

ELECTRONIC LETTER

Early onset, non-progressive, mild cerebellar ataxia co-segregating with a familial balanced translocation t(8;20)(p22;q13)

J M Hertz, B Sivertsen, A Silahatoglu, M Bugge, V Kalscheuer, A Weber, J Wirth, H-H Ropers, N Tommerup, Z Tümer

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Hereditary ataxia is a clinically and genetically heterogeneous group of disorders. Most are progressive and associated with other neurological abnormalities. Early onset, non-progressive cerebellar ataxia (OMIM #117360) has been described as a dominantly inherited disorder associated with isolated vermal atrophy¹⁻³ or generalised atrophy of the cerebellum.^{4,5} This is a rare entity compared with autosomal recessive early onset cerebellar ataxia with retained tendon reflexes (OMIM #212895).⁶

Various disease genes have been identified using rare disease associated balanced chromosomal rearrangements (DBCRs), for example, translocations or inversions that truncate, delete, or otherwise inactivate genes.⁷ DBCRs may occur in at least 1% of patients with autosomal dominant disorders caused by haploinsufficiency, and in many girls affected by X linked recessive disorders. During a systematic search for apparently balanced chromosomal rearrangements associated with abnormal phenotypes,⁷ we identified a four generation family in which a variable neurological phenotype including an early onset, non-progressive, and mild cerebellar ataxia segregates together with a balanced reciprocal translocation.

MATERIALS AND METHODS

Family history

The study was approved by the local ethics committee (no. 1992-2489). The family consists of four generations as shown in fig 1. All family members, except II:2, were personally interviewed and underwent neurological examination by one of us (BS). The affected members in generations III, IV, and V have developed a phenotype of clumsiness starting in early childhood (1-7 years), including gait abnormalities with lurching and frequent falling, which increased upon physical activity. Objective findings included ataxia, dysmetria on finger to nose and/or heel to shin test, tremor, nystagmus, and retained reflexes in the lower limbs. Neurological symptoms and the phenotype of the affected members are presented in table 1. MRI of two of the patients (III:2 and III:4) performed at 49 and 43 years of age, respectively, gave inconclusive results. Anticipation was not observed in the family.

The disease could be traced back to II:2 as the first known affected person of this family. She was deceased at the time of investigation, but a description of her phenotype could be extracted from medical records. She did not have a history of clumsiness or gait disturbances in childhood, and according to the medical records, the first symptom was sudden blindness of the left eye at the age of 34 years. After a remission period of a few months, she developed weakness of the left hand and loss of dexterity. The disease progressed over a period of years and she developed ataxia. The clinical findings included impairment of vibratory sense in the lower

Key points

- We describe a four generation family in which an early onset, non-progressive, mild cerebellar ataxia segregates with a reciprocal translocation, t(8;20)(p22;q13).
- Affected members show variable neurological symptoms including clumsiness, clumsy gait, tremor, and nystagmus. One of the translocation carriers did not display any neurological symptoms suggesting reduced penetrance.
- As it is likely that the disorder in this family is caused by the truncation, deletion or otherwise inactivation of a crucial gene by one of the translocation breakpoints, we mapped the breakpoints using fluorescence in situ hybridisation to a 1 Mb region on chromosome 8 and a 5 Mb region on chromosome 20. Neither of these chromosomal regions includes a known ataxia locus.

extremities, double sided Babinski signs, nystagmus, disc pallor, reduced field of vision, deviation of the tongue to the right, and urinary urge incontinence. She was severely disabled with lower limb paralysis and urinary and bowel incontinence during the last year of her life. She died at 42 years old in 1964 with a diagnosis of multiple sclerosis.

Cytogenetic studies

Metaphase chromosomes were prepared from cultured or EBV transformed peripheral blood lymphocytes according to standard procedures and were analysed by QFQ and GTL banding techniques.

FISH mapping

Fluorescence in situ hybridisation (FISH) was carried out using metaphase chromosomes as described previously.⁸ YACs mapping to 8p22 and 20q13 regions were obtained from the YAC/BAC FISH Mapping Resource Centre (The Max Planck Institute for Molecular Genetics, Berlin, Germany; <http://www.molgen.mpg.de/~cytogen>). For each hybridisation, 150-200 ng biotin labelled total YAC DNA was used.

Abbreviations: DBCR, disease associated balanced chromosomal rearrangement; FISH, fluorescent in situ hybridisation; MS, multiple sclerosis

The chromosomes were visualised under a Leica DMRB epifluorescence microscope equipped with a Sensys 1400 CCD camera (Photometrics) and an IPLab Spectrum imaging software (Vysis).

RESULTS

Cytogenetical analysis

Metaphase analysis of 12 members of the family (III:2; III:4; III:7; III:12; IV:1; IV:2; IV:4; IV:8; IV:9; IV:12; IV:15, and V:1) revealed an apparently balanced reciprocal translocation between the short arm of chromosome 8 and the long arm of chromosome 20. The karyotypes were established as 46,XX/XY,t(8;20)(p22;q13). The family members III:8, III:10, IV:5, and IV:14 had normal karyotypes. II:3 had a normal karyotype, but chromosomes of his wife, II:2, who was deceased at the time of investigation, could not be analysed.

Breakpoint mapping with FISH

Both chromosomal breakpoints were investigated with FISH using chromosome 8 or chromosome 20 specific YACs as hybridisation probes (http://www-genome.wi.mit.edu/cgi-bin/contig/phys_map).

Chromosome 8 breakpoint

Two YAC clones (934d1 and 934e10) gave signals on normal chromosome 8 and der(8) suggesting that they were mapping proximal to the breakpoint. Four YAC clones (760e6, 690f5, 970b6, and 770e9) gave signals on the normal chromosome 8 and der(20) indicating a location distal to the breakpoint. Finally, two overlapping YAC clones (953h12 and 763a7) displayed signals on the normal chromosome 8 and on both derivative chromosomes, suggesting that the translocation breakpoint was within the overlapping region of these YACs. The common STS markers for these two YACs (D8S540, WI-3666, WI-7626, AFMA224WH4, D8S1770, D8S1769, and D8S1711) were localised within chromosome position 30.274.686–31.280.689 at 8p12 (Genome Browser, April 2003 freeze, <http://genome.ucsc.edu/>). These results enabled us to narrow the breakpoint to a ~1 Mb genomic region that includes eight known genes (*RBPMS*, *GTF2E2*, *GSR*, *D8S2298E*, *PPP2CB*, *TEX15*, *PURG*, and *WRN*).

Chromosome 20 breakpoint

This breakpoint was mapped between the proximal YAC clone 908c6 and the distal YAC clone 754b11. YAC-908c6 is positive for seven STS markers (D20S111, D20S863, D20S872, D20S874, WI-7020, WI-8866, and D20S200) and YAC-754b11 is positive for four STS markers (WI-5238, WI-8584, D20S841, and D20S884). The most distal marker, D20S200 on YAC-908c6, is localised to chromosome position 31.563.878–31.764.223, and the most proximal marker, WI-5238 on YAC-754b11, maps to chromosome position 36.367.835–36.568.131 (Genome Browser). These results

localise the breakpoint to a ~1 Mb segment approximately 30 Mb from the telomere of the long arm of chromosome 20, a region containing about 80 known or presumptive genes.

DISCUSSION

In the present study we describe a family in which an early onset, non-progressive, mild form of cerebellar ataxia is associated with a reciprocal translocation t(8;20)(p22;q13). Twelve persons from three generations were translocation carriers and all except one (IV:1) were affected (fig 1). In this pedigree the only person with late onset of the disease is II:2. She had not been investigated cytogenetically, but the presence of neurological symptoms suggested that she was a translocation carrier. However, germ line mosaicism either in this patient or in her cytogenetically normal husband (II:3) cannot be totally excluded.

The disease shows clinical variability in the family, and the symptoms include clumsiness starting in early childhood, abnormal gait characterised by lurching and frequent falling, tremor, ataxia, nystagmus, retained reflexes in the lower limbs, and deterioration of the symptoms upon physical activity (table 1). One of the family members (II:2) had developed multiple sclerosis according to patient records, although the diagnosis was not supported by other findings; MRI was not available at the time she died in 1964, and autopsy was not performed.

The present family might represent either a new autosomal dominant form of cerebellar ataxia or an extended phenotype of the previously reported disorder of early onset, non-progressive cerebellar ataxia with generalised atrophy of the cerebellum or localised vermal atrophy. However, in contrast to all other previously described families with early onset and non-progressive cerebellar ataxia, MRI studies of two of the affected members of the present family did not show any vermal or generalised cerebellar abnormalities. In the family described by Furman *et al*,¹ one of the affected females did not present any MR abnormalities, whereas the other affected family members showed atrophy of the anterior cerebellar vermis.

The inheritance of the disorder in this family is apparently autosomal dominant, as male and female members of the family are equally affected (5M, 7F). However, X linked dominant inheritance cannot be excluded, owing to absence of male to male transmission within the family. In the family described by Fenichel and Phillips,³ a dominantly inherited ataxia was associated with hypoplasia of the cerebellar vermis as demonstrated by MR studies. In this family, a skewed male to female ratio was observed, and two affected males were found to be more severely affected than their female relatives, suggesting X linked inheritance. In contrast, male to male transmission of the disorder has been observed in a similar family described by Kornberg and Shield.⁴ In the present pedigree, the striking co-segregation of the disease

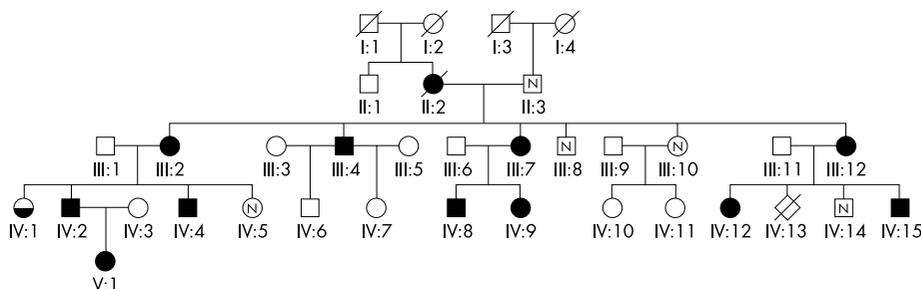


Figure 1 Pedigree of the family showing the co-segregation of an early onset, mild, non-progressive cerebellar ataxia with a reciprocal translocation t(8;20). Open squares or circles indicates an individual without any symptoms and without translocation. Filled squares or circles indicates a patient presenting symptoms and t(8;20). Half filled circles or squares indicates an individual with the translocation t(8;20), but without any symptoms. "N" in an open symbol indicates normal karyotype.

Table 1 Summary of the clinical findings in the translocation carriers

	II:2*	III:2	III:4	III:7	III:12	IV:1†	IV:2	IV:4	IV:8	IV:9	IV:12	IV:15	V:1
Age (years)	42	54	52	48	41	35	33	29	27	24	21	7	7
Age of onset (years)	35	7	3	5	3	–	3	NK	3	3	3	3	1
Clumsiness	NK	+	+	+	+	–	+	+	+	+	+	+	+
Lack of coordination	+	+	+	+	–	–	+	–	–	–	–	–	+
Dysarthria	+	–	–	–	–	–	–	–	–	–	–	–	+
Ataxia	+	–	+	+	–	–	+	–	+	+	+	–	+
Tremor	NK	–	+	–	–	–	–	–	+	–	+	–	NK
Nystagmus	+	–	+	+	–	–	–	+	–	+	–	–	NK
Abnormal reflexes	+	–	–	–	–	–	–	–	–	–	–	–	–
Ataxic gait	+	–	–	–	–	–	–	–	–	–	–	–	+
Dysdiadochokinesia	+	–	–	NK	–	–	–	–	+	–	–	–	NK
Scoliosis	NK	–	+	–	–	–	+	–	–	–	–	–	–
Vibration sense reduced	+	NK	–	+	–	–	+	–	–	–	NK	–	NK

II:2 died at 42 years of age with a diagnosis of multiple sclerosis and was severely disabled; †IV:1 does not have any symptoms.
NK, not known.

with the translocation t(8;20) suggests that the gene responsible for this disorder is located in one of the breakpoint regions and either directly disrupted or otherwise inactivated by the chromosome rearrangement. If so, the phenotype observed in this family may result from haploinsufficiency or from a dominant (toxic or negative) effect of the altered gene product.

The chromosome regions 8p22 and 20q13 do not harbour any known ataxia loci. However, Nagata *et al.*⁹ reported a 3 year old boy with cerebellar ataxia and idiopathic aplastic anaemia with the karyotype 46,XY,t(1;20)(p22;q13.3). Although aplastic anaemia was not a feature of the present family, the occurrence of two independent breakpoints at 20q13 associated with early onset ataxia might point to this region as the primary site of defect. In this context, we do not take the apparent discrepancy between the cytogenetic determination and the FISH mapping of the chromosome 20 breakpoint into consideration. High resolution chromosomal analysis suggests 20q13 as the breakpoint, while the FISH mapping according to Genome Browser place the breakpoint at 20q11.2. This discrepancy might be due to the inherent difficulties with exact identification of translocation breakpoints by conventional banding analysis or to errors in the molecular location of the cytogenetic bands in Genome Browser.

The 1 Mb genomic region at the 8q breakpoint includes eight known genes and there are about 80 known or presumptive genes within the 5 Mb 20q region. As it is likely that the disorder is caused by the truncation, deletion, or otherwise inactivation of a crucial gene by one of the translocation breakpoints, further mapping and cloning of the translocation breakpoints may lead to identification of the actual gene for this disorder.

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Authors' affiliations

J M Hertz, Department of Clinical Genetics, Aarhus University Hospital, DK-8000 Aarhus C, Denmark

B Sivertsen, Department of Neurology, Aarhus University Hospital, DK-8000 Aarhus C, Denmark

A Silahatoglu, M Bugge, N Tommerup, Z Tümer, Wilhelm Johannsen Centre for Functional Genome Research, Department of Medical Genetics, IMBG, The Panum Institute, University of Copenhagen, Denmark

V Kalscheuer, A Weber, J Wirth, H-H Ropers, Max-Planck Institute of Molecular Genetics, Ihnestrasse 73, D-14195 Berlin, Germany

A Weber, Institute of Neuroimmunology, Neuroscience Research Center, Charité University Hospital, D-10098 Berlin, Germany

J Wirth, Developmental Biology and Molecular Pathology, University of Bielefeld, Bielefeld, Germany

Correspondence to: Dr J M Hertz, Department of Clinical Genetics, Aarhus University Hospital, The Bartholin Building, DK-8000 Aarhus C, Denmark; hertz@akh.aaa.dk

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REFERENCES

- Furman JM**, Baloh RW, Chugani H, Waluch V, Bradley WG. Infantile cerebellar atrophy. *Ann Neurol* 1985;17:399–402.
- Taniwa K**, Baraitser M, Wilson J. Dominantly inherited congenital cerebellar ataxia with atrophy of the vermis. *Pediatr Neurol* 1987;3:360–2.
- Fenichel GM**, Phillips JA. Familial aplasia of the cerebellar vermis. Possible X-linked dominant inheritance. *Arch Neurol* 1989;46:582–3.
- Kornberg AJ**, Shield LK. An extended phenotype of an early-onset inherited nonprogressive cerebellar ataxia syndrome. *J Child Neurol* 1991;6:20–3.
- Imamura S**, Tachi N, Oya K. Dominantly inherited early-onset nonprogressive cerebellar ataxia syndrome. *Brain Dev* 1993;15:372–6.
- Harding AE**. Early onset cerebellar ataxia with retained tendon reflexes: a clinical and genetic study of a disorder distinct from Friedreich's ataxia. *J Neurol Neurosurg Psychiatr* 1981;44:503–7.
- Bugge M**, Bruun-Petersen G, Brondum-Nielsen K, Friedrich U, Hansen J, Jensen PKA, Kristoffersson U, Lundsteen C, Niebuhr E, Rasmussen KR, Rasmussen K, Tommerup N. Disease-associated balanced chromosome rearrangements: a resource for large scale genotype-phenotype delineation in man. *J Med Genet* 2000;37:858–65.
- Silahatoglu AN**, Hacıhanefioglu S, Güven GS, Cenani A, Wirth J, Tommerup N, Tümer Z. Not para-, not peri- but centric inversion of chromosome 12. *J Med Genet* 1998;35:682–4.
- Nagata M**, Hara T, Sakamoto K, Ueda K. Aplastic anemia associated with ataxia and chromosome translocation (1;20). *Acta Haematol* 1990;84:198–200.