A new locus for a childhood onset, slowly progressive autosomal recessive spinocerebellar ataxia maps to chromosome 11p15

G J Breedveld, B van Wetten, G D te Raa, E Brusse, J C van Swieten, B A Oostra, J A Maat-Kievit

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The cerebellar ataxias are a heterogeneous group of neurodegenerative disorders, characterised by symptoms and signs of cerebellar degeneration, pyramidal and extrapyramidal features, and variable polyneuropathy. Prominent clinical features are signs of cerebellar ataxia, such as uncoordinated gait and uncontrolled co-ordination of hand, speech, and eye movements, while (extra) pyramidal signs, such as retinal, cardiac, muscle and/or neuronal involvement, are less common. The clinical picture shows a large variation in age at onset and disease progression.

Sporadic ataxias may be attributed to various toxic, inflammatory, paraneoplastic, metabolic, endocrinal, or malabsorption conditions. Hereditary ataxias consist of a large number of autosomal dominant ataxias and ataxias with an autosomal recessive and X-linked mode of inheritance. The remaining ataxias of unknown cause are referred to as idiopathic sporadic cerebellar ataxias.

Most symptomatic ataxias can be diagnosed on the basis of a typical history or by simple laboratory tests. In hereditary ataxias family history is important. However, a negative family history cannot rule out autosomal recessive or X-linked ataxia and even autosomal dominantly inherited ataxia may be missed because of reduced penetrance, the early death of gene carriers before the onset of symptoms, imprinting effects, variable expression, adoption, or non-paternity.¹

Gene defects have been identified for several hereditary forms. Autosomal dominant ataxias are often associated with genes containing unstable expanded trinucleotide repeats, such as polyglutamine-coding CAG repeat expansions in SCA 1, 2, 3, 6, 7, 17 and DRPLA, or trinucleotide or pentanucleotide repeat expansions in (non-) coding regions in SCA 8, 10, and 12. Other mutations have been identified, such as point mutations in FGF14 and SCA14, and several loci, such as SCA 4, 5, 11, 13, 15, 16, 18, 19, 21, 22, 23, and 25 have been mapped.^{2–5} Some autosomal recessive ataxias have been clinically characterised, their genes localised, or their genes and their proteins identified (table 1).^{2–4} The most common form (11–38%) of autosomal recessive ataxia is Friedreich's ataxia (FRDA),^{5–8} which shows a large variation in clinical presentation, that is age at onset and severity of clinical symptoms. Other forms of autosomal recessive ataxia are ataxia teleangiectasia (AT)⁹ or AT-like disorders,¹⁰ ataxia with isolated vitamin E deficiency (AVED),¹¹ abetalipoproteinaemia (ABL),¹² spastic ataxia of Charlevoix-Saguenay (ARSACS),^{13–14} infantile onset spinocerebellar ataxia (IOSCA),¹⁵ ataxia with oculomotor apraxia (AOA1 and 2),^{16–17} and Refsum's disease (RD).^{18–19} Furthermore, inherited metabolic disorders can cause ataxia-like carbohydrate deficient glycoconjugate syndrome,^{20–21} GM₂ gangliosidosis,²² and other disorders (table 1).^{2–4}

Some forms of autosomal recessive ataxia have a specific geographical distribution: the southern Mediterranean area

Key points

- Here we report a non-consanguineous Dutch family with a pure spinocerebellar phenotype with cerebellar ataxia, pyramidal signs, posterior column involvement with deep sensory loss, a postural tremor, and absence of other (non-) neurological features. Neuroimaging shows atrophy of the cerebellum, vermis, pons, and medulla oblongata. Onset of symptoms is in early childhood but, remarkably, the severity of symptoms and progression of the disease within this family is very variable.
- The clinical phenotype of the family is not consistent with any of the known autosomal recessive cerebellar ataxias.
- Using a systematic genome wide scan we mapped the responsible gene for autosomal recessive ataxia in this family to a 5.9 cM interval on chromosome 11p15. A large number of genes and expressed sequence tags are identified in this critical region, but no obvious candidate gene can yet be assigned, as genes for ataxia mostly have different functions and features.

in AVED, Canadian families of French origin in ARSACS, and Finland for IOSCA, while AOA is frequent in Portugal and in Japan and RD is more frequent in the Scandinavian population. The genes and their cognate proteins are known in these autosomal recessive ataxias, except for IOSCA, which has only been localised (10q23–q24).¹⁵ In other forms pathognomonic clinical features may sometimes help to establish the clinical diagnosis: myoclonus and/or epilepsy in progressive myoclonus epilepsy,²³ cataract in Marinesco-Sjogren syndrome,²⁴ retinitis pigmentosa in dorsal column ataxia with retinitis pigmentosa,²⁵ hypogonadism in Holmes syndrome,^{26–27} and chorea in chorea-acanthocytosis²⁸ (table 1). Also there are some inbred families with autosomal recessive ataxia, such as Cayman Island ataxia,²⁹ two Lebanese families with non-progressive congenital cerebellar ataxias,^{30–31} and a Norwegian family with an infantile autosomal recessive inherited ataxia³² (table 1).

Abbreviations: ABL, abetalipoproteinaemia; AOA, ataxia with oculomotor apraxia; ARSACS, spastic ataxia of Charlevoix-Saguenay; AT, ataxia teleangiectasia; AVED, ataxia with isolated vitamin E deficiency; CDG 1a, carbohydrate deficient glycoconjugate syndrome 1a; CMAP, compound muscle action potential; CTX, cerebrotendinous xanthomatosis; FRDA, Friedreich's ataxia; IOSCA, infantile onset spinocerebellar ataxia; MLD, metachromatic leucodystrophy; MSU, maple syrup urine disease; NCV, nerve conduction velocity; PCARP, posterior column ataxia with retinitis pigmentosa; RD, Refsum's disease

Table 1 The Autosomal recessive ataxias, their loci, genes, proteins, onset and distinguishing features²⁻⁴

Autosomal recessive syndrome(s) (references)	Locus	Gene	Protein	Age at onset (years)	Distinguishing features
Friedreich's ataxia 1 (FRDA1)/2 (FRDA2) ^{5 6 7 40}	9q13/9p23	X25/ –	Frataxin/ –	4–40	Hyporeflexia, positive Babinski sign, deep sensory loss, cardiomyopathy, diabetes mellitus, scoliosis
Ataxia teleangiectasia (AT)/AT-like ^{9 10}	11q22–23/11q21	ATM/hMRE11	Phosphatidylinositol 3-kinase/hMRE11 protein	0–20	Teleangiectasia, immune deficiency, cancer, chromosomal instability, elevated AFP
Vitamin E deficiency (AVED) ¹¹	8q13	α -TTP	α -Tocopherol transfer protein	2–52 (<20)	As FRDA but rare cardiomyopathy and diabetes, head titubation
Abetalipoproteinaemia (ABL) ¹²	4q22–24	MPT	Microsomal triglyceride transfer protein	2–52	Steatorrhea, areflexia, retinitis pigmentosa, acanthocytosis, low cholesterol and β -lipoproteins
Spastic ataxia Charlevoix-Saguenay (ARSACS) ^{13 14}	13q12	SACS	Sacsin	Childhood	Spasticity, polyneuropathy, striated retina, mitral valve prolapse
Infantile onset spinocerebellar ataxia (IOSCA) ¹⁵	10q24	–	–	½–1 ½	Ophthalmoplegia, hypotonia, hypacusis, athetosis, peripheral neuropathy
Ataxia with oculomotor apraxia 1 (AOA1)/2 (AOA2) ^{16 17}	9p13/9q34	APTX/SETX	Aprataxin/senataxin	2–18/10–22	Oculomotor apraxia, chorea-athetosis, hypoalbuminaemia, sensory neuropathy, elevated AFP, CPK and cholesterol
Refsum's disease (RD) ^{18 19 41}	10p11-pter, 6q22–24	PHYH, PEX7	Phytoanoyl-CoA hydroxylase, peroxin 7	Childhood	Retinitis pigmentosa, deafness, polyneuropathy, cardiomyopathy, elevated phytanic acid
Carbohydrate deficient glycoconjugate syndrome 1a (CDG 1a) ^{20 21}	16p13	PMM2	Phosphomannomutase 2	Childhood	Hypotonia, mental retardation, failure to thrive, lipodystrophy, hepatic dysfunction, polyneuropathy, retinitis pigmentosa
Tay-Sachs disease (GM ₂ gangliosidosis) ^{22 42}	15q23–24	HEXA	Hexosaminidase A	Child/adulthood	Mental retardation, cherry red spot, blindness, epilepsy, hypotonia, startle response, low hexosaminidase A
Krabbe ⁴³	14q31	GALC	Galactosylceramidase	Child/adulthood	Mental retardation, polyneuropathy, optic atrophy, epilepsy, low galactocerebroside
Metachromatic leucodystrophy (MLD) ⁴⁴	22q13	ARSA	Arylsulfatase A	Child/adulthood	Mental retardation, polyneuropathy, spasticity, optic atrophy, epilepsy, psychiatric symptoms, low arylsulfatase
Wilson's disease ⁴⁵	13q14–21	ATP7B	ATPase Cu transporting β polypeptide	10–30	Liver cirrhosis, Kayser-Fleischer rings, arthritis, nephrocalcinosis, high calcium, low ceruloplasmin, high copper
Cerebrotendinous xanthomatosis (CTX) ⁴⁶	2q33-ter	CYP27A1	Cytochrome 450, subfamily27A1	10–20	Cataract, premature atherosclerosis, spasticity, xanthoma, xanthelasmata, cholesterol and cholestanol elevated
Hartnup ⁴⁷	5p15	–	–	Child/adulthood	Pellagra, emotional instability, aminoaciduria
Maple syrup urine disease (MSU) ⁴⁸	19q13	BCKDHA	Branched chain keto acid dehydrogenase E1 α	Newborn/child	Feeding problems, epilepsy, mental retardation, hypoglycaemia, ketosis
Biotinidase deficiency ⁴⁹	3p25	BTD	Biotinidase	1–2	Hypotonia, epilepsy, optic atrophy, hearing loss, skin rash, alopecia, ketoacidosis, organic aciduria
Carnitine acetyltransferase deficiency ⁵⁰	9q34	CRAT	Carnitine acetyltransferase	Childhood	Hypotonia, mental disturbances, oculomotor palsy, failure to thrive
Gamma-glutamyl cysteine synthetase ⁵¹	6p21	GCLC	Gamma-glutamyl cysteine synthetase	Adult	Haemolytic anaemia, myopathy, polyneuropathy
L-2 Hydroxyglutaric acidemia ⁵²	–	–	–	Childhood	Mental retardation, short stature, leucodystrophy, macrocephaly
Niemann-Pick C ⁵³	18q11–12	NPC1	NPC1 protein	Child/adulthood	Epilepsy, spasticity, hepatosplenomegaly, dementia, psychiatric symptoms
Progressive myoclonus epilepsy (Baltic or Unverricht-Lundborg) ²³	21q22	CSTB	Cystatin B	6–13	Epilepsy, myoclonus, mental deterioration
Marinesco-Sjogren syndrome ²⁴	5q31	MSS	–	Childhood	Cataract, myopathy, hypotonia, short stature, microcephaly, mental retardation, hypergonadotropic hypogonadism
Posterior column ataxia with retinitis pigmentosa (PCARP) ²⁵	1q31–32	AXPC1	–	Childhood	Deep sensory loss, retinitis pigmentosa, areflexia
Boucher Neuhauser syndrome ⁵⁴	–	–	–	10–20	Hypogonadotropic hypogonadism, chorioretinal dystrophy
Holmes syndrome ^{26 27 55}	–	–	–	10–30	Hypogonadotropic/hypergonadotropic hypogonadism
Ataxia with neuronal migration defect ⁵⁶	16q12–22	BFPP	–	Congenital	Bilateral frontoparietal polymicrogyria, mental retardation, epilepsy
Ataxia with deafness and mental retardation ⁵⁷	–	–	–	Congenital	Deafness, mental retardation
Ataxia with saccadic intrusions ⁵⁸	–	–	–	>30	Saccadic intrusions, myoclonic jerks, spasticity, deep sensory loss, fasciculations, pes cavus
Ataxia with optic atrophy and deafness ⁸	6p21–23	–	–	Childhood	Deafness, optic atrophy
Leukoencephalopathy with vanishing white matter ⁵⁹	12/14q24/1//2p23/3q27	EIF2B1, B2, B3 B4, B5	Translocation initiation factor eIF2B 5 subunits	Child/adulthood	Leucodystrophy, ovarian failure, optic atrophy, motor deterioration, epilepsy
Ataxia with axonal neuropathy (SCAN1) ⁶⁰	14q31–32	TDP1	Tyrosyl-DNA phosphodiesterase 1	Child/adulthood	Axonal polyneuropathy, pes cavus
Ataxia with laryngeal abductor paralysis and motor neuropathy ⁶¹	–	–	–	Adult	Dysphonia, motor neuropathy
Ataxia adult onset with thalamic lesions ⁶²	–	–	–	>30	Hyporeflexia, deep sensory loss, axonal polyneuropathy, mild cognitive impairment, bilateral thalamus lesions

Table 1 Continued

Autosomal recessive syndrome(s) (references)	Locus	Gene	Protein	Age at onset (years)	Distinguishing features
Xeroderma pigmentosum A-G ⁶³	9q22, 2q21, 3p25, 19q13, 11p11-12, 16p13, 13q32-33	XPA, XPB, XPC, XPD, XPE, XPF, XPG	–	Child/adulthood	Defective DNA repair, skin atrophy, teleangiectasia, skin cancer, mental retardation
Nijmegen breakage syndrome ⁶⁴	8q21	NBS1	–	Childhood	Microcephaly, short stature, no mental retardation, immunodeficiency, cancer, chromosome instability
Cockayne syndrome a ⁶⁵	5	CKN1	–	Childhood	Retinitis pigmentosa, optic atrophy, short stature, presenile appearance, photosensitivity, deafness
Cerebelloparenchymal disorder II ⁶⁶	–	–	–	>40	Ataxia and dysarthria
Ataxic cerebral palsy ⁶⁷	9p12-q12	–	–	Congenital	Non-progressive ataxic cerebral palsy
Joubert syndrome 1/2 ^{68, 69}	9q34/11p12-q13	JBTS1/CORS2	–/–	Congenital	Vermis hypoplasia, mental retardation, hypotonia, episodic hyperpnea, retinal dystrophy, renal cysts
Behr syndrome ⁷⁰	–	–	–	Childhood	Optic atrophy, mental retardation
Gillespie syndrome ⁷¹	–	–	–	Congenital	Aniridia, mental retardation
Chorea-acanthocytosis ²⁸	9q21	CHAC	Chorein	25–45	Chorea, acanthocytes, epilepsy, peripheral neuropathy, myopathy, self-mutilation, basal ganglia atrophy
Cayman Island ataxia ²⁹	19p13	ATCAY	Caytaxin	Childhood	Hypotonia, mental retardation, non-progressive ataxia
Cerebelloparenchymal disorder III ^{8, 30, 37}	9q34-ter	CLA1	–	Congenital	Short stature, mental retardation
Ataxia, mental retardation, optic atrophy, skin abnormalities (CAMOS) ³¹	15q24–26	CAMOS	–	Congenital	Mental retardation, microcephaly, optic atrophy, short stature, abnormal osmiophilic pattern of skin vessels
Norwegian infantile onset ataxia ³²	20q11–13	CLA3	–	Congenital	No mental retardation, pes planus, short stature, spasticity, non-progressive ataxia

We here describe, using a systematic genome scan, the assignment of a new disease locus to a 5.9 cM interval on chromosome 11p15 in a non-consanguineous Dutch family with childhood onset, slowly progressive autosomal recessive spinocerebellar ataxia without involvement of other (neurological) systems and with variable severity.

METHODS

Patients

A sibship of 12 individuals from a non-consanguineous couple of Dutch descent (fig 1) came to our attention because of the presence of ataxia in five siblings. Their mother, suffering from maturity onset diabetes, died at the age of 86 years and their father at the age of 56 years because of a head trauma: neither they nor their relatives showed ataxia. One of the healthy sibs (III:13) and his daughter (IV:18) were seen for genetic counselling, because they wanted to be informed about their own risk for ataxia and the risk for their children.

Three neurologists (BvW, EB, and JCvS) neurologically investigated all siblings (eight men and four women) and four other closely related family members (fig 1). In addition to clinical evaluation, available medical records and hard copies of neuroimaging were reviewed. All affected individuals except one and one unaffected individual underwent magnetic resonance imaging (MRI) of the cerebrum. An electromyography (EMG) was performed in two patients, and an ophthalmological and neuropsychological examination was performed in one affected individual.

After clinical evaluation five affected individuals (III:7, III:8, III:12, III:15, and III:16) and seven unaffected individuals (III:6, III:9, III:10, III:11, III:13, III:14, and III:17) within the same sibship were defined. Four closely related individuals (IV:18, IV:20, IV:21, and II:3) were found to be without neurological symptoms. Blood samples were collected from 14 individuals (fig 1) of this family. All signed an informed consent under a protocol approved by the Medical Ethics Committee of Erasmus MC, Rotterdam, The Netherlands.

Genomic testing

Genomic DNA was isolated from peripheral leukocytes as described.³³ For the systematic genome scan 381 markers from the ABI Prism Linkage Mapping Set MD 10 (version 2.5) were tested. Additional markers (STRs) for fine mapping were obtained from Marshfield genetic maps 9 and 11³⁴ or newly developed as described.³⁵ STR polymorphisms were amplified using 25 ng genomic DNA in 7.5 µl PCR reactions containing 1×PCR Gold Buffer, 2.5 mM MgCl₂, 10 µM primer pair mix, and 0.4 U AmpliTaq Gold DNA polymerase (Applied Biosystems). Amplification conditions were 10 min at 95°C followed by 35 cycles of 30 s at 95°C; 30 s at 55°C; and 1 min 30 s at 72°C; after a final extension for 5 min at 72°C. PCR products were pooled in panels and loaded on an ABI 3100 automated sequencer. Data were analysed using Gene Mapper Version 2.1 software (Applied Biosystems).

Linkage analysis

Two-point and multipoint linkage analyses were performed using MLINK and LINKMAP.³⁶ Marker order and genetic distances were used from the Marshfield genetic map. LOD scores were calculated assuming ataxia in this family to be an autosomal recessive disorder with 100% penetrance with a gene frequency of 1:2500. No phenocopies were allowed and equal allele frequencies were used because of the limited number of available independent family members.

RESULTS

Clinical data

The first patient (III:15), who was examined at the age of 60, had childhood onset ataxia, causing problems with fine motor movements, tremor of the hands, and slurred speech. His gait became progressively unstable from childhood, and started to interfere with his daily activities after the age of 45. He was able to carry out his work until the age of 48 and became wheelchair dependent at the age of 55. There were no complaints of cognitive impairment or of visual, hearing, or swallowing problems nor did he have weakness or sensory

Figure 1 Pedigree of the family with autosomal recessive spinocerebellar ataxia. Fourteen family members participated in the study, five affected (III:7, III:8, III:12, III:15, and III:16, represented as black symbols in the pedigree) and nine unaffected individuals (II:3, III:6, III:9, III:10, III:11, III:13, III:14, III:17, and IV:18, represented as open symbols in the pedigree). Haplotypes from chromosome 11p15 are shown below the genotyped individuals (black bars indicate risk haplotype and open bars indicate unaffected haplotype). A slash line indicates deceased status.

disturbances in his extremities. Neurological examination showed normal mental status, an upbeat nystagmus, saccadic pursuit eye movements, and cerebellar dysarthria. At inspection fasciculations were present in the forearms, hands, and legs. Neurological examination showed normal strength in all extremities, hypertonia in his legs, and hyperreflexia with Babinski signs bilaterally. Limb ataxia and severe gait ataxia were present with an inability to walk. A low frequency tremor was seen in the hands at rest, increasing with action and intention. Sensory examination showed decreased vibration sense in the legs, indicating impaired posterior column function. Extensive laboratory investigation of acanthocytes, cholesterol, triglycerid, low density lipoproteins, very low density lipoproteins, lactate, pyruvate, thyroid function, vitamin E, lysosomal enzymes, copper and ceruloplasmin, alpha-fetoprotein, and immunoglobulins did not show any abnormalities. An EMG showed a mild decrease of the motor nerve conduction velocity (NCV) of the posterior tibial nerve and compound muscle action potential (CMAP) of the peroneal and median nerve, with absence of the sensible nerve action potential of the sural nerve indicating a very mild axonal polyneuropathy. There

were no signs of denervation or reinnervation in the musculus tibialis anterior, vastus medialis, rectus femoris, or first interosseus. There was a normal H-reflex of the musculus soleus and a normal late F-response, stimulating the medial and peroneal nerve. Ophthalmological examination was normal. MRI of the cerebrum showed atrophy of the cerebellum, vermis, pons, and medulla oblongata (fig 2).

Table 2 summarises the clinical characteristics of the five affected individuals, three males and two females. Mean age at examination was 55.2 years, ranging from 46 to 64 years. The onset of the disease was in childhood. The severity of clinical symptoms (cerebellar ataxia, pyramidal signs, and deep sensory loss) varied from mild to severe. The unaffected family members showed none of the symptoms described in the affected family members. MRI of the cerebrum in the unaffected sibling (III:13) showed no abnormalities.

An autosomal recessive mode of inheritance was assumed as no other affected individuals were found in the extended family. The clinical characteristics of the patients in this family, the variability in severity, and the absence of other (non-) neurological features were inconsistent with any known autosomal recessive syndrome.

Figure 2 MRI scan of the cerebrum of individual III:15 showing atrophy of the cerebellum, vermis, medulla oblongata, and pons.

Table 2 Clinical findings in the affected individuals of the family with autosomal recessive spinocerebellar ataxia (fig 1)					
Patient	III:7	III:8	III:12	III:15	III:16
Sex	M	F	M	M	F
Age at onset (years)	Childhood	Childhood	Childhood	Childhood	Childhood
Age at examination (years)	46	50	56	60	64
Walking	↓ ↓	↓ ↓	(↓ ↓)	↓ ↓ ↓	↓ ↓ ↓
Writing	↓ ↓	↓ ↓		↓ ↓ ↓	↓ ↓ ↓
Nystagmus	-	+	-	+	+
Saccadic pursuit	+	+	-	+	+
Postural tremor	-	-	+	+	-
Dysarthria	+	+	+	+	+
Gait ataxia	+	+	-	+++	+++
Limb ataxia	+	+	+	++	++
Vibration sense	↓	↓	Normal	↓	Normal
Hyperreflexia	+	-	+	+	+
Babinski sign	-	-	-	+	+
EMG	Normal	0	0	Mild axonal neuropathy	0
Neuropsychological examination	Cognitive slowness, mild concentration disturbance	0	0	0	0
MRI scan cerebrum	Atrophy cerebellum and pons	0	Mild atrophy cerebellum and pons	Atrophy cerebellum and pons	Atrophy cerebellum and pons
Ophthalmological examination	0	0	0	Normal	0

+, symptom present; -, symptom absent; 0, not examined; ↓, decreased.

Molecular data

DNA testing for known ataxia genes (SCA 1, 2, 3, 6, 7, DRPLA, FRDA 1) was carried out, but no mutations were found. Several autosomal recessive ataxia loci, such as FRDA 2, ATM, α -TTP, SCAN 1, ARSACS, IOSCA, and AOA 1 and 2 (table 1) were ruled out by testing polymorphic STR markers surrounding these loci (data not shown). A systematic genome scan was started to identify the locus for autosomal recessive ataxia in this family. Markers with positive LOD scores (>1.5) were identified in several chromosomal regions. To exclude or confirm linkage in these regions haplotype analysis was performed and if necessary additional markers were tested from the Marshfield genetic map. Except for loci on chromosomes 9q34 and 11p15 all other chromosomal regions could be excluded. On chromosome 9q34 the region between the markers D9S1856 and D9S279 (0 cM distance of about 500 kb) could not be excluded because markers in this region were uninformative. Also new STR markers, developed from BAC sequences in between, did not confirm or exclude linkage in this region. Testing of additional markers on chromosome 11p15 resulted in the identification of significant linkage of autosomal recessive

ataxia to chromosome 11p15. Both markers D11S1758 and D11S1871 showed an LOD score of 3.2 (table 3). Multipoint linkage analysis using eight additional markers confirmed the position of the gene defect to chromosome 11p15 with a LOD score higher than 3 in the interval D11S1758–D11S1871 (fig 3). Haplotype analysis on this region, suggesting no phenocopies and 100% penetrance, determined the distal boundary of the critical region by a recombination event in subject III:17 between D11S4088 and D11S1758. The proximal boundary is determined by a recombination event in subject III:9 between D11S1338 and D11S1331. These recombination events (fig 1) thus map the gene for autosomal recessive ataxia in this family between D11S4088 and D11S1331, a region of 5.9 cM.

DISCUSSION

The present study describes a new locus on chromosome 11p15 for an autosomal recessive spinocerebellar ataxia in a Dutch family. An autosomal recessive mode of inheritance is assumed as no other affected individuals were found in the extended family. The number of affected siblings in generation III (five out of 12) in this family could suggest an

Figure 3 Multipoint LOD-score analysis of autosomal recessive spinocerebellar ataxia with several markers on chromosome 11p15. The x axis represents the chromosomal position of the markers, indicated as black triangles. Markers from left to right: D11S1318, D11S1758/D11S4088, D11S4146, D11S4181, D11S1871, D11S1760, D11S1331/D11S1338, D11S4149. The y axis indicates the multipoint LOD score.

Table 3 Two-point LOD score table of selected chromosome 11 markers

Marker	Recombination fraction (θ)						
	0	0.01	0.05	0.1	0.2	0.3	0.4
D11S1318	−∞	1.52	1.962	1.931	1.532	0.958	0.334
D11S4088	−∞	1.521	1.962	1.931	1.532	0.958	0.334
D11S1758	3.283	3.218	2.953	2.612	1.9	1.145	0.393
D11S4146	1.175	1.157	1.083	0.982	0.746	0.466	0.165
D11S4181	1.476	1.452	1.352	1.22	0.923	0.581	0.212
D11S1871	3.284	3.218	2.953	2.612	1.9	1.146	0.396
D11S1760	1.477	1.453	1.353	1.22	0.922	0.58	0.212
D11S1338	1.651	1.624	1.509	1.357	1.021	0.643	0.238
D11S1331	1.175	1.158	1.083	0.982	0.746	0.466	0.165
D11S4149	−∞	1.512	1.922	1.858	1.416	0.835	0.261

autosomal dominant mode of inheritance with reduced penetrance and/or variable expression and/or an imprinting effect. However, none of the family members in the extended pedigree showed the symptoms described in affected family members, making this mode of inheritance most unlikely. The clinical characteristics of the patients in this family represent a pure spinocerebellar phenotype with cerebellar ataxia, pyramidal signs, and posterior column involvement with deep sensory loss. In two patients (III:12 and III:15) the cerebellar signs were accompanied by tremor of the hands, which can be described as postural tremor. The combination of postural tremor plus limb ataxia has been referred to as ataxic tremor and is part of cerebellar disease. No other features of neurodegeneration were present. Onset of symptoms was in early childhood, with complaints of clumsiness, awkward writing, and sometimes dysarthria and tremor. Remarkably, the severity of symptoms and progression of the disease within this family are very variable. The presenting symptoms in childhood were very subtle in patients III:7, III:8, and III:12, not interfering with their daily activities until around the age of 40. In patients III:15 and III:16, a more progressive course was present since childhood, leading to wheelchair dependence. Early onset and slow progression are not found in most autosomal dominant ataxias or in Friedreich's ataxia. Also the absence of (non-) neurological symptoms such as optic atrophy, deafness, scoliosis, diabetes, fundus abnormalities, and cardiac involvement argues against Friedreich's ataxia or other known ataxias. The clinical phenotype of the family is not consistent with any of the known autosomal recessive syndromes found in the updated genetic classification of autosomal recessive ataxias given in table 1²⁻⁴: this fact motivated us to look for a new gene for autosomal recessive ataxia in this family.

Before starting genome wide screening several kin loci which can cause autosomal cerebellar ataxia were excluded. First, repeat expansions in the SCA 1, 2, 3, 6, 7, DRPLA, and FRDA 1 genes were excluded. Second, autosomal recessive ataxia loci, such as FRDA 2, ATM, α -TTP, SCAN 1, ARSACS, IOSCA, and AOA 1 and 2 (table 1), were ruled out by testing polymorphic STR markers surrounding these loci. Finally, a genome wide screen was initiated which identified several chromosomal regions. Two regions, chromosome 9q34 and chromosome 11p15, could not be excluded after haplotyping and additional markers were tested. A possible region for autosomal ataxia between D9S1856 and D9S279 (0 cM) could not be excluded due to uninformative markers. However, the region does not overlap with the region on 9q34-qter for non-progressive autosomal recessive ataxia described as cerebelloparenchymal disorder type III^{8 30 37} and AOA 2²⁷ (table 1).

Testing of additional markers on the 11p15 region revealed two fully informative markers (D11S1758 and D11S1871)

which showed no recombination with autosomal recessive ataxia in this family. In a multipoint analysis, significant linkage was found in the region between these markers (LOD>3). Haplotype analyses located the disease locus between D11S4088 and D11S1331, a region of 5.9 cM. Except for D11S1871, no markers were homozygous in all patients. Testing of newly developed markers on closely linked sequences showed that this homozygosity was not enlarged, so it is probably caused by inheritance by state rather than by descent (data not shown). In this region no other locus for autosomal recessive ataxia has been described providing further evidence for locus heterogeneity.

Many genes and expressed sequence tags have been identified in the critical region of 5.9 cM (about 5 Mb),³⁸ but no clear obvious candidate gene can be assigned. Molecular genetic research over the last decade has led to a new classification of autosomal dominant ataxias,³⁹ consisting of 25 different types of SCA.^{2 3} In the last few years autosomal recessive ataxias have increasingly been investigated and proven to be genetically heterogeneous (table 1). These genes play a role in metabolic homeostasis, cell cycling, and DNA repair systems. Also chaperone genes involved in recessive ataxias have been described.²⁻⁴

It is difficult to assign a likely candidate gene in this critical region because these genes mostly have different functions and features. As Friedreich's ataxia, a very common form of autosomal recessive ataxia, is mainly caused by a trinucleotide (GAA) repeat in intron 1 of the FRDA gene,⁵ it might be interesting to look for genes with a trinucleotide repeat in their genomic sequences. Determination of the repeat length in patients versus controls in this family might suggest the pathogenic effect leading to autosomal recessive ataxia in this family. Differences in expanded repeat sizes between the affected siblings, due to instability of the expanded repeat when transmitted, could well explain the intrafamilial clinical variability of the ataxia.⁷ Also, testing of additional autosomal recessive families with similar clinical features might reduce the size of the critical region and therefore simplify identification of the genetic defect. Finding the responsible mutation for autosomal recessive ataxia in this family will provide new tools towards diagnosis, understanding of the underlying pathophysiology of this disease, and finally and hopefully, better strategies for therapeutic intervention.

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Authors' affiliations

G J Breedveld, G D te Raa, B A Oostra, J A Maat-Kievit, Department of Clinical Genetics, Erasmus MC, Rotterdam, The Netherlands

B van Wetten, E Brusse, J C van Swieten, Department of Neurology, Erasmus MC, Rotterdam, The Netherlands

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Correspondence to: Dr J A Maat-Kievit, Department of Clinical Genetics, Erasmus MC, Westzeedijk 112, 3016 AH Rotterdam, The Netherlands; j.a.maat@erasmusmc.nl

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