

PAPER

Patients with horizontal gaze palsy and progressive scoliosis due to *ROBO3* E319K mutation have both uncrossed and crossed central nervous system pathways and perform normally on neuropsychological testing

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Polymerase chain reaction conditions are available on <http://jnnp.bmjournals.com/supplemental>.

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Background: Horizontal gaze palsy and progressive scoliosis (HGPPS) is caused by mutations of the *ROBO3* gene, which encodes a receptor associated with axonal guidance during development. Although there is evidence for uncrossed cuneatal and corticospinal tracts in HGPPS, it is unclear whether other central nervous system pathways are involved.

Objective: To study two patients with HGPPS homozygotic for the *ROBO3* E319K mutation using a variety of neurophysiological and neuropsychological tests.

Methods: A battery of neuropsychological tests was applied to assess various cognitive and perceptual functions. The corticospinal, somatosensory and auditory pathways were evaluated using appropriate neurophysiological tests. To access motor pathways to the neck muscles, electromyographic recordings were obtained from the sternocleidomastoideus and splenius capitis muscle during active head rotation.

Results: Both patients performed normally on manual dexterity, complex sensory and visuospatial functions, reading and general intelligence tests. Motor evoked potentials in both patients showed uncrossed corticospinal tracts for the extremities, although in one patient, electromyography indicated pyramidal tract crossing for the neck muscles. Although somatosensory evoked potentials showed uncrossed somatosensory fibres subserving proprioception and light touch, right median nerve somatosensory evoked potential in one patient indicated a partial lemniscal crossing. Sympathetic skin response and blink reflex showed a midline crossing of the spinothalamic and quintothalamic tracts. Brain stem auditory evoked potentials indicated a lack of crossing in the level of the trapezoid body.

Conclusions: Our patients with the *ROBO3* E319K mutation show normal perceptual and cognitive functions and have both crossed and uncrossed motor, sensory and auditory pathways.

Horizontal gaze palsy and progressive scoliosis (HGPPS) is a rare autosomal recessive disorder characterised by absent conjugate lateral eye movements with preserved vertical gaze and progressive scoliosis.^{1–5} Although the disorder has been known for over three decades, its pathogenesis remained obscure until Jen *et al*³ reported that homozygotic mutations in the *ROBO3* gene are present in patients with HGPPS. The *ROBO3* protein belongs to a family of transmembrane receptors that are expressed in the growth cone of elongating axons, guiding them to contralaterally located target neurones during nervous system development. Ten different mutations (6 missense, 2 frameshift, 1 nonsense, 1 splice site) located in different domains of the encoded protein have been identified and are thought to diminish the function of this receptor,³ with recent imaging and neurophysiological studies providing evidence for the presence of uncrossed motor and sensory pathways in patients with HGPPS.^{3–7}

Although detection of *ROBO3* gene mutations has advanced our understanding of the molecular signalling mechanisms that lead to crossing of longitudinal motor and sensory tracts, several issues remain unsolved. Thus, although there is evidence for lack of crossing of the long descending pyramidal tracts and the ascending medial

lemniscal projections, it is presently unclear whether other pathways that normally cross the midline are affected and whether the various *ROBO3* mutations produce the same anatomical phenotype. Patients with HGPPS seem to face little functional consequences, but it is not known how these patients perform on standardised neuropsychological tests.³

To deal with these issues, we examined two brothers affected by HGPPS, both of whom were homozygotic for the *ROBO3* E319K mutation.

PATIENTS AND METHODS

Patient history, physical and neurological examination

We studied two brothers, aged 54 (patient 1) and 45 years (patient 2), who are members of the previously described GD family.³ In addition, we evaluated four of their five siblings. Detailed medical and neurological histories were taken and physical and neurological examinations were carried out using standard methods.

Abbreviations: BAEP, brain stem auditory evoked potential; EMG, electromyography; FDI, first dorsal interosseus; HGPPS, horizontal gaze palsy and progressive scoliosis; SSR, sympathetic skin response

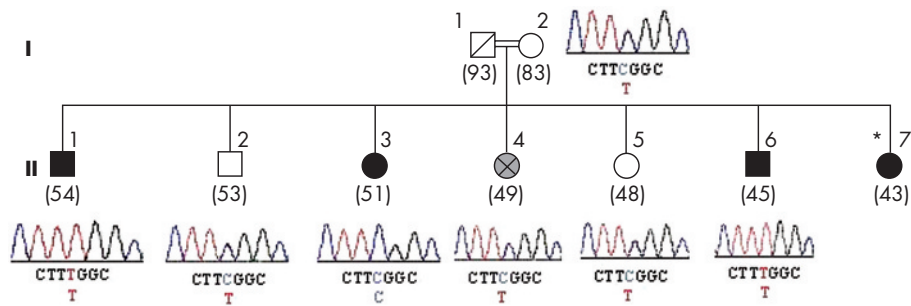


Figure 1 Family with horizontal gaze palsy and progressive scoliosis (HGPPS). Homozygotic mutation (955G→A) of the *ROBO3* gene was found in the two affected brothers (II-1, II-6), whereas heterozygotic mutation was present in the 49-year-old sister (II-4), with progressive external ophthalmoplegia and myopathy, as well as in the mother (I-2) and in two asymptomatic siblings (II-2, II-5). The third asymptomatic sibling (II-3) had two normal alleles. The age at examination (in years) is shown in parentheses below each patient. Filled symbols, patients with HGPPS; grey-shaded symbol, patient with progressive external ophthalmoplegia and myopathy; *patient with HGPPS not available for DNA testing.

Mutation analysis

Genomic DNA was extracted from whole blood of all consenting family members. All 28 exons and flanking introns of the *ROBO3* gene were amplified using primers as previously described.³ Polymerase chain reaction conditions are described in the supplementary data (available online at <http://jnnp.bmjournals.com/supplemental>). Automated and bidirectional sequencing of all exons and flanking intronic regions was carried out on the ABI Prism 3100 Genetic Analyser (PE-Applied Biosystems, Foster City, California, USA).

Magnetic resonance imaging

Magnetic resonance imaging of the brain was carried out using a 1.5-T scanner (Sonata, Siemens, Germany).

Neuropsychological assessment

Manual dexterity, complex sensory and spatial–visuoperceptual functions, reading and general intelligence were assessed. Tests of sensory function focused on tactile inattention (face–hand test), graphesthesia (adaptation of Rey’s test by substituting Greek characters for Latin ones) and stereognosis (version of the manual form perception test).⁸ Five shapes (circle, triangle, square, diamond and octagon) and five objects of daily use (toothbrush, tennis ball, comb, large cup, and a sweet in a wrapper) were presented to the patients in a random order, with vision occluded. The patient was then asked to point to the object from a selection of drawings representing the 10 objects. The number of objects matched correctly was taken as the

stereognosis score. Finger agnosia was examined using the finger localisation test.^{9,10} In the first part of the test, the patient was asked to identify fingers of their concealed hand touched by the examiner in a random order on a diagram. In the second part, two fingers were touched simultaneously. The patient’s ability to perceive and reproduce directional patterns of tactile stimulation was assessed with a modified version of the tactile finger recognition test that is part of the Halstead–Reitan battery.¹¹ In our version the patient was given four sequences of finger taps (two in a left–right and two in a right–left direction) to each hand in the ipsilateral hemispace. The procedure was repeated in the contralateral hemispace (ie, left hand placed to the right of the patient’s midline). All the tests listed above were carried out without visual feedback.

Right–left orientation was assessed using 10 simple tasks, such as “Show me your left hand” and “Show me my right eye”.¹² Manual dexterity was assessed with the grooved pegboard test.¹³ The presence of visual neglect was examined with the line bisection test.¹⁴ In addition, a line bisection test with sequential stimulus presentation was used.¹⁵ The test required the patient to mark the midpoint of 16 horizontal and 16 vertical lines located in the middle of a white sheet of paper. Four line lengths were used (50, 100, 150 and 200 mm, four trials of each length). Two key aspects of reading, phonological decoding and sight-word recognition, were assessed through timed oral word-reading tasks. The sight-word efficiency test consists of 150 high-frequency words arranged by order of increasing difficulty in four columns on a single sheet, whereas the pseudoword reading

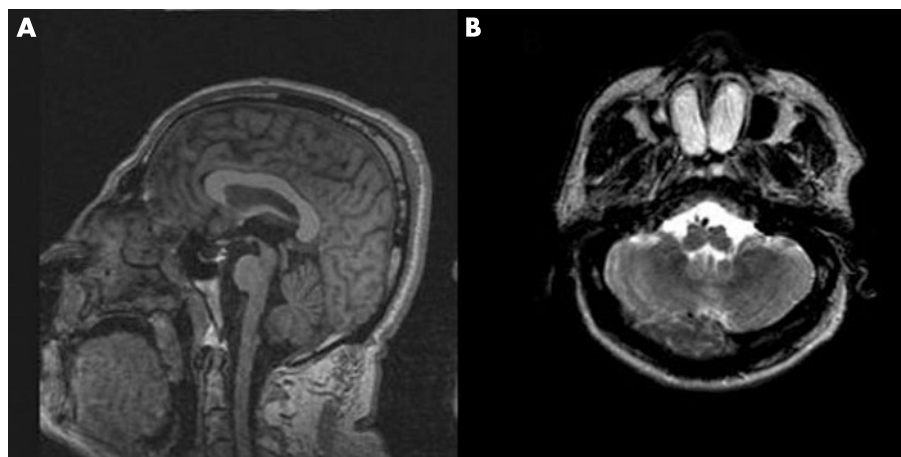


Figure 2 Normal corpus callosum (A) and flattening of the anterior surface of medulla oblongata in patient 1 (B).

efficiency test contains 75 pseudowords constructed by changing two or more sounds in the word stimuli. Finally, general intelligence was assessed using the Greek version of the Wechsler Abbreviated Scales of Intelligence, with normative data adjusted for age and education (Simos *et al*, 2005, unpublished data).

Motor evoked potentials

Motor evoked potentials were obtained using a magnetic stimulator (MagLite r25, Dantec, Skovlunde, Denmark) with a circular magnetic coil with an outside diameter of 14 cm (MMC 140, Medtronic, Minneapolis, Minnesota, USA). The centre of the coil was placed about 1 cm lateral to the vertex to stimulate the leg area and 2 cm posterior and 2–3 cm lateral to electrode Cz (according to the international 10–20 system) to stimulate the finger area. Surface recording electrodes were placed on the belly tendons of the first dorsal interosseus (FDI) muscle and the anterior tibialis muscle on each side. The responses were recorded with a standardised electrodiagnostic system (Neuropack2, Nihon Kohden, Tokyo, Japan). The same device was also used for the following neurophysiological studies, including the brain stem auditory evoked potentials (BAEPs).

Electromyography

Concentric needle electrodes were inserted into the left sternocleidomastoideus and the right splenius capitis muscles to assess muscle activity during voluntary rightward head rotation.

Median nerve somatosensory evoked potentials

Electrical stimulation with square-wave pulses was delivered by a bipolar surface electrode at the rate of four 0.3-ms pulses per second to the left and right median nerves at the wrist. Signal intensity was adjusted to slightly above threshold for producing a thumb twitch. A total of 500 responses was averaged. The recording electrodes (scalp needles) were placed at 2 cm behind C3 (C3') and C4 (C4') to record the cortical N20 response. The midfrontal site Fz was used as reference.

Blink reflex

The blink reflex was recorded from the orbicularis oculi muscle (lower eyelid) using surface electrodes referenced to the chin. The supraorbital nerves were stimulated successively using a 0.3-ms electrical pulse at an intensity of 17 mA. Four traces were recorded and superimposed.

Sympathetic skin response

The sympathetic skin response (SSR) was recorded with surface electrodes placed on the palms and the soles of the feet referenced to the dorsum of the hand and foot, respectively. The left median nerve was stimulated with brief

electrical pulses (0.2 ms duration) with an intensity of 30 mA. Four responses were superimposed.

Audiograms

Audiograms were taken using a Clinical Audiometer Orbiter 922, V.2 (Madsen Electronics, Minnetonka, Minnesota, USA) in a special soundproof chamber. Air conduction thresholds were estimated for frequencies ranging between 125 Hz and 8 kHz. The frequency range for bone conduction tests was 250 Hz to 4 kHz.

Tympanometry and acoustic reflex

Tympanograms and stapedius reflexes were obtained using an Impedance Audiometer (Interacoustics AZ 26, Assens, Denmark). Ipsilateral stimulus frequencies were 0.5, 1, 2 or 4 kHz at intensities ranging between 70 and 110 db hearing level. The contralateral stimulus was delivered through a TDH-39 headphone at the same frequencies, intensity ranging between 70 and 120 db hearing level.

Brain stem auditory evoked potentials

BAEPs were recorded to alternated (rarefaction/condensation) clicks of 0.1-ms duration presented at an intensity of 80 dB and at a rate of 13 Hz. The filters were set between 50 Hz and 3 kHz. Recordings were carried out bilaterally to monaural stimulation through mastoid needle electrodes referenced to Cz.

RESULTS

Family investigations

A detailed pedigree of the GD family³ is shown in fig 1. In this family, consanguineous parents (I-1, I-2) gave birth to seven children, three of whom are affected by HGPPS. The two brothers evaluated here (II-1 and II-6) are homozygotic for the *ROBO3* E319K mutation (fig 1). The third affected sibling is a 43-year-old sister (II-7) who presents the typical clinical picture of HGPPS, but no genetic studies have been carried out in her case. In addition, a 49-year-old sister (II-4), affected by a progressive neurological disorder that is clinically distinct from HGPPS, was examined. Since adolescence, she has experienced progressive external ophthalmoplegia (with prominent eyelid ptosis) and progressive myopathy. Scoliosis is not part of her clinical picture. Analysis of her DNA derived from peripheral blood has not shown mitochondrial DNA changes. She has refused a muscle biopsy. Analysis of the entire coding sequence of the *ROBO3* showed heterozygosity for the E319K mutation (fig 1).

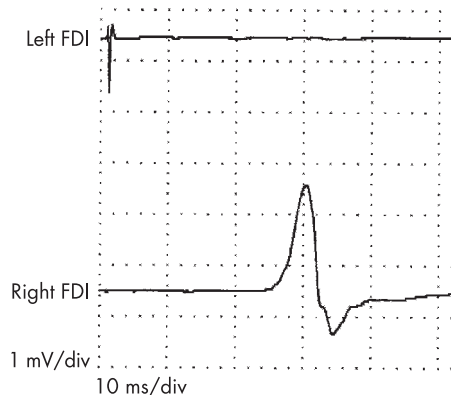


Figure 3 Motor evoked potentials (patient 2). Stimuli of 50–60% of the device power were applied to the right motor area. Recordings were obtained simultaneously from the left and right first dorsal interosseus (FDI) muscle. A response was evoked only in the right FDI.

Table 1 Performance on standardised intelligence and reading tests

Patient	WASI verbal	WASI performance	Sight-word-reading efficiency test	Pseudoword-reading efficiency test
1*	92	88	96	86
2†	87	93	90	85

WASI, Wechsler Abbreviated Scales of Intelligence.

*Standard scores based on data for 105 neurologically intact elderly people (age range 55–69 years, mean (SD) 61.5 (3) years, mean years of education 5 (2) years). †Data based on 85 healthy controls (age range 40–50 years, mean (SD) 49 (2) years, mean (SD) years of education 5 (2) years).

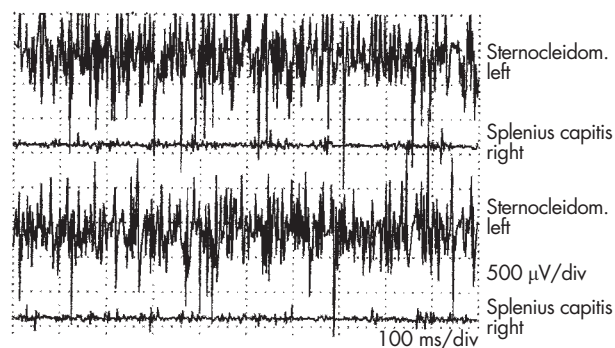


Figure 4 Electromyography recordings using concentric needle electrodes during rotation of the head to the right (patient 2). Normal activity was noted in the left sternocleidomastoideus (Sternocleidom.) and no or little activity was noted in the right splenius capitis.

Patients

Both brothers are known to have horizontal gaze palsy since childhood, with scoliosis appearing in adolescence. Although both underwent corrective spine surgery, physical examination showed a marked right curved thoracic scoliosis. Neurological examination showed that both patients did not have conjugate horizontal eye movements with preserved vertical gaze. Abrupt head jerks (preceded by an eye blink) were used for looking left and right. With the head held still, vergence eye movements substituted for attempted lateral gaze. Vertical saccade velocities were in the low normal range and vertical optokinetic nystagmus were preserved. The vestibulo-ocular reflex was present in the vertical but not in the horizontal plane. A horizontal pendular (at times asymmetrical) nystagmus was present in the primary position. The pupils were equal and reacted normally to light and accommodation consensually. Visual acuity was 20/30 bilaterally in patient 1, and 20/30 on the right and 20/25 on the left eye in patient 2. Funduscopy yielded no abnormal findings. Testing of the corneal reflex produced a normal consensual response. Speech had a nasal quality and a slight hearing loss was noted on the right side in both patients. Muscle power and muscle tone were normal, and tendon reflexes were brisk. Plantar responses were flexor bilaterally. The gait was normal, although both patients had a slight difficulty with tandem walking. In addition, they had difficulty performing alternating movements with the upper and the lower extremities simultaneously. No mirror movements were noted. Examination of the sensory system and coordination was normal.

Magnetic resonance imaging

On the midsagittal T1-weighted view, the corpus callosum and the pons were shown to be normal (fig 2A). On the axial T2-weighted image at the base of the skull, there was flattening of the anterior surface of the medulla oblongata, with the pyramids appearing hypoplastic (fig 2B).

Neuropsychological findings

Both patients are left handed, as indicated by a score of -0.9 and -1.0 on the Edinburgh Handedness Inventory for patient 1 and patient 2, respectively.¹⁶ Patient 1 reported early preference for the left hand for most daily activities, but he was forced to use his right hand in childhood for writing. He made no errors on the tactile inattention, graphesthesia, stereognosis, finger agnosia, right-left orientation and finger sequencing tests (tactile finger recognition test), a typical finding among neurologically intact adults. His performance on the line bisection test did not present any omissions. On the single line at a time bisection task, he showed the

expected leftward bias (tendency to estimate the middle of the horizontal line slightly to the left of the true midline). The size of leftward midline displacement increased with line length (mean D was 1.8, 2.5, 3.6 and 4 mm for line lengths of 50, 100, 150 and 200 mm, respectively). This trend is typical for neurologically intact people across the lifespan.¹⁷ As shown in table 1, the patient performed in the average to low-average range for his age and education on word reading and general intelligence tests.

Patient 2 showed a similar profile, with the exception of a slight difficulty in discriminating digits 3 and 4 of the left hand (he correctly identified light-touch stimuli to either digit after five consecutive repetitions). He correctly identified three of eight letters traced on the palm of his left or right hand, and all his errors were visually similar letters to the target (eg, A for Δ , Σ for Z, P for Φ).

Motor evoked potentials

Magnetic pulses delivered at 50–60% of the maximum intensity elicited only ipsilateral responses in the FDI and anterior tibialis muscles, with peak latencies of about 22 and 30 ms, respectively, in both patients (fig 3). Stronger stimuli evoked bilateral responses, as magnetic pulses of high intensity inevitably reach the contralateral cortex. Central motor conduction time to the arms and legs (left and right) was normal in both patients (about 7 ms in the arms and 15 ms in the legs).

Electromyography

Normally, rightward head rotation is associated with contraction of the left sternocleidomastoideus and the right splenius capitis muscles, and electromyographic (EMG) data were consistent with this pattern in patient 1. In patient 2, voluntary head rotation to the right was associated with normal EMG activity in the left sternocleidomastoideus muscle, but no or little activity was noted in the right splenius capitis (fig 4). On the other hand, contraction in the splenius capitis muscle was noted during neck extension.

Median nerve somatosensory evoked potentials

Ipsilateral N20 responses with normal latencies were noted in both patients. In patient 2, however, stimulation of the right median nerve also evoked an equal contralateral response (fig 5). In patient 1, lower-amplitude cortical responses were recorded contralaterally to the stimulus applied on either side. These were also recorded on left median nerve stimulation in patient 2, but also ipsilaterally to the stimulus, in an age-matched control (fig 5).

Blink reflex

Stimulation on either side elicited a normal R1 ipsilateral to the stimulus and a normal R2 bilaterally (fig 6).

Sympathetic skin response

Normal responses were recorded on left median nerve stimulation from both palms and soles (fig 7).

Audiograms

Conventional audiometry thresholds were in the normal range of values (0–15 dBHL) for the entire frequency range (125–8000 Hz) on the left side in both patients. However, on the right side, both brothers showed sensorineural hearing loss at high frequencies (>4 kHz).

Tympanometry

Measurement of the physical volume and the static compliance showed normal values bilaterally. The tympanogram showed normal pressures in the middle ear cavity bilaterally, with peak compliance between 0 and 50 daPa (tympanogram

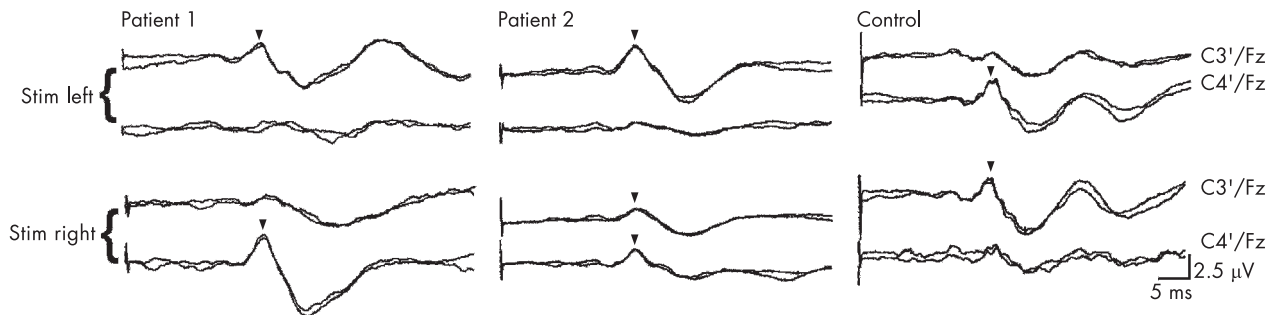


Figure 5 Somatosensory evoked potentials of the median nerve. Recordings of the cortical responses (N20) were obtained simultaneously bilaterally. Left median nerve stimulation (Stim) evoked an N20 response ipsilateral in the patients with HGPPS (patients 1 and 2) and contralateral in the age-matched control. Right median nerve stimulation evoked an equal bilateral response in patient 2, an ipsilateral response only in patient 1 and a normal contralateral response in the control.

type A). The eustachian tube function tests (Valsalva–Toynbee, pressure-swallow) showed normal function.

Acoustic reflex

Uncrossed and crossed acoustic reflexes could not be elicited bilaterally (on either side) even with the use of maximal stimulus intensities.

Brain stem auditory evoked potentials

Waves I, II and III were found to be absent on right ear stimulation in both patients, indicating peripheral damage. On left ear stimulation, recordings from the left side showed waves I, II and III, and a complex of waves IV and V, whereas recordings from the right side showed an absent wave II.

Waves III and a complex of waves IV and V were present (fig 8). The latency of wave I was prolonged.

DISCUSSION

We carried out neuropsychological tests and neurophysiological investigations on two brothers homozygotic for the *ROBO3* E319K mutation. Our MEP results, showing that stimulation of motor cortex evoked ipsilateral responses, are similar to previous observations,^{3,4} and suggest that the descending motor pathways to the upper and lower extremities were uncrossed in these patients. Also, EMG studies, obtained in patient 2, were consistent with uncrossed

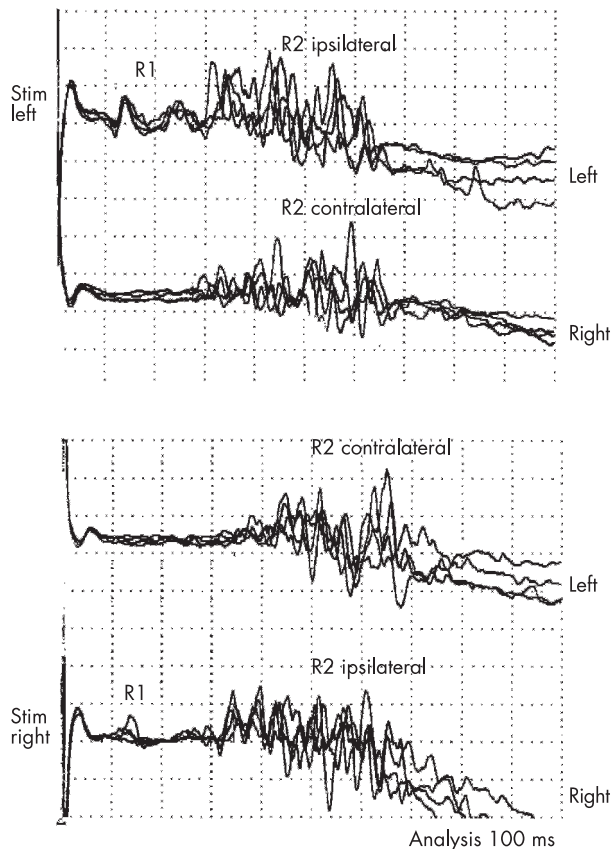


Figure 6 Blink reflex (patient 1). R1 was elicited ipsilaterally to the stimulus (Stim) and R2 on both sides.

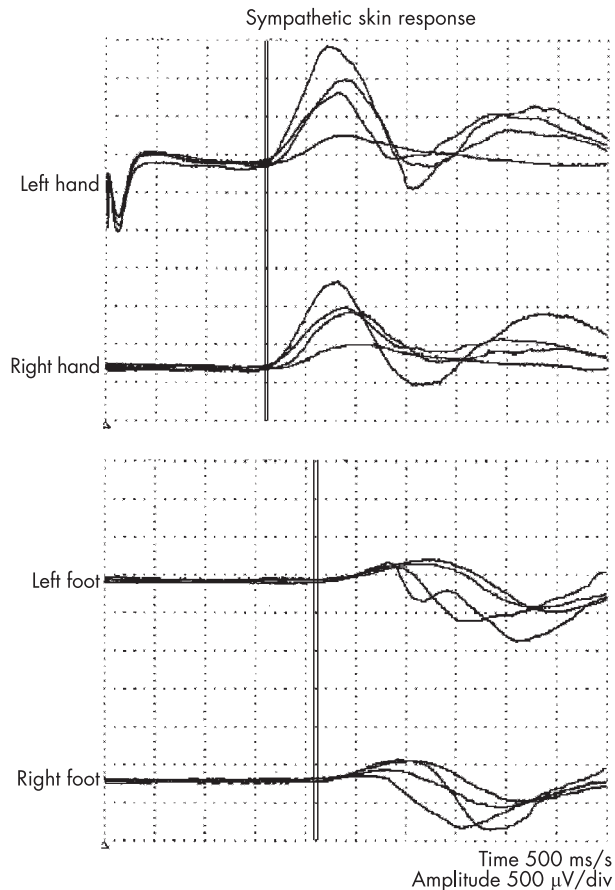


Figure 7 Sympathetic skin response. Stimulation of the left median nerve (indicated by the stimulus artifact at the beginning of the first trace) evoked normal responses on both palms and soles (patient 1).

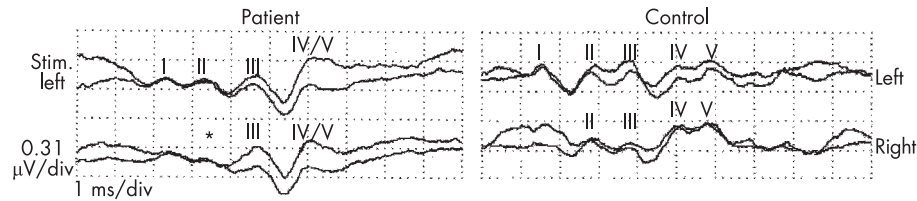


Figure 8 Brain stem auditory evoked potentials. Simultaneous left and right recordings on left ear stimulation (Stim.). In patient 1 with HGPPS wave I was delayed and no obvious wave II (*) was recorded contralaterally.

motor pathways to the neck muscles that are responsible for head rotation. These EMG recordings showed that rightward head rotation induced contraction in the left sternocleidomastoid muscle without concomitant contraction in the right splenius capitis muscle (as would have been expected in the normal). However, in patient 1, a rightward head rotation induced contraction both of the left sternocleidomastoid and of the right splenius capitis, thus suggesting crossover of the pyramidal tract to the neck muscles in this patient. These data indicate intrafamilial variability in the phenotypic expression of the same genetic defect (*ROBO3* E319K mutation).

A similar intrafamilial variability was also apparent for the sensory system. Thus, although in patient 1 the obtained somatosensory evoked potentials were ipsilateral to the stimulus (suggesting uncrossed funiculus cuneatus as previously reported^{3,4}), right-sided stimuli in patient 2 evoked bilateral responses, suggesting a partial crossing of the right cuneate tract. This possibility is supported by functional MRI results (unpublished data), which showed that, although movements of the left fingers induced activation of the left sensory cortex, movements of the right fingers induced activation of both the right and the left parietal cortices. A small N20 evoked ipsilateral to the stimulus in the control is believed to be volume conducted from the contralateral hemisphere as suggested by Kakigi *et al.*,¹⁸ who studied 15 normal volunteers. Differentiation between the right and left cortical responses in tibial somatosensory evoked potential, when using a single midline recording electrode (*Cz'*), is not possible because of the vicinity of the left and right sensory foot areas in the midline of the scalp. Distinguishing could be possible when more recording channels are used.⁴

Our data differ from those of MacDonald *et al.*³ and Jen *et al.*,³ who found a complete lack of crossing of the dorsal column–medial lemniscal system. As the patients with HGPPS studied by those authors had different types of *ROBO3* gene mutations (than the E319K substitution), the observed transfamilial variability probably relates to the distinct amino-acid substitutions in the *ROBO3* protein. However, our observations on the intrafamilial variability in the phenotypic expression of the same genetic defect (*ROBO3* E319K mutation), as described earlier, suggest that additional factors are involved.

In contrast with the above data, the pathways for the blink reflex and for the SSRs seemed to be normally crossed in our patients. Indeed, the appearance of SSRs bilaterally on left median nerve stimulation indicates the presence of a crossed pathway involving the spinothalamic tract.¹⁹ Hosokawa *et al.*²⁰ and Terakawa *et al.*²¹ have reported impaired light touch and pain sensation contralateral to the lesion in their patients with HGPPS who had had either a capsular or a putaminal haemorrhage, respectively, but their patients were not characterised at the genetic level. Regarding the blink reflex, stimulation on either side elicited a normal R1 ipsilaterally to the stimulus and an R2 bilaterally. The occurrence of the second response (R2), recorded contralaterally to the

stimulus, indicates a midline crossing link between nucleus spinalis n. trigemini and the contralateral nucleus n. facialis.²²

Evaluation of the auditory system using BAEPs showed that when the left ear was stimulated, waves I, II, III and a complex of waves IV and V were recorded ipsilaterally, whereas only waves III and a complex of waves IV and V were recorded contralaterally (fig 8). As the source of wave II is thought to be the nucleus cochlearis and that of wave III the nucleus of the superior olivary complex, failure to record wave II contralaterally indicates a lack of crossing of the axons that form the trapezoid body.²³ Failure to record a crossed acoustic reflex, as shown here, is also consistent with an absent trapezoid body. On the other hand, the bilateral recording of waves III, IV and V on left ear stimulation indicates the presence of auditory pathways that span the brain stem rostrally of the trapezoid body (olivary complex, nucleus lemnisci lateralis, commissura colliculi inferiores). The presence, however, of peripheral damage of the auditory nerve (mainly on the right side) limits the interpretation of these findings.

Our patients with HGPPS showed no mirror movements, although these are known to occur in other disorders characterised by defective axonal crossing, such as Kallmann syndrome, Klippel–Feil syndrome and congenital hemiparesis.^{24,25} Transcranial magnetic stimulations in patients with Kallmann syndrome have evoked bilateral responses, with the ipsilateral response often being more pronounced, thus suggesting that the motor pathways are predominantly uncrossed.²⁴ However, in contrast with HGPPS, in which both the motor and somatosensory pathways are uncrossed, the sensory pathways in Kallmann syndrome are normally crossed.²⁴ This could relate to the fact that mirror movements occur in Kallmann syndrome but not in HGPPS.

The pathophysiology of the progressive scoliosis, a rather consistent feature of this disorder, remains unclear. Disturbances in the regulation of the muscle tone of paraspinal muscles, initiated by uncrossed pyramidal tract and perhaps rubrospinal tract, have been suggested.^{3,26}

Despite their uncrossed or partially crossed motor, somatosensory and auditory pathways, our patients performed normally on manual dexterity, complex sensory and spatial–visuoperceptual functions, and on reading and general intelligence tests. Hence, crossing of motor and somatosensory pathways may not be essential for these complex functions in humans. The presence of a normal corpus callosum, a structure formed by the massive crossing of axons that connect the two cerebral hemispheres, may permit the integration of sensory input from the two hands and the cognitive processes that require interhemispheric connections,²⁷ thus accounting for the above results.

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