

LETTER TO JMG

Cerebellar hypoplasia and quadrupedal locomotion in humans as a recessive trait mapping to chromosome 17p

S Türkmen, O Demirhan, K Hoffmann, A Diers, C Zimmer, K Sperling, S Mundlos



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Background: Congenital hereditary non-progressive hypoplasia of the cerebellum is a rare condition, frequently associated with other neuropathology such as lissencephaly. Clinically, the condition is associated with variable degrees of mental retardation, microcephaly, seizures, and movement disorders due to ataxia. In severe cases, patients are unable to ambulate independently, but nevertheless do use bipedal locomotion.

Methods and Results: Here we present a family with seven affected members, five of whom never learned to walk on two legs but have fully adapted to quadrupedal palmigrade locomotion. These subjects show signs of cerebellar ataxia and are mentally retarded. MRI analysis demonstrated hypoplasia of the cerebellum and the cerebellar vermis as well as a small nucleus dentatus and a thin corpus callosum but no other malformations. We show, by a genome-wide linkage scan, that quadrupedal locomotion is a recessive trait linked to chromosome 17p.

Conclusions: Our findings have implications for understanding the neural mechanism mediating bipedalism, and, perhaps, the evolution of this unique hominid trait.

walk. In spite of this wide variety of clinical symptoms and general difficulties in balance and coordination, these patients walk bipedally. Only in extremely severe cases may bipedal walking not be possible and affected individuals use either wheelchairs or other forms of assistance, but quadrupedal walking as an alternative method of locomotion has not been reported. We present here a family with a so far undescribed condition that is associated with the inability to walk bipedally and functional adaptation resulting in highly efficient quadrupedal locomotion (QL).

METHODS AND RESULTS

Patient characteristics

The family originates from south-eastern Turkey and is of Kurdish origin. The parents are second cousins and healthy. There are 18 children, five of whom use QL only. One affected sibling died at the age of 26 of unknown causes. Another brother and a sister are bipedal but have similar neurological features and a lesser degree of cognitive impairment compared to the other four living affected subjects (fig 1). The index patient is a now 28 year old man born after uneventful gestation and delivery. He began to move on the distal portions of his four extremities at the end of his first year and never walked upright. He is mentally retarded based on clinical assessment. On physical examination moderate thoracic kyphosis was present, but x ray analysis of his spine showed no bony abnormalities. He had disproportionate short stature with a height of 150 cm and an arm span of 171 cm. Head circumference was normal. A thorough neurological examination revealed mildly decreased muscle tone with normal strength and normal deep tendon reflexes, a moderate degree of cerebellar ataxia, and a slight intentional tremor with dystonia but without pyramidal signs. He had dysarthria, bilateral dysmetria, and dysdiadochokinesia. The cranial nerves showed no abnormalities apart from a minor bilateral external ophthalmoplegia. Contractures were not observed. He preferred to walk on his four extremities in a broad based manner showing a highly unusual gait with his entire hands and feet touching the ground (palmigrade walking) and fully stretched knee and elbow joints (fig 2; a supplementary video is available at <http://www.jmedgenet.com/supplemental>). He was able to stand upright with his body leaning against a wall or a tree but for walking he quickly returned to QL. When assisted he was able to walk a few steps but exhibited strong abasia and astasia as well as ataxia and slight dysmetria. These movement disturbances were not aggravated by eye closure. The other three affected subjects had similar neurological features with gradual differences in the degree of cerebellar and dystonic elements, and all walked on all fours. All affected subjects move around freely and participate most of the time in the daily work of the family in the fields. They have not attended school, and understand some words of their

Gait is achieved through complex regulation of the central nervous system involving, for example, the cerebral cortex, the basal ganglia, and the cerebellum. In quadrupedal animals, the coordination of rhythmic forelimb and hindlimb activity requires interaction of the spinal cord with the brainstem and the basal ganglia. Human infants crawl on all fours mainly using a hands and knees pattern by the age of 9 months, walk without support between a year and 15 months, and run at 18 months.¹ During this crucial period, the child's brain matures to effectively control this remarkable transition. However, little is known about the neurological control of bipedality. Using SPECT (single photon emission computed tomography) analysis, the medial primary sensorimotor area, supplementary motor area, and also the cerebellar vermis and the visual cortex were shown to be active during walking.² The cerebellum is of particular importance in controlling, initiating, and adjusting stance and gait.³ Lesions or congenital defects of the cerebellum cause incoordination of the muscles resulting in irregular gait and falling (ataxia).⁴ Gait ataxia, also called frontal ataxia, is a clinical entity associated with wide based unsteady gait with upright trunk and frequent falls.⁵ This condition may result from unilateral frontal lobe lesions. Many other conditions with abnormal gait have been described that are subsumed under the term movement disorders.⁶ These conditions are clinically extremely heterogeneous ranging from mildly abnormal gait to the inability to

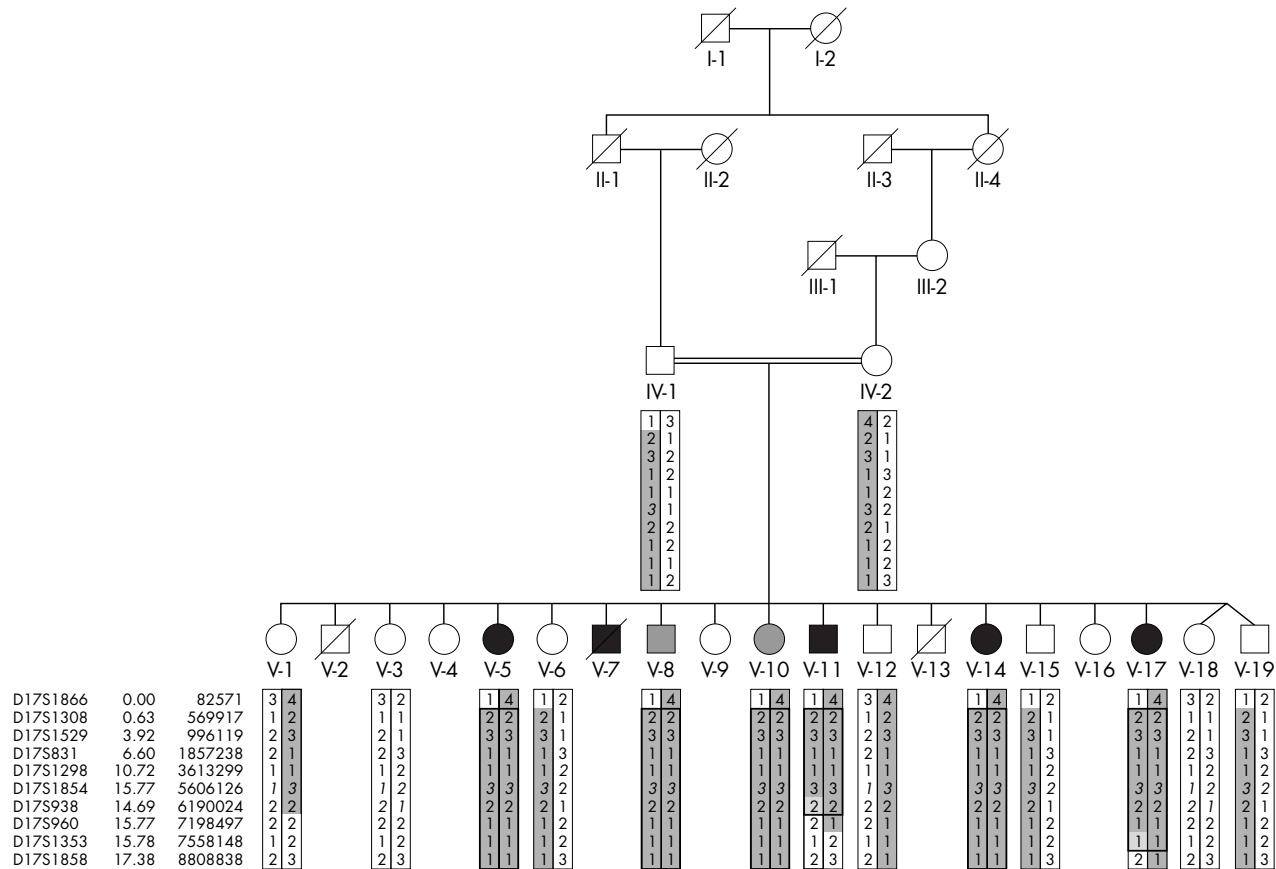


Figure 1 Pedigree of the QL family with haplotypes. The bipedal brother and sister are depicted in grey. One affected brother who also used QL died at the age of 26 of unknown cause. Microsatellite markers are given on the left with cM according to the Marshfield map (sex averaged), and the physical locations are given on the right (Assembly: NCBI 35, July 2004; Genebuild: Ensembl, Nov 2004, database version: 36.35i). The region of homozygosity is boxed, the affected allele is shown in dark grey and the unaffected in white, and uninformative markers are in light grey.

language (Kurdish) well enough to communicate. Their cognitive abilities are severely impaired. They know their own names and are able to verbally express their basic needs. They understand and carry out simple commands correctly.

MRI and blood and DNA analysis

Cranial magnetic resonance imaging revealed a number of characteristic changes in all affected subjects including the bipedal brother and sister (fig 3). All affected individuals had similar findings consisting of hypogenesis and midline clefting of the cerebellar vermis. The posterior fossa was fluid filled and normal sized. In all cases the superior half of the vermis was formed, whereas the inferior section was not. The dentate nucleus was atrophic. The fourth ventricle was enlarged. Brainstems including midbrain and pons were of normal size. Except for general brain atrophy in all subjects and mild hypoplasia of the corpus callosum in four patients, no associated supratentorial anomalies were found; in particular there was no cortical dysplasia, lissencephaly, or grey matter heterotopia. The father and an unaffected heterozygous brother had normal MRIs. Thus, in contrast to the QL phenotype, the brain malformation is fully penetrant.

Blood was collected from all family members after informed consent. The necessary ethics committee approval was obtained. Concentrations of vitamin E and B12 as well as cholesterol and triglycerides were within normal ranges, ruling out major metabolic causes for the disease. DNA was extracted and subjected to high density micro array using the

10K Affymetrix SNP chip. Analysis of the SNP data revealed a single locus for homozygosity on chromosome 17p between 0.00 and 15.78 cM. Microsatellite markers confirmed homozygosity between markers D17S1866 and D17S960 (fig 1). Including all six affected and seven unaffected individuals, a peak multipoint LOD score of 5.37 was calculated between markers D17S831 and D17S1298 using the program SimWalk v2.91. No other significant chromosomal region was observed. The region contains a large number of genes but no obvious candidates for this condition.

DISCUSSION

Hypoplasia of the cerebellum is seen in a variety of congenital conditions including heritable diseases such as Joubert syndrome and sporadic conditions such as the Dandy-Walker malformation, or is due to exogenous factors such as intrauterine exposure to drugs. Other conditions with cerebellar hypoplasia have been described that are associated with other variable features such as short stature⁷ or optic atrophy.⁸ Recently, mutations in the very low density lipoprotein receptor (VLDLR) have been described in an autosomal recessive condition prevalent in the Hutterite population of North America.⁹ This condition, also referred to as disequilibrium syndrome, is characterised by non-progressive cerebellar hypoplasia and truncal ataxia as well as by cortical gyral simplification associated with moderate to profound mental retardation.¹⁰ The VLDLR gene encodes a receptor for reelin, whose pathway guides neuroblast migration in the cerebral cortex and the cerebellum. Mutations in



Figure 2 Quadrupedal walking by three affected subjects. Note palmigrade walking with hands fully touching the ground. Knees, elbow joints, and back are straight, and there is a rhythmic alternating pattern of motion most of the time (see also supplementary video at <http://www.jmedgenet.com/supplemental>). (Photographs are published with consent.)

reelin cause autosomal recessive lissencephaly with cerebral hypoplasia in humans and the reeler phenotype in mice which is characterised by impaired motor coordination, tremors, and ataxia. These conditions have been subsumed under the term lissencephaly with cerebral hypoplasia.¹¹ The affected individuals reported here have some overlapping features with other non-progressive cerebellar hypoplasias. These include ataxia, intentional tremor, mental retardation, strabismus, and dysarthria, but abnormalities of gyration as reported for the VLDLR mutations were not observed. Interestingly, all the patients with VLDLR mutations learned to walk very late and some were described as having such a severe form of movement disorder that independent walking was not possible. Similar observations were made in a different form of cerebellar hypoplasia described in a large inbred Lebanese family. However, in none of these cases has compensatory QL been described.¹⁰ We conclude that QL is specific to the family described here and not a compensatory mechanism for their ataxia. However, we cannot exclude that early and sufficient treatment might have altered the outcome in the affected subjects. The genetic defect in this family disrupts the normal development of the cerebellum, the nucleus dentatus, and the corpus callosum. In addition, it is likely to affect yet unknown neuronal circuits that control bipedality.

Quadrupedal palmigrade walking, as observed in this family, may occur as a transient stage on the way to bipedality in normal infants but never persists. In adult humans creeping on hands and feet is generally considered to be exceedingly inefficient,¹² but QL affected individuals do this in an efficient manner moving around effectively and without discomfort. As they move, their knee and elbow joints show almost no flexion, their backs are kept straight, and their hands touch the ground mainly on the palms. This way of walking is distinct from the knuckle walking of the

great apes, who bear their weight on the dorsal surface of their middle phalanges.¹³ Knuckle walking has been regarded as the ancestral method of locomotion based on the anatomy of wrist and phalangeal bones.¹⁴ The phenotype described here demonstrates that a single gene defect can result in efficient palmigrade walking in humans in spite of a wrist that is generally thought to be anatomically not adapted to this form of locomotion.

Atavistic phenotypes, defined as the reappearance of an ancestral characteristic in individual members of a species, such as the appearance of supernumerary nipples in humans or polydactyly in horses,¹⁵ are of potential relevance for identifying single genes involved in the evolution of specific traits. From the genetic view point, however, this approach appears rather superficial since mutations typically disrupt gene function rather than revert a gene to its ancestral state. However, if gene inactivation results in a phenotype resembling an ancestral state, it can be speculated that genetic changes in this gene may have contributed to the evolution of this trait. Primary microcephaly is considered such a disorder, whereby the brain size of affected individuals resembles that of early hominid ancestors. This disorder is due to mutations in a number of so called microcephaly genes which show either relatively mild phenotypes with comparatively normal development, or severe phenotypes with profound mental retardation, severe epilepsy, and frequent early death. It has been hypothesised that genes associated with adaptive evolution in the human lineage are linked to the mild phenotypes because mutations in these genes are more likely to be advantageous.¹⁶ Indeed, comparison of the evolutionary rates of microcephaly related genes showed a remarkable consistence with this hypothesis.¹⁷ Genes causing mild phenotypes were shown to be associated with adaptive evolution, whereas genes that cause the severe phenotypes were not. In this respect, the QL gene is a good



Figure 3 MRI of the index patient showing coronal (A), sagittal (B), and transverse (C) sections. Note cerebellar hypoplasia and hypogenesis and midline clefting of the cerebellar vermis (A, B arrows), enlargement of the fourth ventricle (C, arrow), and hypoplasia of the corpus callosum (B).

candidate for an evolutionarily relevant gene. The identification of a positively selected gene involved in the evolution of bipedalism could be the first step in unravelling the underlying genetic network and may offer molecular evidence for selective processes driving the evolution of our species.

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A supplementary video is available at <http://www.jmedgenet.com/supplemental>

Authors' affiliations

S Türkmen, K Hoffmann, S Mundlos, Institut für Medizinische Genetik, Charité, Universitätsmedizin Berlin, Berlin, Germany

O Demirhan, Department of Medical Biology and Genetics, Faculty of Medicine, Cukurova University, Adana, Turkey

A Diers, Abteilung für Neuropädiatrie, Charité, Universitätsmedizin Berlin, Berlin, Germany

C Zimmer, Abteilung für Neuroradiologie der TU München, Munich, Germany

K Sperling, Institut für Humangenetik, Charité, Universitätsmedizin Berlin, Berlin, Germany

S Mundlos, Max Planck Institut für Molekulare Genetik, Berlin, Germany

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Correspondence to: Stefan Mundlos, Institut für Medizinische Genetik, Charité, Augustenburger Platz 1, 13353 Berlin, Germany; stefan.mundlos@charite.de

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