

The Inherited Ataxias

Introduction

The inherited ataxias are a complex group of neurodegenerative disorders. The clinical phenotype is characterised by a progressive cerebellar ataxia variably associated with neuropathy, ocular abnormalities, pyramidal and extrapyramidal signs, cognitive dysfunction and seizures. In some recessive inherited ataxias there is more widespread multisystem involvement. Over the last two decades a tremendous collaborative effort has resulted in the identification of many causative genes for these rare disorders. These genes have led to the implication of a large variety of processes such as polyglutamine neurotoxicity, mitochondrial DNA impairment, RNA processing dysfunction, DNA repair and cellular metabolism failure. Hereditary ataxias can be divided into autosomal dominant, recessive, X-linked and mitochondrial on the basis of the respective inheritance.

Autosomal dominant cerebellar ataxias

The autosomal dominant cerebellar ataxias (ADCA) or spinocerebellar ataxias (SCA) are a group of conditions for which twenty eight loci have been identified to date (Table 1). Disease onset is usually between 30 and 50 years of age, although early onset in childhood and onset after 60 years have been reported. The prognosis is variable depending on the underlying cause of the spinocerebellar ataxia subtype. The most common among these conditions SCA1, 2, 3 and 6, together with 7, 17 and DRPLA are caused by the expansion of a CAG repeat sequence within the coding region of specific genes. The CAG sequence encodes an abnormal polyglutamine (polyQ) tract in the encoded proteins named ataxins 1, 2, and 3 (SCA1,2,3), alpha 1A-voltage-dependent calcium channel (SCA6), ataxin 7 (SCA7), TATA box binding protein (SCA17), and atrophin 1 (DRPLA) respectively. These SCAs have several common clinical-pathological features. The second group of SCAs, including SCAs 8, 10, and 12, are caused by a repeat expansion located outside of the coding region of the disease genes leading to dysregulation of gene expression. While the molecular mechanisms underlying SCAs 8 and 10 are unclear, SCA12 appears to be caused by dysregulation of the activity of the crucial enzyme protein phosphatase 2 (PP2) in cerebellar Purkinje cells. Cerebellar ataxia and neurodegeneration in SCAs 5, 13, 14, and 27, are caused by alterations in amino acid composition in beta-III spectrin (SPTBN2), potassium channel KCNC3, protein kinase C (PRKCG) and fibroblast growth factor 14 (FGF14) respectively. The genes and, therefore, the mutations that cause the remaining SCAs have yet to be identified and characterised.

In the pre-genomic era, ADCAs have been particularly controversial in terms of nomenclature and classification. Harding first proposed a classification based on the clinical symptoms. She grouped them in three main categories (Table 2).¹ So far Harding's classification has not

been overridden by the genetic classification and is still valuable as a guideline in clinical practice and to prioritise genetic tests for diagnosis. ADCA type I is characterised by ataxia of the gait variably associated with ophthalmoplegia, pyramidal and extra pyramidal signs, cognitive impairment, optic atrophy, or peripheral neuropathy. The clinical features in this group of ataxias are caused by a combination of degeneration of the cerebellum, basal ganglia, cerebral cortex, optic nerve, pontomedullary systems, spinal tracts, or peripheral nerves. ADCA type II is distinct from ADCA type I by the presence of pigmentary retinopathy. A third group, ADCA type III includes relatively pure cerebellar ataxias where the degenerative process is limited to the cerebellum. ADCAs I and III are clearly genetically heterogeneous, whereas at least two different genes are associated with ADCA II. The vast majority of ADCA II families seem to be caused by SCA7 (Table 2).²

Spinocerebellar ataxias are rare disorders. Epidemiological studies have found prevalence rates between 0.9-3.0:100.00.^{3,4} In some geographically isolated regions, the frequency is much higher due to a "founder effect"⁵ for example in Cuba, the Azorean island Flores and in the south of Italy for SCA 2, 3 and 1 respectively (⁵ Giunti unpublished data). The most common types worldwide among the SCAs are SCA1, 2, 3 and 6. These four conditions account for at least 57% of all SCA families.⁶⁻⁷ The following section focuses on the clinical and genetic features of the SCAs due to CAG expansion.

SCAs due to expanded CAG repeats

SCA1, SCA2, SCA3, SCA6, SCA7 and DRPLA have common clinical and genetic features. Longer expansions are associated with an earlier onset and more severe progression of disease. CAG repeats are unstable and tend to expand further mainly through paternal transmission. This leads to a more severe phenotype and an earlier age at onset in successive generations (a phenomenon called anticipation). Anticipation is rarely observed in SCA6 where the CAG tends to be smaller and more stable.

Another common feature among these disorders is the progressive neurodegeneration of specific neuronal subsets with the formation of polyQ-containing protein aggregates leading to characteristic nuclear or cytoplasmic inclusions.⁸

In SCA1 the cerebellar ataxia is associated with pyramidal sign, ophthalmoplegia, and, in later stages, with sensorimotor peripheral neuropathy and extrapyramidal features. In SCA2, slow saccades and the absence of tendon reflexes characterise the clinical picture. There are reported families with parkinsonism and other extrapyramidal disorders such a dystonia. SCA3 has the most variable presentation. The most common phenotype is characterised by cerebellar ataxia and pyramidal signs although it may present with parkinsonism associated



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The inherited ataxias are a complex group of neurodegenerative disorders

Table 1: Genes/loci and molecular defects accounting for the SCAs.

*SCAs 19 and 22 are likely allelic forms of the same gene. ** The gene encoding puratrophin 1 lies on the same chromosomal region of SCA4 gene. D, deletions; MM, missense mutations; SNS, single nucleotide substitutions; U, unknown. (modified from reference 2).

SCA subtype	Chromosomal location	Gene/Locus	Protein	Mutation	Main clinical features
SCA1	6p22.3	ATXN1	Ataxin 1	CAG repeat	Ataxia, pyramidal signs, neuropathy, ophthalmoplegia
SCA2	12q24.13	ATXN2	Ataxin 2	CAG repeat	Ataxia, slow saccades, neuropathy
SCA3	14q32.12	ATXN3	Ataxin 3	CAG repeat	Ataxia, pyramidal signs, ophthalmoplegia, neuropathy, dystonia
SCA4	16q24-qter	SCA4	U	U	Ataxia, sensory neuropathy
SCA5	11q13.2	SPTBN2	Beta-III spectrin	D, MM	Almost pure cerebellar ataxia
SCA6	19p13.13	CACNA1A	CACNA1A	CAG repeat	Almost pure cerebellar ataxia
SCA7	3p14.1	ATXN7	Ataxin 7	CAG repeat	Cerebellar ataxia, pyramidal signs, pigmentary maculopathy
SCA8	13q21	KLHL1AS	Kelch-like 1	CTG repeat	Ataxia, sensory neuropathy
SCA9	Reserved	U	U	U	
SCA10	22q13.31	ATXN10	Ataxin 10	ATTCT repeat	Ataxia and epilepsy
SCA11	15q14-q21.3	SCA11	U	U	Almost pure cerebellar ataxia
SCA12	5q32	PPP2R2B	PPP2R2B	CAG repeat	Ataxia, tremor
SCA13	19q13.33	KCNC3	KCNC3	MM	Ataxia, mental retardation
SCA14	19q13.42	PRKCG	PRKCG	MM	Ataxia, myoclonus dystonia
SCA15	3p24.2-pter	ITRP1	ITRP1	D	Almost pure cerebellar ataxia
SCA16	8q23-q24.1	U	U	U	Almost pure cerebellar ataxia
SCA17	6q27	TBP	TBP	CAG repeat	Ataxia, chorea, psychiatric manifestations, dementia, epilepsy
SCA18	7q31-q32	U	U	U	Ataxia, sensory neuropathy
SCA19*	1p21-q21	U	U	U	Ataxia, myoclonus, cognitive impairment
SCA20	11	U	U	U	Ataxia, disphonia
SCA21	7p21.3-p15.1	U	U	U	Ataxia, parkinsonism
SCA22*	1p21-q23	U	U	U	Ataxia
SCA23	20p13-p12.2	U	U	U	Ataxia, sensory neuropathy
SCA24	1p36	U	U	U	Almost pure cerebellar ataxia
SCA25	2p21-p15	U	U	U	Ataxia, sensory neuropathy
SCA26	19p13.3	U	U	U	Almost pure cerebellar ataxia
SCA27	13q33.1	FGF14	FGF14	MM	Ataxia tremor mental retardation
SCA28	18p11.22-q11.2	U	U	U	Ataxia, ophthalmoplegia
DRPLA	12p13.31	ATN1	Atrophin 1	CAG repeat	Ataxia, myoclonus, seizures, psychiatric manifestation, dementia
Undefined**	16q22.1	PLEKHG4	Puratrophin 1	5' SNS	Ataxia, sensory neuropathy

with sensory motor peripheral neuropathy even a spastic paraparesis with minimal cerebellar ataxia. SCA6 typically has a pure phenotype but dystonia or parkinsonism have been described. SCA7 is characterised by maculopathy, cerebellar degeneration and pyramidal signs. The maculopathy can precede the appearance of the cerebellar ataxia by up to 20 years. SCA17 is distinguished by pronounced cognitive impairment/psychosis and behavioural changes plus parkinsonism, chorea and seizures in addition to cerebellar ataxia. DRPLA is very rare and the phenotype is variable, with dementia, psychosis, seizures, chorea and myoclonus and can mimic Huntington's disease.

The autosomal recessive ataxias

The autosomal recessive ataxias are a group of neurodegenerative disorders with early onset (<20 years).¹ However, since genetic tests have been introduced in clinical practice, it has become apparent that the age at onset can be variable (e.g. presentation of Friedreich's

ataxia or AOA2 in adulthood).

Pathogenetically they can be divided into two main categories:

1. Lack of energy control and oxidative stress are the main underlying mechanisms that lead to neurodegeneration. This group includes Friedreich's ataxia (FRDA), ataxia with isolated vitamin E deficiency (AVED), abetalipoproteinaemia and Cayman ataxia.
2. Defects in DNA repair and processing. This group includes ataxia telangiectasia (AT) and AT-like disease, Nijmegen breakage syndrome, AOA1, AOA2 and spinocerebellar ataxia with peripheral neuropathy (SCAN) (Table 3).

Friedreich's ataxia

FRDA is the most common inherited spinocerebellar ataxia with estimated prevalence of one in 30,000-50,000 in the Caucasian population and carrier frequency of 1 in 85.⁹⁻¹⁰

FRDA is rare in American Indian, African and Asian populations.¹¹

In more than 95% of the patients it is caused by a homozygous GAA repeat expansion in the first intron of the FRDA gene.¹² The remaining 2-5% are compound heterozygotes for one GAA expansion and a micro deletion or point mutation on the other allele. Therefore genetic testing is widely available and to date there have been no reported cases of two point mutations. Age at onset is between 5-25 years of age. There are two main phenotypes. Early onset FRDA is characterised by ataxia, deep sensory loss, hyporeflexia, nystagmus, extensor plantars, optic atrophy and deafness which is variably associated with scoliosis, cardiomyopathy and diabetes. MRI in these cases shows cervical spinal cord atrophy with normal cerebellum. The second phenotype, which has onset of ataxia after 25 years of age, is associated with pyramidal features and retained tendon reflexes. The MRI shows mild midline cerebellar atrophy.

Table 2: Modified Harding's classification of ADCAs. **A British ADCAII family negative for the SCA7 mutation has been reported.²

ADCA Type	ADCA I	ADCA II	ADCA III
Clinical Presentation	Cerebellar syndrome with ophthalmoplegia / pyramidal / extrapyramidal signs / cognitive impairment / peripheral neuropathy	Cerebellar syndrome with pigmentary retinopathy	Pure cerebellar syndrome
Neuropathology	Degeneration of the cerebellum, with basal ganglia / cerebral cortex / optic nerve / ponto-medullary systems / spinal tracts / peripheral nerves	Cerebellar and pigmentary retinal degeneration	Cerebellar degeneration
Genetic loci	SCAs 1, 2, 3, 4, 8, 10, 12, 13, 17, 18, 19/22, 20, 21, 23, 24, 25, 27, 28, DRPLA	SCA7**	SCAs 5, 6, 11, 14, 15, 16, 26

Table 3: Genes/loci and molecular defects accounting for autosomal recessive ataxias.

AR = autosomal recessive; D = deletions; I = insertions; MM = missense mutations; NM = nonsense mutations; FM = frameshift mutations.

AR ataxias	Genomic Location	Gene/Locus	Protein	Mutation	Main clinical features
Friedreich's ataxia	9q13	FRDA	Frataxin	GAA repeat (intronic)	Ataxia sensory loss, Hyporeflexia, cardiomyopathy, diabetes
Ataxia with vitamin E deficiency	8q13.1-13.3	TTPA	Alpha tocopherole transfer	FM/MM	Friedreich like phenotype but with head tremor and retinopathy
Abetalipoproteinaemia	4q24	MTP	Microsomal triglyceride transfer	MM	Friedreich like phenotype but with retinopathy, acanthocytosis Steatorrhea
Cayman ataxia	19p13.3	ATCAY	Caytaxin	MM	Ataxia mental retardation
Ataxia telangiectasia	11q22-23	ATM	Ataxia telangiectasia mutated	D, MM	Telangiectasias, immune deficiency predisposition to cancer increase alpha fetoprotein
Ataxia telangiectasia-like disorder	11q21	MRE11	Meiotic recombination 11	MM/NS	Milder course than AT
Ataxia with oculomotor apraxia (AOA1)	9p13	APTX	Aprataxin	I,D,MM	Ataxia choreoathetosis, oculomotor apraxia, hypolabuminaemia
Ataxia with oculomotor apraxia (AOA2)	9p34	SCAR1	Senataxin	MM/NSM	Ataxia choreoathetosis, neuropathy increased alphafetoprotein/CK
Spinocerebellar ataxia with axonal neuropathy	14q31	TDP1	Tyrosyl-DNA phosphodiesterase1	MM	Ataxia ,neuropathy, hypolabuminaemia, hypercholesterolaemia

The age at onset and severity of disease are inversely correlated with expansion size, and there is a direct correlation with the systemic symptoms.¹³⁻¹⁴ The expansion interferes with the FRDA gene transcript. The size of the smaller allele has a closer relationship to the phenotype because it is the major determinant of the amount of the encoded protein, frataxin.

Frataxin is a mitochondrial protein that appears to be involved in iron handling (storage and transport), biosynthesis of iron-sulphur (Fe-S) centres, oxidative phosphorylation and antioxidant function.¹⁵⁻¹⁸

Treatment trials have focused on antioxidants. An open label trial using CoQ10 and Vitamin E in FRDA patients for four years reported an improvement in cardiac function.¹⁹ Idebenone, a derivate of CoQ10, seems to have an effect on cardiac hypertrophy but not on cardiac function.²⁰ However, it is unclear if antioxidants affect neurological symptoms.

Ataxia with isolated vitamin E deficiency

AVED is caused by a mutation in the alpha-tocopherol transfer protein responsible for transport of the vitamin E into very-low density lipoproteins. Vitamin E in the plasma is reduced to less than 10%.²¹

This condition is more prevalent in North Africa and in the Mediterranean population.²² The phenotype is similar to FRDA with early onset. Frequently a head tremor with less prominent sensory peripheral neuropathy

and pigmentary retinopathy help distinguish AVED from FRDA.

Different mutations are responsible for the severity of the phenotype. Truncating mutations lead to a very early onset and severe progression of the disease. Conversely, missense mutations result in a less severe phenotype.²¹

Vitamin E is an antioxidant; its deficiency causes neurodegeneration through lipid peroxidation of the membranes and oxidative stress.²³ Vitamin E supplementation can modify disease progression and, if the therapy starts early, the occurrence of cerebellar ataxia.

Abetalipoproteinaemia

The disease is due to mutations in the gene that codes for a subunit of the microsomal triglyceride transfer protein (MTP).²⁴ These mutations seem to prevent formation of VLDL, thereby reducing vitamin E level. Vitamins A and K are also reduced due to fat malabsorption. In addition to the neurological signs seen in AVED, acanthocytosis and retinopathy are also present.

Cayman ataxia

Cayman ataxia is a rare form of cerebellar ataxia identified in an inbred population of the Gran Cayman Island.²⁵ Affected individuals are homozygous for mutations in the ATCAY gene encoding caytaxin. The protein is similar to the alpha-tocopherol binding protein. Patients with this condition present early onset hypotonia, cerebellar ataxia and psy-

chomotor retardation. Neuroimaging shows atrophy of the cerebellum.

Ataxia telangiectasia

AT is a common recessive ataxia with prevalence of 1 per 100,000 live births in the USA.²⁶ Typically the age at onset is before five years and progression is rapid with significant deterioration within a few years. The clinical features are oculocutaneous telangiectasias, cerebellar ataxia, immune defects and an increase risk of malignancy, especially leukaemia. A high serum alpha fetoprotein is present. In AT, cells are hypersensitive to ionising radiation which can be a useful diagnostic test.

AT is caused by mutations in the ATM gene.²⁷ The protein encoded by this gene is involved in transduction, in mitogenic signals and meiotic recombination cell-cycle control regulating responses through other tumour suppression proteins P53, CHK1 and CHK2.²⁸

The ataxia telangiectasia-like disorder (ATLD) is clinically very similar to AT. Age of onset is later and the progression less severe. It is distinct from AT by the absence of telangiectasia and high alpha fetoprotein. Another similar condition to AT is the Nijmegen syndrome(NBS)²⁹ characterised by microcephaly and psychomotor delay development. ATLD and NBS are due to mutations in the MRE11 and NBS1 genes respectively. Both of these proteins are involved in DNA repair. There is only symptomatic treatment for all these conditions.

Ataxia with oculomotor apraxia (AOA)

This syndrome has two distinct conditions, AOA type 1 and 2. Both AOA1 and AOA2 have onset later than AT, usually above 7 in AOA1 and 10 in AOA2, although adult onset has been reported.³⁰ AOA1 and AOA2 are caused by mutations in aprataxin (APTX) and in senataxin (SETX) respectively. Cerebellar ataxia and sensory motor peripheral neuropathy are common findings. Oculomotor apraxia is common in AOA1 and occurs in nearly half of patients with AOA2. Extrapyramidal signs, such as chorea and dystonia are present, in addition to mild cognitive impairment. In contrast to AT, neither AOA1 or 2 have immune disorders nor the tendency to develop cancer. AOA1 has hypoalbuminemia and hypercholesterolemia in AOA1 and increased alpha-fetoprotein and in some cases an increase of CK in AOA2. An allelic variant of AOA2 is a rare form of autosomal dominant juvenile lateral sclerosis (ALSA4).

Genetic counselling

In autosomal dominant ataxia, 50% of the offspring, independent of sex, will inherit the

mutant allele. However, genetic counselling is complex. In SCA families there is a large inter and intra-familial phenotypic variability, largely, but not entirely due to the CAG repeat instability.

It is particularly challenging when the CAG repeat is highly unstable, for example in SCA7. In this condition, it is not uncommon for an affected individual to have no family history or in some cases the presence of a late onset visual failure without cerebellar ataxia in one of the grandparents.

Genetic counselling is also problematic for subjects with intermediate alleles that have the potential to expand in future generations. Pre-symptomatic and pre-natal testing are also more difficult when the disorder is inherited from an affected father. SCA8 represents a particular problem for genetic counselling as neither the size nor penetrance of pathogenic alleles is known with any certainty. Several ADCA families have been reported in which a SCA8 expansion does not segregate with the affected phenotype. Subjects with the expansion remain unaffected in old age.³¹ Until further clarification on the pathogenesis of this mutation

becomes available, in the authors opinion, SCA8 genetic testing for diagnostic and pre-symptomatic purposes is inappropriate.

Genetic counselling for the recessive ataxias is more straightforward. In a family with one affected child, the risk to subsequent pregnancies is 1 in 4. Two thirds of unaffected siblings will be carriers. Where a genetic test is available, prenatal diagnosis and carrier screening can be carried out.

Conclusion

The inherited ataxias are a relatively common heterogeneous group of neurodegenerative disorders. In the last two decades a collaborative effort has been successful in identifying the genetic defects that underlie several of these conditions, which have made genetic testing possible. However, a disease modifying treatment is available only for AVED.

Establishing a precise diagnosis is important for clarifying the condition and its prognosis. For the great complexity of these conditions, the multidisciplinary approach is of great value in the management for both patients and their carers.

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References

- Harding AE. Clinical features and classification of inherited ataxias. In: Harding AE and Deufel T, editors. *Inherited ataxias*. Vol 61. New York: Raven, 1993:1-14.
- Duenas AM, Gould R, Giunti P. *Molecular pathogenesis of spinocerebellar ataxias*. Brain 2006;129:1357-70.
- van de Warrenburg B, et al. *Spinocerebellar ataxias in the Netherlands: Prevalence and age at onset variance analysis*. Neurol 2002;58:702-08.
- Craig K, et al. *Molecular epidemiology of spinocerebellar ataxia type 6*. Ann Neurol 2004;55:752-54.
- Silveira I et al. *Trinucleotide repeats in 202 families with ataxia a small expanded (CAG)_n allele at the SCA17 locus*. Arch.Neurol. 2002;59:623-29.
- Moseley M et al. *Incidence of dominant spinocerebellar and Friedreich triplet repeats among 361 ataxia families*. Neurology. 1998;51(6):1666-71.
- Schols L et al. *Autosomal dominant cerebellar ataxias: clinical features, genetics and pathogenesis*. The Lancet Neurol 2004;3(5):291-304.
- Zoghbi and Orr. *Annu Rev Neurosci* 2000;23:217-47.
- Taroni F, Di Donato S. *Pathways to motor incoordination: The inherited ataxias*. Nature reviews 2004;5:641-55.
- Lopez -Aralndis JM et al. *Friedreich's ataxia: an epidemiological study in Valencia, Spain, based on consanguinity analysis*. Neuroepidemiology 1995;14:14-19.
- Cossee M et al. *Evolution of the Friedreich's ataxia trinucleotide repeat expansion: founder effect and premutations*. Proc. Natl. Acad. Sci USA 1997;94:7452-7.
- Campuzano V et al. *Friedreich's ataxia: autosomal recessive disease caused by an intronic GAA triplet repeat expansion*. Science 1996;271:1423-7.
- Durr A et al. *Clinical and genetic abnormalities in patients with Friedreich's ataxia*. N.Enl J Med 1996; 335:1169-75.
- Montermini L et al. *Phenotypic variability in Friedreich ataxia: role of the associated GAA triplet repeat expansion*. Ann Neurol 1997;41:675-82.
- Bradley JL et al. *Clinical, biochemical and molecular genetic correlations in Friedreich's ataxia*. Hum. Mol. Genet 2000;9:275-82.
- Cavadini P et al. *Assembly and iron-binding properties of human frataxin, the protein deficient in Friedreich ataxia*. Hum Mole Gent 2002;11:217-27.
- Babcock M et al. *Regulation of mitochondrial iron accumulation by Yfh1p, a putative homolog of frataxin*. Science 1997;276:1709-12.
- Gakh O et al. *Mitochondrial iron detoxification is a primary function of frataxin that limits oxidative damage and preserves cell longevity*. Hum Mol Genet 2006;15:467-79.
- Hart P et al. *Antioxidant treatment of patients with Friedreich ataxia: four-year follow-up*. Arch Neurol 2005;62:621-6.
- Ribai P et al. *Neurological, cardiological, and oculomotor progression in 104 patients with Friedreich ataxia during long-term follow-up*. Arch Neurol. 2007;64:558-64.
- Ouahuchi K et al. *Ataxia with isolated vitamin E deficiency is caused by mutations in the alpha-tocopherol transfer protein*. Nat. Gent. 1995;9:141-5.
- Cavalier L et al. *Ataxia with isolated vitamin E deficiency: heterogeneity of mutations and phenotypic variability in a large number of families*. Am J Hum Genet 1998;62:301-10.
- Yokota T et al. *Delayed-onset ataxia in mice lacking alpha-tocopherol transfer protein: model for neuronal degeneration caused by chronic oxidative stress*. Proc. Natl. Acad. Sci. 2001;98:15185-90.
- Sharp D et al. *Cloning and gene defects in microsomal triglyceride transfer protein associated with abetalipoproteinemia*. Nature 1993;365:65-9.
- Nystuen A et al. *A cerebellar ataxia locus identified by DNA pooling to search for linkage disequilibrium in an isolated population from the Cayman Islands*. Hum Mole Genet 1996;5:525-31.
- Swift M, et al. *The incidence and gene frequency of ataxia-telangiectasia in the United States*. Am J Hum Genet. 1986;39:573-83.
- Savitsky K et al. *A single ataxia telangiectasia gene with a product similar to PI-3 kinase*. Science. 1995;268:1700-1.
- Fogel BL, Perlman S. *Clinical features and molecular genetics of autosomal recessive cerebellar ataxias*. Lancet Neurol. 2007;6:245-57.
- Ball LG, Xiao W. *Molecular basis of ataxia telangiectasia and related diseases*. Acta Pharmacologica Sinica 2005;26:897-907.
- Criscuolo C et al. *Ataxia with oculomotor apraxia type 1 in Southern Italy: late onset and variable phenotype*. Neurology. 2004;63:2173-5.
- Worth P, Houlden H, Giunti P, Davies MB, Wood N. *Large expanded repeats in SCA8 are not confined to patients with cerebellar ataxia*. Nat Genet. 2000Mar;24(3):214-15.