

Supplementary Note

Case reports

Case 1. An 18-year-old Japanese boy (BAB1474) was born to non-consanguineous healthy parents after an uneventful pregnancy. There was no family history of neurological diseases. Soon after birth, long-segment Hirschsprung disease was noted and an ileostomy was placed at 3 days of life. He has a pale skin color, but hypopigmented patches were not observed. He had heterochromic irides bilaterally. Abnormal brainstem auditory evoked potentials (BAEPs) revealed neurosensory deafness. Brain computed tomography identified bilateral hypoplasia of the semicircular canal. He has no dysmorphic features. Nystagmus, spasticity and delayed developmental milestones were noted at 3 months of age. He rolled over at 9 months, sat at 12 months, and walked at 2 years. He had an episode of a generalized seizure at age 6 months.

At 10 years of age, he was attending a school for deaf-mutes. His height was less than the 5th percentile. No apparent intellectual delay was noted. He required orthosis for walking because of spastic diplegia. He had a contracture on his left ankle. Upper limb function was almost normal. Hyperreflexia in the lower limbs, positive Babinski and Chadock signs and ankle clonus were observed. By the age of 16 years, his ability to walk with support gradually diminished. Distal tendon reflexes of lower limbs were decreased and the ankle clonus disappeared. Muscle atrophy, pes cavus, decreased sensation were noted in the lower extremities. T2-weighted brain MRI revealed abnormal myelination (**Fig. 1a**). NCV at age 10 to 18 years were all reduced (median nerve 20.1 m/sec, tibial nerve 21.7 m/sec at 10 years of age, median nerve 23.0 m/sec, tibial 18.5 m/sec, peroneal nerve 20.3 m/sec at 14 years of age, and median 21.9 m/sec, tibial 10.6 m/sec, peroneal nerve 16.8 m/sec at 18 years of age). The W-index, a biometric index to

asses dystrophic canthorum on the basis of ocular measurements, was 1.77 at age 18. Secondary sexual characteristics were not evident until the age of 15 years.

Case 2. Clinical and neuropathological findings of this patient (BAB1442) were described elsewhere¹⁵. Since 1992 he has become progressively weaker. He has developed swallowing difficulties and currently tolerates a soft mashed diet. He no longer attempts to feed himself or to walk. Ataxic tremor has become more evident.

Case 3. The 2-year-old Caucasian boy (BAB1916) was born to non-consanguineous parents after an uneventful pregnancy and delivery. One of his two maternal half brothers has semilateral conductive hearing loss and white hair patches. The other shows a hypopigmented patch of the abdomen and attention deficit disorder. No other neurological diseases are found in any family members. Soon after birth he was diagnosed with long-segment Hirschsprung disease that required placement of an ileostomy. Due to his swallowing difficulty, a gastrostomy was placed. He also manifested complete neurosensory deafness resulting in absent BAEPs. Dysmorphic features were absent. Congenital nystagmus was noted. No skin or hair hypopigmentation was noted. He has segmental heterochromic irides. He showed reduced tearing and diminished sweating with heat intolerance. At 4 months of age, he showed spasticity in his extremities with brisk deep tendon reflexes. His head circumference was at the 10th percentile. His electroencephalography was normal. His development was delayed. He could not sit, but he barely rolled over at 15 months of age. His head circumference fell to below the 5th percentile. At the age of 2 years, he is still mostly fed by a gastric tube. He has reduced strength and tone in facial and limb muscles. Deep tendon reflexes were diminished at the patella, absent at the ankles, and trace at the biceps. Plantar responses are equivocal. He has bilateral crossed adductor reflexes at the knees. The T2-weighted head magnetic resonance imaging showed remarkable delay in myelination in the

subcortical white matter (**Fig. 1a**). Both motor and sensory NCVs were markedly reduced (ulnar nerve; 28.8 m/sec, peroneal nerve; 32.6 m/sec and sural nerve; 18.7 m/sec).

Case 4. This 9-year-old girl (BAB1866) was born to non-consanguineous Caucasian parents from an uneventful pregnancy and delivery. No family history of neurological diseases was noted. Soon after birth she was diagnosed with long-segment Hirschsprung disease and colostomy and ileostomy were placed. Her neurosensory deafness was noted at age 9 months. She had bilateral cochlear implants at age 2 years. Because of iris heterochromia and patchy hypopigmentation on the nape of her neck, she was diagnosed with Waardenburg syndrome. She was floppy at birth. Global developmental delay was evident; she sat at 9 months, walked at 22 months, spoke one word at 3 years and sentences at 6 years of age. Mild mental retardation and behavioral difficulties with lack of cooperation and attention were noted. Pes cavus foot deformity was noted at age 5 years. At the age 9 years, she showed mild dysarthria. She had tapering lower extremities, progressive pes cavus with intoeing and a wide-based gait with a foot drop. Reflexes were increased in the upper extremities and at the knees and diminished at the ankles. Plantar responses were equivocal bilaterally. NCV at ages 6 and 9 years revealed significant reduction in all extremities (median nerve; 16 m/sec, ulnar nerve; 21 m/sec, distal peroneal nerve; 14 m/sec, and tibial nerve; 17 m/sec at years old). Brain computed tomography was normal. MRI was not available due to the cochlear implant.