ON-LINE APPENDIX

Patient B (Algeria)

He had his first surgical intervention 3 days after birth for total colonic Hirschsprung disease (HD). Pigmentation of the skin and hair were normal, but he had irides heterochromia. No dysmorphic features were present except for a familial hypertelorism. He had profound bilateral SNHL and received a cochlear implant at 3 years of age, which allowed a favorable evolution. He walked at 27 months. Vestibular evaluation showed a reduced canal function on both sides but symmetric responses to the otolith testing. The contact was good. He was treated with oxcarbazepine for epilepsy.

Patient C (France/Portugal)

He is the first child of an unrelated couple with no familial history. He started walking within the normal range. A profound bilateral SNHL was diagnosed at 2 years of age. Vestibular testing showed a severely impaired canal function, with complete areflexia on the horizontal canal on the left side. Otolith function was absent on the left side but was normal on the right side. He walked at 15 months. At 30 months, he received a left cochlear implant. At the time of the clinical genetic consultation, 31 months, he presented with bilateral segmental heterochromia of the irides. His fundus showed hypopigmentation corresponding to the hypoplastic segments of the irides. There were no skin or hair pigment changes. The nasal root was high and broad with a bilateral epicanthus. He did not have any intestinal features, and his neurologic development was normal.

Patient D (Belgium)

The index case (patient D1) had HD, including the sigmoid, without pigmentary alterations. Growth, height, and head circumference were in the normal range. At 6 weeks of age, he showed profound bilateral SNHL. He underwent cochlear implantation. Both his younger brother and mother carry the mutation. The brother (patient D2) had profound SNHL diagnosed at 6 weeks of age and received a cochlear implant. He showed no HD and no pigmentary alterations. Their mother had SNHL and was recently diagnosed with trigeminal neuralgia on the right side.

Patient E (France)

Short-segment HD was diagnosed at 3 months of age and led to rectosigmoid ablation with anastomosis. He walked at 17 months with balance perturbations. Intellectual development and peripheral neurologic examination findings were normal. He had 2 hypopigmented skin patches and bright blue irides. Profound SNHL was diagnosed at 2 years of age and led to a cochlear implant into the right ear at 3 years 6 months of age. Vestibular evaluation showed a complete loss of function. Despite a hearing-threshold improvement, his language evolution was not remarkable.

Patient G (France)

He had intestinal occlusion during the first week of life that led to colostomy and ileoanal anastomosis. He had several septicemic episodes. He had blue eyes without any other pigmentary abnormality. At age 5, due to the severity of the intestinal problems, he was unable to attend regular speech re-education and his communication was reduced to a familial sign code. Audiometric assessment showed a profound SNHL with no hearing aid benefit. Vestibular evaluation showed a complete loss of vestibular function. Cochlear implantation was performed at 6 years of age. Hearing thresholds improved, but some language retardation persisted.

Patient H (Australia)

Delayed meconium and abdominal distension led to diagnosis of short-segment HD in the neonatal period. Transverse colostomy was performed at day 15. She had hypotonia, adducted thumbs, poor sucking, and a roving nystagmus. SNHL was suspected in the neonatal period. Neurologic problems included severe intellectual handicap and slowly progressive ataxia. She had decreased sweating and probable alacrima, light brown/red hair, fair skin, and unusual irides heterochromia with blue and brown radial segmentations. She showed mild dysmorphism, including a high nasal bridge, short philtrum, prominent upper lip, and relative hypertelorism. A brain MR imaging showed a striking bilateral symmetric hypointensity in the region of the globus pallidus.

Patient I (France/Reunion Island)

She was born at term (birth weight, −1 SD [2800 g]; birth length, −2.5 SD [46 cm]; and birth head circumference, 0 SD [34 cm]). She started walking at 15 months. SNHL was diagnosed at 2 years due to delayed speech. She fell frequently until cochlear implantation at 3 years. Vestibular evaluation showed a decreased canal function on both sides, particularly on the right side. Otolith function was also very asymmetric, with the right side worse than the left side. She had irides heterochromia as the sole depigmentation feature. Neurologic examination findings were normal at the 4 years 6 months of age.

Patient J (France)

He had his first hospitalization for surgical treatment of HD at 6 months and had several subsequent occlusions due to fibrous adhesions. He had irides heterochromia and small hypopigmented skin patches on his knees. Deafness was suspected at 6 months. Auditory brain stem responses were recorded with no V waves by using 100 dB stimulations on both sides. Hypotonia was suspected, associated with vestibular problems, and no extensive neurologic examination was performed. Audiometry confirmed profound SNHL at 8 months. Vestibular evaluation showed a complete loss of vestibular function. Hearing aids provided a small benefit, and he received a cochlear implant in the right ear at 2 years 6 months of age. He showed an important benefit of the hearing rehabilitation associated with specialized speech therapy and succeeded in developing oral language. This allowed him to attend a normal school with light speech re-education.

Patient L (France)

HD was diagnosed in the first weeks after birth. He started walking within the normal range. His neurologic examination findings were normal. At school, he had learning difficulties, and attention deficit/hyperactivity disorder, which was successfully treated with methylphenidate, was diagnosed at 10 years of age. He had bright blue irides and synophrys. A bilateral mild SNHL was diagnosed at 4 years of age, which progressed to moderate SNHL at 16 years of age.

Patient M (Nigeria/France)

Soon after birth, she showed hypotonia and a respiratory insufficiency that necessitated intubation. Intestinal occlusion occurred at 48 hours, and the rectal biopsy was consistent with an intestinal pseudo-obstruction. She also had esophageal dyskinesia. Despite gastrostomy, she was fed exclusively by parenteral nutrition until death at of 6 years of age due to febrile respiratory decompensation. Nerve-conduction velocities were severely reduced, and hypotonia and encephalopathy were persistent. Brain MR imaging showed hypomyelination. She had bright blue irides, an albinoid-like fundus of the eyes, a light prototype with hyperpigmented macules on her lower limbs, and hypopigmented patches that appeared progressively. Auditory brain stem response showed a profound bilateral SNHL.

On-line Table: *SOX10* mutations and clinical findings in patients included in the study[a]

Patient	Sex	Nucleotide	Protein	Phenotype	Remarks	Reference
A	M	c.126_127delGCinsCT	p.Arg43X	WS4	De novo	Pingault et al[14]
B	M	c.391A>C	p.Asn131His	PCWH	De novo	This article[b]
C	M	c.398A>G	p.Glu133Gly	WS2	De novo	This article
D	M	c.519C>G	p.Tyr173X	WS4	Familial	This article[c]
E	M	c.644_648delGGCAC	p.Arg215ProfsX64	WS4	De novo	This article[c]
F	M	c.700C>T	p.Gln234X	PCWH	De novo	Pingault et al[14]
G	M	c.811delA	p.Ile271SerfsX15	WS4	Sporadic	This article[c]
H	F	c.921delA	p.Gly308AlafsX3	PCWH		This article[c]
I	F	c.1040delC	p.Pro347HisfsX10	WS2	De novo	This article
J	M	c.1058delA	p.Ala354CysfsX2	WS4		This article[d]
K	M	c.1114C>T	p.Gln372X	PCWH	De novo	Pingault et al[14]
L	M	c.1195_1196delCA	p.Gln399ValfsX2	WS4	De novo	This article[c]
M	F	c.1401A>C	p.*467TyrextX86	PCWH	De novo	This article[c]
N	M	Full gene deletion	p.0?	PCWH	De novo	Bondurand et al[11]

[a] cDNA numbering refers to the sequence of NM_006941.3, with the A of the *ATG* initiation codon numbered as nucleotide 1.

[b] This mutation was reported in a recent article that described functional analyses of missense mutations.[19]

[c] This mutation was mentioned in a recent review that did not provide a clinical description.[2]

[d] This mutation was reported in a poster by Touraine RL et al[1] (below), which did not provide a clinical description.

1. Touraine RL, Attie-Bitach T, Pelet A, et al. Expression of Sox10 in human embryo and fetal brain accounts for a neurological phenotype in Waardenburg type 4 spectrum. *Am J Hum Genet* 1998;63:A174