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Methods for the Screening and Treatment of Spinocerebellar Ataxias

Pushpendra Mani Mishra[1], Dr. Vimal Kishor Singh[2]

[1]Department of Biotechnology, Delhi Technological University, New Delhi 110042, India

[2]Founder & O/I, Stem Cell Research Laboratory, Department of Biotechnology, Delhi Technological University, New Delhi 110042, India

Abstract: ***Spinocerebellar ataxias (SCAs) are a heterogeneous group of inherited neurodegenerative disorders that occurs in autosomal dominant manner. The disease shares the similar molecular mechanism as other neurodegenerative disorders such as Alzheimer's and Parkinson's disease in which mutant protein form due to defective/ mutant DNA, these proteins accumulate inside neuronal cells and cause Neurodegeneration. The disorders affect mainly cerebellar regions, cerebellar connections, and its associated pathways in addition to other brain regions. The general characteristics of SCAs are cognitive impairment, depression, and motor deficits. The most prominent symptom observed in SCAs patients is ataxia with other varying non-ataxia symptoms in the majority of phenotypes. The modern classification strategies of the disorder is based upon expanding genotype. Due to overlap in clinical manifestation of many SCAs types, Genetic test, and various screening tools, for instance, Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET) and Electromyography used to confirm the accumulation of mutant protein and aberrant neuronal mechanism responsible for the causation of particular phenotype. Nucleotides repeat expansion which is the basis of genetic disorder of SCAs can be determine by sequencing procedure. Similarly, techniques such as polymerase chain reaction (PCR) and gel electrophoresis with other molecular techniques and appliances used for the screening of patients in large number. The aim of this study was to explore the methods available for the screening of SCAs which form the basis of differential genetic diagnosis and list all the distinguishable clinical features and treatments available for SCAs.***

Keywords: Ataxia, Neuronal disorder, Spinocerebellar, Movement disorder, Neurodegenerative disease.

1. Introduction

The term ataxia refers to the loss of body balance and coordination while performing movements[1]. Conventionally, the autosomal dominant inherited ataxia is called spinocerebellar ataxia (SCA)[2]. Typical clinical features of SCAs are gait ataxia, appendicular ataxia followed by dysarthria, ocular difficulties in moving surrounding like saccadic eye movement, diplopia. Noncerebellar eye movement abnormalities are ocular "stare", blepharospasm, gaze palsies, ptosis and slowed saccades. Intention tremor on the finger to nose testing, dysmetria, widened stance and difficulty with gait, mainly when turning and rebound phenomena are characteristic cerebellar abnormalities[3].

The age of onset of disease is variable usually it is adult onset[4]. The worldwide prevalence of Autosomal dominant spinocerebellar ataxia is found to be 1to 5 cases per 100,000 population[5, 6]. Among all SCAs, SCA 3 is most common type which also known as Machado-Joseph disease (MJD) followed by SCA 1, 2, 6 and 7[7-21]. The site of mutation in different regions of the genome responsible for the numerous SCA types, several of the gene associated with this mutant site have already identified. Based upon the types of mutations, SCAs are categorized in 3 main group, group 1st is refers to SCAs with expanded CAG/polyQ ataxia, nonprotein coding repeat expansion ataxia comes under 2nd group and SCAs with conventional mutations (deletion, insertion, duplication, frameshift, and missense) kept in group 3rd. In SCAs most coalescing feature is a pattern of neurodegeneration, often clinician associate the disorder with clinical features which reflects the region of brain damage.[3] A growing body of evidence suggest the similar molecular mechanism behind the disease as other neurodegenerative diseases. Although based upon the types of mutation SCAs kept in 3 group but on the basis of genetic mechanism of disease, SCAs falls into four categories. Here it is noteworthy that the above 4 categories is for those SCAs in which the responsible gene has been identified already. The first category is SCAs with exonic triplet CAG repeats, for instance, SCA 1, 2, 3, 6, 7, 17, dentatorubropallidoluysian atrophy (DRPLA), and SCA 8 (partly), these codes for long, abnormal polyglutamine tracts within translated protein and results in a gain of toxic functions to these translated proteins. The second category is of SCAs with intronic or non-coding repeat expansion SCA 10, 12, 31, 36 and SCA 8(partly), some of these may involve in RNA-mediated toxicity. SCA 5, 11, 13, 14, 19/22, 23, 26, 27, 28, 29, and 35 with point mutations (including small insertions or deletions) may involve in a gain of novel function, haploinsufficiency or even dominant negative effect classified in category three of classification of the genetic mechanism. In last category the 4th one, SCAs with large duplications or deletions as SCA 15 and 20 have kept, they may result in gene dosage mechanisms i.e. under or over translation of the relevant protein products.[2]

2. Historical Perspective

The earliest practice of designating a disease with the term ataxia originate in the middle of the 19th century when Tabes dorsalis is named as Locomotor ataxia (a clinical term) by the French neurologist Duchenne de Boulogne. Autosomal dominant hereditary ataxia is referred as SCA, SCAs have assigned a different number based on its order of discovery. The term spinocerebellar ataxia first used in 1950 was based on the model of Friedreich ataxia. In the year, 1993 discovery of unstable CAG trinucleotide repeat expansion in SCA 1 disorder opens the way for the identification of mutations behind other autosomal dominant inherited SCAs.

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The method used previously for the identification and analysis of disease was linkage analysis. Gene discovery is the most recent method of identification of disorder. In the 20th century classification and neuropathological approaches to ataxia was based on the pivotal work of Greenfield and Holmes. The classification categories were based on the neuropathological characters such as spinocerebellar degeneration, or cerebellar cortical atrophy, olivopontocerebellar atrophy. However, this classification was not proper and the general consensus acceptance never reached. A new classification done by the professor Anita Harding in the beginning of 80s of the 20th century change the situation. SCAs were classified into four different types by Harding based on the specific characteristics, the four types are given as follows: The characteristics associated with Type 1 were cerebellar ataxia with optic atrophy, dementia, ophthalmoplegia, extrapyramidal signs, and amyotrophy. Disease symptoms ophthalmoplegia and extrapyramidal signs with retinal degeneration were kept in Type 2. The third category of classification (Type 3) was implicated with pure cerebellar ataxia. Type 4 was defined with the symptoms myoclonia and deafness in addition to cerebellar ataxia. Figure-1 exhibit most important events of ataxia on the historical timeline. Table-1 articulate the description of these important major historical proceedings on ataxia.[22, 23]

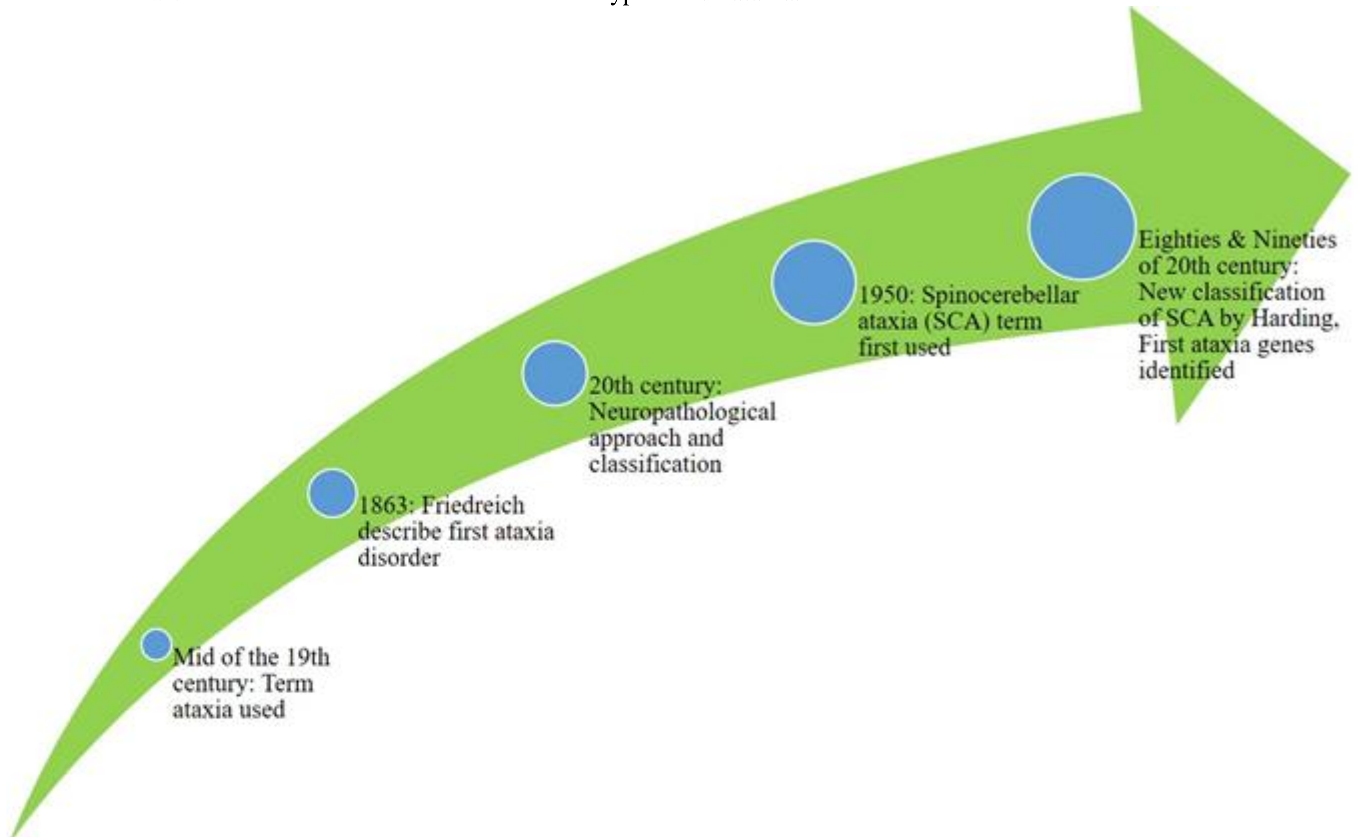

Figure 1: Most important events of ataxia on historical timeline

Table 1: Most important Historical occurrences of ataxia

Period	*Historical occurrence*
Mid of the 19th century	Term ataxia used to designate a disease (Tabes dorsalis termed as locomotor ataxia)
1863	Friedreich describe in details the first ataxia disorder
20th century	Neuropathological approach to ataxia and Neuropathological category based classification of ataxia established
1950	A historical term first used in 1950s based on Friedreich ataxia as a model
Eighties of 20th century	New classification of SCA by Harding based on genetic and clinical criteria
1993	Identification of mutation causing dominantly inherited SCAs started, unstable expansion of a translated CAG repeats cause SCA-1, identified
Nineties of 20th century	Clinical research establish that the SCA-1, SCA-2, SCA-3 Patients demonstrate additional symptoms in addition to ataxia while SCA-6 is an almost pure cerebellar ataxia

3. Symptoms and Visible Characteristics

SCAs are a group of complex disease which is heterogeneous in genotypic as well as phenotypic sense. The phenotypic heterogeneity implies that the different phenotype is determined by the same genotype, genotypic heterogeneity defined as the presence of the same phenotype although the genotypes are different.[24] The modern or new classification of ataxia is based on the order of discovery of locus of mutation. The number of genes have determined which implicated with these discovered locus although few of them yet to be determined, the most common features related to disease are uncoordinated movement, eye and speech impairments, cognitive decline, neuropathy, and spasticity.[4, 25] The current status of genetic testing is limited and cannot offer testing for all types of ataxia. The initial decision of genetic testing for a particular type of ataxia based on the clinical features that differentiate among many types, patient disease history and family disease history.[26] Table-2 summarizes the particular gene/locus, mutation, average onset time, average disease duration and clinical

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features associated with SCAs types. The clinical symptoms is also included non-ataxia symptoms in addition to the ataxia symptoms associated with different SCAs.

Table 2: SCA types, their genes, mutations, average onset, average duration and distinguished clinical features

SCAs Types	*Gene/ Locus*	*Mutation*	*Ranges in Years (Average onset)*	*Ranges in Years (Average durations)*	*Distinguish Clinical Features*
SCA 1	*ATXN1*	CAG repeat	<10 to>60 (3rd-4th decade)	10-28 (15)	**Pyramidal signs**, Peripheral neuropathy,
SCA 2	*ATXN2*	CAG repeat	<10 to>60 (3rd-4th decade)	1-30 (10)	**Slow saccades**, Peripheral neuropathy, Decreased DTRs, Dementia
SCA 3	*ATXN3*	CAG repeat	10-70 (4th decade)	1-20 (10)	**Pyramidal sign**, Amyotrophy fasciculations, sensory loss, Lid retraction, nystagmus, and decreased saccade velocity,
SCA 4	16q22.1	Unidentified	19-72 (4th-7th decade)	(Decades)	**Sensory axonal neuropathy,** Deafness
SCA 5	*SPTBN2*	Missense, in frame deletion	10-68 (3rd-4th decade)	(>25 years)	**Pure cerebellar ataxia (late onset)**, Pyramidal sign (early onset)
SCA 6	*CACNA1A*	CAG repeat	19-71 (5th-6th decade)	(>25 years)	**Pure cerebellar ataxia late onset**
SCA 7	*ATXN7*	CAG repeat	0.5-60 (3rd-4th decade)	Early onset correlate with shorter duration, 1-45 (20)	**Pigmentary macular degeneration**
SCA 8	*ATXN8*	CTG & CAG repeat	1-65 (4th decade)	(Normal life span)	**Pyramidal sign**, Sometimes brisk DTRs, decreased vibration sense, Rarely, cognitive impairment, Slowly progressive
SCA 9	*Not Assigned*				
SCA 10	*ATXN10*	ATTCT Penta nucleotide expansion	12-48 (4th decade)	(9 years)	**Seizures**
SCA 11	*TTBK2*	Frameshift	15-70 (age 30 years)	(Normal life span)	**Pure cerebellar ataxia**
SCA 12	*PPP2R2B*	CAG repeat	8-62 (4th decade)		**Upper extremity tremor**, Slowly progressive ataxia, Subtle parkinsonism possible, Action tremor in the 30s, Hyperreflexia, Cognitive/psychiatric disorders including dementia
SCA 13	*KCNC3*	Missense	Adulthood or childhood	Unknown	**Intellectual disability**, Short stature
SCA 14	*PRKCG*	Missense	3-70 (3rd-4th decade)	1-30 (Decades)	**Pure cerebellar ataxia,** Early axial myoclonus
SCA 15	*ITPR1*	Deletion & Missense	7-66 (4th decade)	(Decades)	**Pure cerebellar ataxia**
SCA 16	*ITPR1*	Deletion & Missense	20-66 (age 39 years)	(1-40 years)	**Pure cerebellar ataxia,** Head tremor
SCA 17	*TBP*	CAG repeat	3-55 (4th decade)	(>8 years)	**Chorea**, dystonia, myoclonus, epilepsy, Mental deterioration
SCA 18	7q22-q32	Unidentified	12-25 (adolescence)	(Decades)	**Posterior column loss**, Decreased tendon reflexes, Dysarthria, Nystagmus, Ataxia with early sensory/motor neuropathy
SCA 19/22	*KCND3*	Deletion & Missense	10-51 (4th decade)	(Decades)	**Pure cerebellar ataxia,** slowly progressive, Myoclonus, Hyperreflexia, rare cognitive impairment
SCA 20	11q12.2-11q12.3	Duplication	19-64 (5th decade)	(Decades)	**Spasmodic dysphonia** or **Spasmodic coughing**, Bradykinesia, Hyperreflexia, Early dysarthria
SCA 21	*TMEM240*	Missense &Nonsense	30-Jun	(Decades)	Mild to severe early-onset cognitive impairment
SCA 23	*PDYN*	Missense	(5th-6th)	(>10 years)	**Late onset**, Abnormal eye movements, Dysarthria, Reduced vibration and position sense
SCA 25	*SCA25*	Unidentified	1.5-39	Unknown	Sensory neuropathy
SCA 26	*EEF2*	Missense	26-60	Unknown	Irregular visual pursuits, Dysarthria
SCA 27	*FGF14*	Missense & Frameshift	7-20 (age 11 years)	(Decades)	Orofacial dyskinesia, Cognitive deficits, Early-onset tremor
SCA 28	*AFG3L2*	Missense	12-36 (age 19.5 years)	(Decades)	**Early onset**, Increased tendon reflexes, Ptosis, Ophthalmoparesis, Nystagmus
SCA 29	*ITPR1*	Missense	Early Childhood	(Lifelong)	**Congenital**, Learning deficits
SCA 30	4q34.3-q35.1	Unidentified	45-76	(Lifelong)	Hyperreflexia
SCA 31	*BEAN1*	TGGAA Penta nucleotide repeat	61.2 (3rd-4th decade)	Unknown	**Pure cerebellar ataxia** late onset, usually >50 years
SCA 34	*ELOVL4*	Missense	Early Childhood (4th or 5th decade)	Unknown	Skin changes disappear in adulthood
SCA 35	*TGM6*	Missense &deletion	Teenage to late	Unknown	**Pyramidal sign**

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			adulthood		
SCA 36	*NOP56*	GGCCTG Hexanucleotide Repeat	Adulthood	Unknown	**Lower motor neuron involvement**, Hyperreflexia, Tongue atrophy, Muscle fasiculations
SCA 37	1p32	Unidentified	Adulthood	Unknown	Abnormal vertical eye movements
SCA 38	*ELOVL5*	Missense	Adulthood	Unknown	Axonal neuropathy, Adult onset
SCA 40	*CCDC88C*	Missense	Adulthood	Unknown	Brisk reflexes, Spasticity, Adult onset
DRPLA	*ATN1*	CAG repeat	20	Unknown	**Myoclonic epilepsy**, Dementia, Seizures, Chorea
SCA 42	*CACNA1G*	Missense	Highly Variable	Unknown	Saccadic pursuit, Mild pyramidal signs

·DTR, deep tendon reflex

Symptoms in Bold typeface represent unique or characteristic feature of the particular SCA type

4. Methods for screening of SCAs

Numerous methods of identification of different types of SCAs applied in hospitals and research laboratory for screening, Figure-2 display the available methods for primary/ initial screening of different types of SCAs. Theses screening methods helpful in the construction of Algorithm for differential genetic diagnosis of SCAs.

Figure-2 Screening methods helpful in the construction of differential genetic testing algorithm for SCAs

The detail descriptions of screening methods of SCAs are as follows:

4.1 Electrophysiological

The basis of this method is an electrophysiological measurement of masseter reflex. The initial study was done on the patients of SCA type 2 and 3 by Antonio Garcia et al., the device used for the study was electromyography (EMG) system (Medelec-Synergy EMG/PE; Cardinal Health, UK). Masseter reflex measurement is a reliable test that discriminates between the SCA type 2 and 3, although this method was used for primary screening purpose.[27]

4.2 Radiological

A study carried by Yoshio Murata et al. found the certain characteristics feature of the brain of MJD patients in MRI study. The MRI study demonstrates the atrophy of temporal and frontal lobe in addition to Globus pallidus, abnormality in afferent and efferent cerebellar tracts also reported. These features may helpful in finding difference between sporadic olivopontocerebellar atrophy (sOPCA) and MJD.[28] Another published work of Yoshio Murata et al. signify the distinguishable feature of SCA 6 from other SCAs forms, in an MRI study of the brain. The MRI study shows the affected cerebellar region and its afferent and efferent system.[29] MRI is the steadfast method to find the affected brain regions in SCAs patient and other neurodegenerative disorder but it is not a confirmatory test for SCAs types, due to several overlap in clinical characteristics.

4.3 Biochemical

A study done by Marcelle R. Morrison and Roger N. Rosenberg on the brain of Machado-Joseph disease patients led the finding that there were an elevation in steady state level of many proteins such as glial fibrillary acidic protein complex, J protein complex, and L protein complex in the cerebellar and cortex region of brain in comparison to the control brain protein analysis.[30]

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4.4 Radiochemical

An comparative analysis of dopamine transporter and regional cerebral glucose metabolism (rCMRglu) by using [11C]d-threo-methylphenydate ([11C]dMP) and [18F]fluorodeoxyglucose ([18F]FDG) respectively and Positron emission tomography (PET) screening carried by Ullrich Wüllner et al., in patients with SCA 1, 2, 3 and 6 in comparison to Parkinson disease (PD) patients and healthy controls. Their findings reflect the specific pattern of neuronal susceptibility met in each polyglutamine disorder. The specific pathological features observed in patients with SCA 1, SCA 2, SCA 3 and SCA 6 provide a stepping stone for the identification of disorder among several pathotypes. They observed no significant change in the striatal [11C]dMP binding potential (BPdMP) but reduce rCMRglu in the cerebellum and brain stem of SCA 1 patients. . In SCA 2 patient's striatal BPdMP was evidently reduced, putamen and caudate nucleus region showed the 57 and 55% of BPdMP reduction respectively. An increment in the rCMRglu was noted in the temporal cortical region of interest (ROI) analysis. The dopamine terminal (DAT) loss was throughout striatum and similar to PD with a more severely affected putamen. Particularly in the case of SCA 2 mutation, the dopaminergic system was sensitive. Pathological features of SCA 3 demonstrated the marked reduction of striatal BPdMP. The same degree of reduction of BPdMP in the putamen (29%) and caudate (20%) were observed. Brainstem, Thalamus and putamen region of brain displayed, the reduce level of rCMRglu, the area of decreased metabolism extended from cerebellar midline structures to adjacent pons and midbrain. An increased metabolism was observed in the superior and middle temporal gyri. The loss of DAT observed in SCA 3 patients but it was less severe in comparison to patients with SCA 2. The loss of dopaminergic cells and global synaptic impairment might contribute to the alterations of DATs in SCA 3 patients. Reduced rCMRglu level was observed in the putamen region of patients with SCA 6. Differentiated brain regions with the increase and decrease metabolic activity were observed in temporal gyri (superior, middle) and Cerebellum respectively in patients with SCA 6.[31] A study done by Bing-wen Soong and Ren-shyan Liu in asymptomatic gene carriers of MJD demonstrate a regional decrease in brain glucose metabolism. They used positron emission tomography (PET) with [18F]-2-fluoro-2-deoxy-D-glucose (FDG) to record the metabolic changes in the asymptomatic carrier.[32]

4.5 Molecular and Genetic

Molecular and genetic testing techniques depend on the diverse types of mutation implicated in different SCAs types. The most common type of mutation is trinucleotide (CAG) repeats found in coding regions of genes in SCA 1, 2, 3, 6, 7, 17 and DRPLA. Bidirectional transcribed CTG and CAG repeats in 3'UTR ATXN8OS region as well as ORF ATXN8 region found in SCA 8. The nontranslated mutation found in SCA 10, SCA 12 and SCA 31, pentanucleotide repeat ATTCT and TGGAA found in the intronic region of SCA 10 and SCA31 respectively, CAG repeats present in 5'UTR of SCA 12. Hexanucleotide repeats GGCCTG found in the intronic region of genes in SCA 36. The conventional mutations (missense, deletion, duplication and frameshift) has reported in SCA type 5, 11, 13, 14, 15, 16, 20,21,23,26, 27, 28, 29,34, 35, 38, 40 and 42 and DRPLA.[23, 33-50] Table-2 demonstrate the particular mutation and associated SCAs types. The most reliable and popular method of screening of spinocerebellar ataxia is Genetic diagnosis which relies upon Genetic material DNA and molecular techniques. The molecular genetic screening method used in different parts of the world in various races of Human population. In most of the SCAs where the mutation is due to nucleotides repeats, PCR screening technique is used to amplify the mutated region of the genomic fragment, analysis of amplified region is done with gel electrophoresis or automated sequencer.[51-56]

The other molecular techniques include repeat expansion detection (RED) method, Linkage analysis, Whole-Exome sequencing, Whole genome sequencing and whole mitochondrial sequencing. Kerstin Lindblad et al. used the RED method to detect CAG repeats in SCA 7 patients and in their family, in the RED method they used thermostable DNA ligase to detect repeats directly from DNA.[57] Lourdes Martorell et al. detected CAG/CTG expansion in SCA 1 and MJD patients by using the RED method.[58] The detection of CAG repeat expansion in MJD patients by RED method demonstrated in another publication by Kerstin Lindblad et al.[59] A published work of Kokoro Ozaki et al. and Je´ro^me Delplanque et al. demonstrate the use of linkage analysis in determination of mutation in SCA 34 and SCA 21 respectively. In the Genome-wide linkage analysis, they used SNP array chip for mutation detection. Most of the SCAs which cannot be identified by molecular techniques such as PCR, RED, and linkage analysis method can identify by Whole exome sequencing, whole genome sequencing or whole mitochondrial sequencing. Sequencing technique most preferably used for the identification of Conventional mutations linked SCAs.[23, 36, 37] Numerous combination of molecular techniques and appliances which also include variants of PCR are used for the genetic screening of SCAs.[60-72]

5. Algorithm for the differential genetic diagnosis of SCAs

Differential genetic diagnosis of SCAs depend upon the number of factors, to proceed for the genetic diagnosis it is very much important that the details of clinical history, family history and outcomes of all neurological examination must be known. The first step is to rule out all the acquired (non-genetic) cause of ataxia such as vitamin deficiencies, multiple sclerosis, vascular disease, primary or metastatic tumors, alcoholism, or paraneoplastic diseases associated with occult carcinoma of the breast, ovary, or lung and then proceed for the genetic testing. Figure-3 describe the steps involve in differential genetic diagnosis of SCAs.[23, 73, 74]

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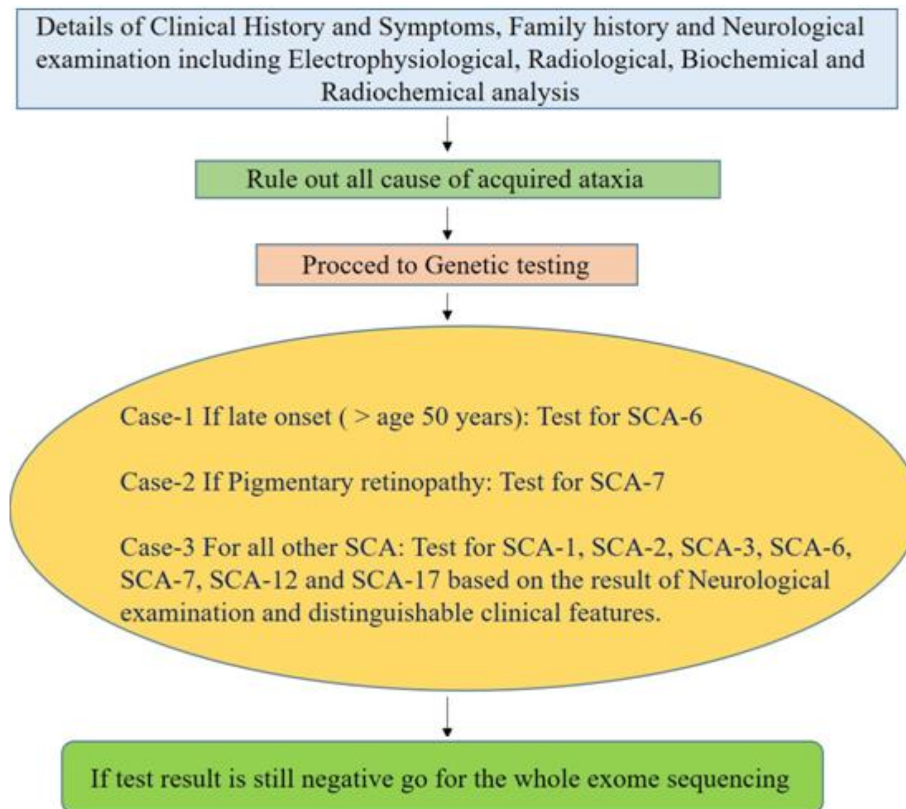

Figure 3: Algorithm for differential genetic diagnosis of SCAs

6. Approaches for the treatment of SCAs

In most of hereditary ataxia, only supportive treatment is possible these includes centrally acting drugs such as 5-hydroxytryptophan, buspirone and physostigmine and thyrotropin-releasing hormone and D-cycloserine.[22] To develop the definite and possible cure for ataxia patients many approach and different experimentation have been carried out and ongoing. A study done by Song Tan et al., in SCA 3 patients determined the potential of Nerve growth factor for the treatment of SCA 3. A clinical assessment of effect of N-acetylcysteine on 18 patients of Spinocerebellar disease by Dr. Roswell Eldridge demonstrate a marked improvement in degrees of ataxia, dysarthria and oculomotor disturbance from disease condition. Jia-Li Jin et al., experimentation on 16 SCAs patients (Genetically diagnosed and confirmed) including SCA-1, SCA 2 and SCA 3 establish the improvement in motor and balancing ability after receiving intrathecal and intravenous infusion of umbilical cord Mesenchymal Stem cells (MSCs). The laboratory examinations demonstrated that the umbilical cord-MSC therapy was safe. In addition to clinical study of human subjects, In vivo and In vitro studies on Cell lines and Animal Models determine the possibilities of cure in Human subjects. A study by Vladimir F. Lazarev et al., in Cell and Fly model of spinocerebellar ataxia 3 prove the Neuroprotective role of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) binding drugs such as Deprenyl (DEP) and 2-amino-4,7 dimethyl benzothiazole (PGL). GAPDH form the complex with protein with long polyglutamine repeats. Additional approaches which could be possible for the treatment of ataxia enlisted by David D. Bushart et al., in his review paper, These are (1) RNA interference and Antisense Oligonucleotide-based strategies (2) Heat Shock Protein (Hsp) 70 and Hsp 27 activation (3) Use of Histone deacetylase (HDAC) Inhibitor (4) Expression of Calcium binding protein and Inhibitor of Intracellular Calcium release store (5) Dantrolene and Glutamate transport activator (6) Potassium channel modulator and Calcium-activated potassium channel activators. The RNA interference or Antisense oligonucleotide strategies have been used in mouse model of SCA 1, SCA 3 and SCA 7 for silencing of specific mutant allele which leads to the improvement in condition from disease state. It may have relevance for the treatment of SCAs in human subjects. Lymphoblastoid cells derived from SCA 7 patient show reduced expression of Hsp70 and Hsp27, activation of these two proteins may have neuroprotective benefit. In SCA 3 mouse model H3 and H4 histone found to be hypo acetylated it suggest the presence of HDAC over activity, use of HDAC inhibitor Sodium butyrate in SCA 3 mouse model improve Histone acetylation and increase the expression of gene which were suppressed earlier in cerebellum region. HDAC inhibitors may have therapeutic promise for the treatment of some forms of SCA, particularly those which display repressed gene transcription condition. Drug-mediated treatments which increase the glutamate uptake, increase expression of calcium binding proteins, or inhibit intracellular calcium release store and modulate potassium channel might be promising candidates for treating neuronal dysfunction and synaptic physiology across different cause of SCAs. Table-3 summarize the possible available and continuing treatment methods for SCAs with brief description.[75-81]

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Table 3: Possible treatment types of SCA and their descriptions

Treatment Types	Description
Deprenyl (DEP) and 2-amino-4,7-dimethylbenzothiazole (PGL)	Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) binding drugs have neuro-protective activity in cell and fly (Drosophila) model of SCA-3
Human Umbilical derived Mesenchymal Stem cells (MSCs)	Intrathecal and Intravenous injection of Umbilical MSCs to Human ataxia patients (SCA-1, SCA-2 and SCA-3) improve the motor and balancing ability.
N-acetylcysteine	Medication in Spinocerebellar disease patients demonstrate improvement in degrees of ataxia, dysarthria, and oculomotor disturbance from disease condition.
Nerve growth factor (NGF)	Intramuscular injection effective in treating patients with SCA3.
RNA interference based and Antisense oligonucleotide based strategies	Silence specific alleles may have relevance for the treatment of polyglutamine in SCAs.
Heat shock protein (Hsp) 70 and Hsp 27 activation	Hsp70 and Hsp27activators may promote clearance and degradation of polyglutamine proteins, have neuroprotective benefits in SCAs
Histone deacetylase (HDAC) inhibitor	HDAC inhibitors may have therapeutic promise for SCA which display repressed gene transcription.
Molecules increase expression of calcium binding protein or inhibit intracellular calcium release store	It may improve neuronal health and limit calcium-mediated neuronal toxicity
Dantrolene and glutamate transport activator	Improve synaptic physiology
Small-conductance calcium-activated potassium (SK) channel activators	Treatment of neuronal dysfunction

7. Conclusion

This review illustrates the clinical manifestation and available diagnostic methods and treatment of neurodegenerative disorder SCAs. It is very necessary for the individual patients and their family to come to an appropriate diagnosis to confirm the disorder and affected regions of the body. The gold standard test for SCAs is a Molecular and Genetic diagnosis, Although Physiological, Radiological, and Radiochemical methods are not confirmatory tests but it is helpful in the determination of affected brain region and extent of damage occurs to the brain and construction of algorithm for the differential genetic diagnosis of SCAs. These test may also confirm the anticipated consequence to the body as the Nervous system is a master controller of organs and organs associated functions. This review also summarize the outcome of various experimental approaches for the treatment of SCAs.

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Author Profile

Pushpendra Mani Mishra received the Bachelor of Technology in Genetic Engineering from SRM University, Chennai in 2013 and Master of Technology in Biotechnology from Delhi Technological University, Delhi in 2016. He has past research experience from Emerging Pathogen Institute, University of Florida, USA and Institute of Genomics and Integrative Biology-CSIR, New Delhi, India.

Dr. Vimal Kishor Singh, O/I, Stem Cell Research Laboratory, Department of Biotechnology, Delhi Technological University, Delhi, India

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