispheres and vermis; Hyperintense lateral putaminal rim	Moderate atrophy of both cerebellar hemispheres and vermis	Moderate atrophy of both cerebellar hemispheres and vermis	Moderate atrophy of both cerebellar hemispheres and vermis

Table 4 (continued)

Mutation	p. R138S	c.664G > A (p.R215H)	c.664G > A (p.R215H)	c.664G > A (p.R215H)	c.664G > A (p.R215H)
Mechanism	Formation of an additional phosphorylation site in PDYN by the p. R138S mutation may affect processing or trafficking of mutant protein; decreased the levels of Leu-enkephalin-Arg and Dyn B; located in the nonopioid domain of PDYN and may affect N-terminal trimming of the 8 kDa and 10 kDa PDYN processing intermediates; proteins involved in cell adhesion, synaptogenesis, secretory pathways, and signal transduction were up- or downregulated	n.a	n.a	n.a	n.a
Pathology	Marked alterations in expression of crucial components of the opioid and glutamate systems	n.a	n.a	n.a	n.a
References	[11]	[42]	[42]	[42]	[42]
Mutation	c.664G > A (p.R215H)	c.638A > G (p.R213H)	c.638A > G (p.R213H)	c.600 T > C (p.H200H)	c.436A > C (p.M146L)
Age of onset (years)	30	n.a	10	n.a	n.a
Gender	Female	Female	Female	n.a	n.a
Genetic mode	AD	n.a	n.a	n.a	n.a
Segregated with the disease	+	n.a	n.a	n.a	n.a
Gait ataxia	+	+	+	n.a	n.a
Limb ataxia	n.a	n.a	n.a	n.a	n.a
Dysarthria	+	+	+	n.a	n.a
Oculomotor impairment	+	n.a	n.a	n.a	n.a
Other	Gaze nystagmus; cerebellar tremor; decreased deep tendon reflex in lower extremities	Head tremor; hyperreflexia	Had mild ataxia before the age of 10 years; hyperreflexia	Likely benign mutation	Benign mutation

Table 4 (continued)

Mutation	c.664G > A (p.R215H)	c.638A > G (p.R213H)	c.638A > G (p.R213H)	c.600 T > C (p.H200H)	c.436A > C (p.M146L)
MRI	Moderate atrophy of both cerebellar hemispheres, vermis and middle cerebellar peduncle	n.a	Atrophy outside the globus pallidus and "hot cross bun" (HCB) sign in the brain stem; cerebral blood flow scintigraphy performed simultaneously with the MRI showed a greater reduction of blood flow in the brain stem than in the cerebellum	n.a	n.a
Mechanism	n.a	n.a	n.a	n.a	n.a
Pathology	n.a	n.a	n.a	n.a	n.a
References	[42]	[46]	[46]	[45]	[45]

n.a means not assess

Genetic counseling of SCA23

Genetic counseling is essential for individuals of childbearing age or people who desire to make family planning decisions, in addition, preferably in a genetic professional sector. Not only in SCA23, the other SCAs are also applicable and valid. Genetic counselling requires the cooperation of several experts, including at least one hereditary physician and one psychologist, whose basic responsibility is to provide information on diagnosis, risk, prognosis, medical aspects, and to assess psychological integrity. While it also calls for the cooperation of psychiatrists, neurologists, nurses and social workers [93]. During genetic counseling, doctors demand to understand the mental needs of sufferers to further communication. Regarding to the concerns of patients during genetic counseling, a study conducted in Brazil showed that about 57% of patients and their families claim questions about etiological diagnosis and/or disclosure of high-risk status, and 17% ask challenges about the improvement of quality of life. A few humans, about 3%, believe that heredity/inheritance is the greatest concern. Pre-test interviews are a valuable tool to clarify counselors' matters and promote better communication among patients, family members, and genetic counseling teams. The effectiveness of the genetic hereditary process is largely related to cultural values, previous disease experience, social and financial background, and family dynamics [94].

Prognosis of SCA23

Longitudinal studies on the prognosis of patients with SCA23 have not been carried out, so it is difficult to determine the accurate prognosis of individual patients. Assuming that the condition continues to progress, the shortening of life expectancy is worth affirming [20]. Diallo et al. conducted prospective studies on the prognosis of some types of SCAs, and studies showed that the rate of disease progression is the strongest predictor of death. The prognosis of SCA23 still needs further study [95]. Clinical scale SARA and ICAR are the most commonly used clinical tools to monitor the disease progression of SCAs. Testing the quantitative performance score of specific motor ability is extremely important to measure the effect of disease evolution on gait and upper limb motor coordination. These tests can be invoked as significant indicators of the phased results of interventional treatment trials [96].

Prospects for the future

It is worth affirming that SCAs, including SCA23, will appear "preclinical markers" before the typical ataxia syndromes, including specific symptoms, neuroimaging, electrophysiological structural manifestations and so on. After finding these markers, we may be in a position to give relevant intervention as soon as possible, and then affect the progress of the disease [97]. This is the direction that we still need to work hard in the future. Furthermore, there will be new breakthroughs in the treatment of the disorder, as well as the relationship between genotypes and phenotypes.

Conclusion

SCA23, one type of SCAs, is a group of hereditary disorders characterized by gait ataxia accompanying with other specific symptoms. Based on literatures, there are 16 mutations have been reported (Table 4). Big Dyn of PDYN plays an essential function in Pathophysiological mechanisms, while common mechanisms of SCAs get incremental attention. Diagnosis requires a comprehensive of clinical syndrome, neuroimaging, and gene detection. Additionally, differential diagnosis is necessary for inherited diseases. Exploration of the relationship between genotype and phenotype remains to be discussed, in which epigenetics may show a potential role. Discovering of precision therapy as the focus-treatment is indispensable, despite supporting care has been confirmed. In brief, further work is required to unlock the unknown of the SCA23 to promote our cognitive.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

References

1. Harding AE (1983) Classification of the hereditary ataxias and paraplegias. Lancet 1(8334):1151–1155
2. Sullivan R, Yau WY, O'Connor E, Houlden H (2019) Spinocerebellar ataxia: an update. J Neurol 266(2):533–544
3. Paulson HL, Shakkottai VG, Clark HB, Orr HT (2017) Polyglutamine spinocerebellar ataxias—from genes to potential treatments. Nat Rev Neurosci 18(10):613–626
4. Jayadev S, Bird TD (2013) Hereditary ataxias: overview. Genet Med 15(9):673–683
5. Storey E, Gardner RJ (2012) Spinocerebellar ataxia type 20. Handb Clin Neurol 103:567–573
6. Yuan Y, Zhou X, Ding F, Liu Y, Tu J (2010) Molecular genetic analysis of a new form of spinocerebellar ataxia in a Chinese Han family. Neurosci Lett 479(3):321–326
7. Urbanek MO, Krzyzosiak WJ (2016) RNA FISH for detecting expanded repeats in human diseases. Methods 98:115–123
8. Johnson JO, Stevanin G, van de Leemput J, Hernandez DG, Arepalli S, Forlani S et al (2015) A 7.5-Mb duplication at chromosome 11q21–11q22.3 is associated with a novel spastic ataxia syndrome. Mov Disord 30(2):262–266
9. Trott A, Houenou LJ (2012) Mini-review: spinocerebellar ataxias: an update of SCA genes. Recent Pat DNA Gene Seq 6(2):115–121
10. Verbeek DS, van de Warrenburg BP, Wesseling P, Pearson PL, Kremer HP, Sinke RJ (2004) Mapping of the SCA23 locus involved in autosomal dominant cerebellar ataxia to chromosome region 20p13–12.3. Brain 127(Pt 11):2551–2557
11. Bakalkin G, Watanabe H, Jezierska J, Depoorter C, Verschuuren-Bemelmans C, Bazov I et al (2010) Prodynorphin mutations cause the neurodegenerative disorder spinocerebellar ataxia type 23. Am J Hum Genet 87(5):593–603
12. Fawcett K, Mehrabian M, Liu YT, Hamed S, Elahi E, Revesz T et al (2013) The frequency of spinocerebellar ataxia type 23 in a UK population. J Neurol 260(3):856–859
13. Liu YT, Tang BS, Wang JL, Guan WJ, Shen L, Shi YT et al (2012) Spinocerebellar ataxia type 23 is an uncommon SCA subtype in the Chinese Han population. Neurosci Lett 528(1):51–54
14. Jezierska J, Stevanin G, Watanabe H, Fokkens MR, Zagnoli F, Kok J et al (2013) Identification and characterization of novel PDYN mutations in dominant cerebellar ataxia cases. J Neurol 260(7):1807–1812
15. Mascalchi M, Vella A (2018) Neuroimaging applications in chronic ataxias. Int Rev Neurobiol 143:109–162
16. Ito K, Ohtsuka C, Yoshioka K, Maeda T, Yokosawa S, Mori F et al (2019) Differentiation between multiple system atrophy and other spinocerebellar degenerations using diffusion kurtosis imaging. Acad Radiol 26(11):e333–e339
17. Kim M, Ahn JH, Cho Y, Kim JS, Youn J, Cho JW (2019) Differential value of brain magnetic resonance imaging in multiple system atrophy cerebellar phenotype and spinocerebellar ataxias. Sci Rep 9(1):17329
18. Xue Y, Ankala A, Wilcox WR, Hegde MR (2015) Solving the molecular diagnostic testing conundrum for Mendelian disorders in the era of next-generation sequencing: single-gene, gene panel, or exome/genome sequencing. Genet Med 17(6):444–451
19. Richards CS, Bale S, Bellissimo DB, Das S, Grody WW, Hegde MR et al (2008) ACMG recommendations for standards for interpretation and reporting of sequence variations: revisions 2007. Genet Med 10(4):294–300
20. Whaley NR, Fujioka S, Wszolek ZK (2011) Autosomal dominant cerebellar ataxia type I: a review of the phenotypic and genotypic characteristics. Orphanet J Rare Dis 6:33
21. Soong BW, Morrison PJ (2018) Spinocerebellar ataxias. Handb Clin Neurol 155:143–174
22. van Gaalen J, Kerstens FG, Maas RP, Härmark L, van de Warrenburg BP (2014) Drug-induced cerebellar ataxia: a systematic review. CNS Drugs 28(12):1139–1153
23. Pedroso JL, Vale TC, Braga-Neto P, Dutra LA, França MC, Jr., Teive H A G, et al (2019) Acute cerebellar ataxia: differential diagnosis and clinical approach. Arq Neuropsiquiatr 77(3):184–193
24. Kotwal SK, Kotwal S, Gupta R, Singh JB, Mahajan A (2016) Cerebellar ataxia as a presenting feature of hypothyroidism. Acta Endocrinol (Buchar) 12(1):77–79
25. Elhadd TA, Linton K, McCoy C, Saha S, Holden R (2014) A hitherto undescribed case of cerebellar ataxia as the sole presentation of thyrotoxicosis in a young man: a plausible association. Ann Saudi Med 34(5):440–443
26. Moore DS (2017) Behavioral epigenetics. Wiley Interdiscip Rev Syst Biol Med. https://doi.org/10.1002/wsbm.1333

27. Rd S, Dr C, H S, (2020) Invited review: epigenetics in neurodevelopment. Neuropathol Appl Neurobiol 46(1):6–27
28. Harvey ZH, Chen Y, Jarosz DF (2018) Protein-based inheritance: epigenetics beyond the chromosome. Mol Cell 69(2):195–202
29. Waddington CH (2012) The epigenotype. Int J Epidemiol 41(1):10–13
30. Felsenfeld G (2014) A brief history of epigenetics. Cold Spring Harb Perspect Biol. https://doi.org/10.1101/cshperspect.a018200
31. Biemont C (2010) From genotype to phenotype. What do epigenetics and epigenomics tell us? Heredity (Edinb) 105(1):1–3
32. Bazov I, Sarkisyan D, Kononenko O, Watanabe H, Taqi MM, Stalhandske L et al (2018) Neuronal expression of opioid gene is controlled by dual epigenetic and transcriptional mechanism in human brain. Cereb Cortex 28(9):3129–3142
33. Rothbart SB, Strahl BD (2014) Interpreting the language of histone and DNA modifications. Biochim Biophys Acta 1839(8):627–643
34. Esteller M (2007) Cancer epigenomics: DNA methylomes and histone-modification maps. Nat Rev Genet 8(4):286–298
35. Reid MA, Dai Z, Locasale JW (2017) The impact of cellular metabolism on chromatin dynamics and epigenetics. Nat Cell Biol 19(11):1298–1306
36. Safi-Stibler S, Gabory A (2020) Epigenetics and the developmental origins of health and disease: parental environment signalling to the epigenome, critical time windows and sculpting the adult phenotype. Semin Cell Dev Biol 97:172–180
37. Cavalli G, Heard E (2019) Advances in epigenetics link genetics to the environment and disease. Nature 571(7766):489–499
38. Cuevas-Sierra A, Ramos-Lopez O, Riezu-Boj JI, Milagro FI, Martinez JA (2019) Diet, gut microbiota, and obesity: links with host genetics and epigenetics and potential applications. Adv Nutr 10(suppl_1):S17–S30. https://doi.org/10.1093/advances/nmy078
39. Aleksandrova K, Romero-Mosquera B, Hernandez V (2017) Diet, gut microbiome and epigenetics: emerging links with inflammatory bowel diseases and prospects for management and prevention. Nutrients. https://doi.org/10.3390/nu9090962
40. Bert SA, Robinson MD, Strbenac D, Statham AL, Song JZ, Hulf T et al (2013) Regional activation of the cancer genome by long-range epigenetic remodeling. Cancer Cell 23(1):9–22
41. Cao R, Wang L, Wang H, Xia L, Erdjument-Bromage H, Tempst P et al (2002) Role of histone H3 lysine 27 methylation in polycomb-group silencing. Science 298(5595):1039–1043
42. Satoh S, Kondo Y, Ohara S, Yamaguchi T, Nakamura K, Yoshida K (2020) Intrafamilial phenotypic variation in spinocerebellar ataxia type 23. Cerebellum Ataxias 7:7
43. Ruano L, Melo C, Silva MC, Coutinho P (2014) The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. Neuroepidemiology 42(3):174–183
44. Schicks J, Synofzik M, Beetz C, Schiele F, Schöls L (2011) Mutations in the PDYN gene (SCA23) are not a frequent cause of dominant ataxia in Central Europe. Clin Genet 80(5):503–504
45. Fogel BL, Lee JY, Lane J, Wahnich A, Chan S, Huang A et al (2012) Mutations in rare ataxia genes are uncommon causes of sporadic cerebellar ataxia. Mov Disord 27(3):442–446
46. Saigoh K, Mitsui J, Hirano M, Shioyama M, Samukawa M, Ichikawa Y et al (2015) The first Japanese familial case of spinocerebellar ataxia 23 with a novel mutation in the PDYN gene. Parkinsonism Relat Disord 21(3):332–334
47. Hauser KF, Aldrich JV, Anderson KJ, Bakalkin G, Christie MJ, Hall ED et al (2005) Pathobiology of dynorphins in trauma and disease. Front Biosci 10:216–235
48. Ludwig M, Leng G (2006) Dendritic peptide release and peptide-dependent behaviours. Nat Rev Neurosci 7(2):126–136
49. Riters LV, Cordes MA, Stevenson SA (2017) Prodynorphin and kappa opioid receptor mRNA expression in the brain relates to social status and behavior in male European starlings. Behav Brain Res 320:37–47
50. Bloodgood DW, Hardaway JA, Stanhope CM, Pati D, Pina MM, Neira S et al (2020) Kappa opioid receptor and dynorphin signaling in the central amygdala regulates alcohol intake. Mol Psychiatry. https://doi.org/10.1038/s41380-020-0690-z
51. Schwarzer C (2009) 30 years of dynorphins–new insights on their functions in neuropsychiatric diseases. Pharmacol Ther 123(3):353–370
52. Bazov I, Sarkisyan D, Kononenko O, Watanabe H, Taqi MM, Stålhandske L et al (2018) Neuronal expression of opioid gene is controlled by dual epigenetic and transcriptional mechanism in human brain. Cereb Cortex 28(9):3129–3142
53. Kuzmin A, Madjid N, Terenius L, Ogren SO, Bakalkin G (2006) Big dynorphin, a prodynorphin-derived peptide produces NMDA receptor-mediated effects on memory, anxiolytic-like and locomotor behavior in mice. Neuropsychopharmacology 31(9):1928–1937
54. Kreek MJ, Bart G, Lilly C, LaForge KS, Nielsen DA (2005) Pharmacogenetics and human molecular genetics of opiate and cocaine addictions and their treatments. Pharmacol Rev 57(1):1–26
55. Trezza V, Damsteegt R, Achterberg EJ, Vanderschuren LJ (2011) Nucleus accumbens μ-opioid receptors mediate social reward. J Neurosci 31(17):6362–6370
56. Levran O, Yuferov V, Kreek MJ (2012) The genetics of the opioid system and specific drug addictions. Hum Genet 131(6):823–842
57. Silvia RC, Slizgi GR, Ludens JH, Tang AH (1987) Protection from ischemia-induced cerebral edema in the rat by U-50488H, a kappa opioid receptor agonist. Brain Res 403(1):52–57
58. Baskin DS, Hosobuchi Y, Loh HH, Lee NM (1984) Dynorphin(1–13) improves survival in cats with focal cerebral ischaemia. Nature 312(5994):551–552
59. Macdonald RL, Werz MA (1986) Dynorphin A decreases voltage-dependent calcium conductance of mouse dorsal root ganglion neurones. J Physiol 377:237–249
60. Rusin KI, Giovannucci DR, Stuenkel EL, Moises HC (1997) Kappa-opioid receptor activation modulates Ca2+ currents and secretion in isolated neuroendocrine nerve terminals. J Neurosci 17(17):6565–6574
61. Hauser KF, Mangoura D (1998) Diversity of the endogenous opioid system in development. Novel signal transduction translates multiple extracellular signals into neural cell growth and differentiation. Perspect Dev Neurobiol 5(4):437–449
62. Knapp PE, Itkis OS, Zhang L, Spruce BA, Bakalkin G, Hauser KF (2001) Endogenous opioids and oligodendroglial function: possible autocrine/paracrine effects on cell survival and development. Glia 35(2):156–165
63. Caudle RM, Dubner R (1998) Ifenprodil blocks the excitatory effects of the opioid peptide dynorphin 1–17 on NMDA receptor-mediated currents in the CA3 region of the guinea pig hippocampus. Neuropeptides 32(1):87–95
64. Lai SL, Gu Y, Huang LY (1998) Dynorphin uses a non-opioid mechanism to potentiate *N*-methyl-D-aspartate currents in single rat periaqueductal gray neurons. Neurosci Lett 247(2–3):115–118
65. Chen L, Gu Y, Huang LY (1995) The mechanism of action for the block of NMDA receptor channels by the opioid peptide dynorphin. J Neurosci 15(6):4602–4611
66. Tang Q, Gandhoke R, Burritt A, Hruby VJ, Porreca F, Lai J (1999) High-affinity interaction of (des-Tyrosyl)dynorphin A(2–17) with NMDA receptors. J Pharmacol Exp Ther 291(2):760–765
67. Tan-No K, Esashi A, Nakagawasai O, Niijima F, Tadano T, Sakurada C et al (2002) Intrathecally administered big dynorphin, a prodynorphin-derived peptide, produces nociceptive behavior through an *N*-methyl-D-aspartate receptor mechanism. Brain Res 952(1):7–14

68. Watanabe H, Mizoguchi H, Verbeek DS, Kuzmin A, Nyberg F, Krishtal O et al (2012) Non-opioid nociceptive activity of human dynorphin mutants that cause neurodegenerative disorder spinocerebellar ataxia type 23. Peptides 35(2):306–310
69. Yakovleva T, Marinova Z, Kuzmin A, Seidah NG, Haroutunian V, Terenius L et al (2007) Dysregulation of dynorphins in Alzheimer disease. Neurobiol Aging 28(11):1700–1708
70. Hauser KF, Knapp PE, Turbek CS (2001) Structure-activity analysis of dynorphin A toxicity in spinal cord neurons: intrinsic neurotoxicity of dynorphin A and its carboxyl-terminal, nonopioid metabolites. Exp Neurol 168(1):78–87
71. Sherwood TW, Askwith CC (2009) Dynorphin opioid peptides enhance acid-sensing ion channel 1a activity and acidosis-induced neuronal death. J Neurosci 29(45):14371–14380
72. Hugonin L, Vukojević V, Bakalkin G, Gräslund A (2006) Membrane leakage induced by dynorphins. FEBS Lett 580(13):3201–3205
73. Madani F, Taqi MM, Wärmländer SK, Verbeek DS, Bakalkin G, Gräslund A (2011) Perturbations of model membranes induced by pathogenic dynorphin A mutants causing neurodegeneration in human brain. Biochem Biophys Res Commun 411(1):111–114
74. Marinova Z, Vukojevic V, Surcheva S, Yakovleva T, Cebers G, Pasikova N et al (2005) Translocation of dynorphin neuropeptides across the plasma membrane. A putative mechanism of signal transmission. J Biol Chem 280(28):26360–26370
75. Hugonin L, Vukojević V, Bakalkin G, Gräslund A (2008) Calcium influx into phospholipid vesicles caused by dynorphin neuropeptides. Biochim Biophys Acta 1778(5):1267–1273
76. Smeets CJ, Zmorzyńska J, Melo MN, Stargardt A, Dooley C, Bakalkin G et al (2016) Altered secondary structure of Dynorphin A associates with loss of opioid signalling and NMDA-mediated excitotoxicity in SCA23. Hum Mol Genet 25(13):2728–2737
77. Watanave M, Hoshino C, Konno A, Fukuzaki Y, Matsuzaki Y, Ishitani T et al (2019) Pharmacological enhancement of retinoid-related orphan receptor α function mitigates spinocerebellar ataxia type 3 pathology. Neurobiol Dis 121:263–273
78. Huang M, Verbeek DS (2019) Why do so many genetic insults lead to Purkinje cell degeneration and spinocerebellar ataxia? Neurosci Lett 688:49–57
79. Shimobayashi E, Kapfhammer JP (2018) Calcium signaling, PKC gamma, IP3R1 and CAR8 link spinocerebellar Ataxias and Purkinje cell dendritic development. Curr Neuropharmacol 16(2):151–159
80. Nibbeling EAR, Duarri A, Verschuuren-Bemelmans CC, Fokkens MR, Karjalainen JM, Smeets C et al (2017) Exome sequencing and network analysis identifies shared mechanisms underlying spinocerebellar ataxia. Brain 140(11):2860–2878
81. Yan H, Pablo JL, Wang C, Pitt GS (2014) FGF14 modulates resurgent sodium current in mouse cerebellar Purkinje neurons. Elife 3:e04193. https://doi.org/10.1085/jgp.201912390
82. Schmitz-Hübsch T, Coudert M, Tezenas du Montcel S, Giunti P, Labrum R, Dürr A et al (2011) Depression comorbidity in spinocerebellar ataxia. Mov Disord 26(5):870–876
83. Bushart DD, Murphy GG, Shakkottai VG (2016) Precision medicine in spinocerebellar ataxias: treatment based on common mechanisms of disease. Ann Transl Med 4(2):25
84. Scoles DR, Pulst SM (2019) Antisense therapies for movement disorders. Mov Disord 34(8):1112–1119
85. Scoles DR, Pulst SM (2018) Oligonucleotide therapeutics in neurodegenerative diseases. RNA Biol 15(6):707–714
86. Thomas EA, D'Mello SR (2018) Complex neuroprotective and neurotoxic effects of histone deacetylases. J Neurochem 145(2):96–110
87. Kampinga HH, Bergink S (2016) Heat shock proteins as potential targets for protective strategies in neurodegeneration. Lancet Neurol 15(7):748–759
88. Serrano M (2018) Epigenetic cerebellar diseases. Handb Clin Neurol 155:227–244
89. Shuvaev AN, Hosoi N, Sato Y, Yanagihara D, Hirai H (2017) Progressive impairment of cerebellar mGluR signalling and its therapeutic potential for cerebellar ataxia in spinocerebellar ataxia type 1 model mice. J Physiol 595(1):141–164
90. Nishizawa M, Onodera O, Hirakawa A, Shimizu Y, Yamada M (2020) Effect of rovatirelin in patients with cerebellar ataxia: two randomised double-blind placebo-controlled phase 3 trials. J Neurol Neurosurg Psychiatry 91(3):254–262
91. Rodríguez-Labrada R, Velázquez-Pérez L, Ziemann U (2018) Transcranial magnetic stimulation in hereditary ataxias: diagnostic utility, pathophysiological insight and treatment. Clin Neurophysiol 129(8):1688–1698
92. Tsai YA, Liu RS, Lirng JF, Yang BH, Chang CH, Wang YC et al (2017) Treatment of spinocerebellar Ataxia with mesenchymal stem cells: a phase I/IIa clinical study. Cell Transplant 26(3):503–512
93. Orozco-Gutiérrez MH, Cervantes-Aragón I, García-Cruz D (2017) Ethical considerations in presymptomatic diagnosis of autosomal dominant spinocerebellar ataxias. Neurologia 32(7):469–475
94. do Nascimento-Marinho AS, de Faria-Domingues-de-Lima MA, Vargas FR (2015) Analysis of pre-test interviews in a cohort of Brazilian patients with movement disorders. J Community Genet 6(3):259–264
95. Diallo A, Jacobi H, Cook A, Giunti P, Parkinson MH, Labrum R et al (2019) Prediction of survival with long-term disease progression in most common Spinocerebellar ataxia. Mov Disord 34(8):1220–1227
96. Sarro L, Nanetti L, Castaldo A, Mariotti C (2017) Monitoring disease progression in spinocerebellar ataxias: implications for treatment and clinical research. Expert Rev Neurother 17(9):919–931
97. Maas RP, van Gaalen J, Klockgether T, van de Warrenburg BP (2015) The preclinical stage of spinocerebellar ataxias. Neurology 85(1):96–103