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D. Pareyson, F. Taroni, S. Botti, et al. *Neurology* 2000;54;1696 DOI 10.1212/WNL.54.8.1696

This information is current as of October 27, 2012

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http://www.neurology.org/content/54/8/1696.full.html

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## Cranial nerve involvement in CMT disease type 1 due to early growth response 2 gene mutation

**Article abstract**—Mutations in the gene coding for the Schwann cell transcription factor early growth response 2 (EGR2), which seems to regulate myelinogenesis and hindbrain development, have been observed in few cases of inherited neuropathy. The authors describe a unique combination of cranial nerve deficits in one member of a Charcot-Marie-Tooth 1 family carrying an *EGR2* mutation (Arg381His). This finding further supports the role of EGR2 in cranial nerve development. **Key words:** Charcot-Marie-Tooth disease—EGR2—Cranial nerves—Myelin genes—Demyelinating neuropathy.

NEUROLOGY 2000;54:1696-1698

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The demyelinating variety of Charcot-Marie-Tooth disease (CMT1) is usually associated with a duplication on chromosome 17p11.2, encompassing the peripheral myelin protein 22 (*PMP22*) gene (CMT1A). Micromutations involving the *PMP22* gene or the myelin protein zero gene (*MPZ*) (CMT1B) are rarely found; the more common X-linked variety (CMTX) is associated with connexin-32 mutations.<sup>1,2</sup> In other cases, no mutation is found. Some families do not demonstrate linkage with any of these loci, providing evidence for the existence of another locus (CMT1C).<sup>1</sup>

Mutations in the early growth response 2 gene (*EGR2*) have been demonstrated in very few cases of CMT1,<sup>3,4</sup> Dejerine—Sottas disease (DSD),<sup>5,6</sup> and congenital hypomyelinating neuropathy.<sup>3</sup> EGR2 is a Schwann cell transcription factor that binds DNA through three zinc-finger domains,<sup>3</sup> and is thought to regulate the expression of late myelin genes such as *MPZ* and myelin basic protein, thus playing a key role in myelinogenesis.<sup>3</sup> Homozygous mice knocked out for *Krox-20*, the murine orthologue of *EGR2*, have no compact myelin in the peripheral nervous system.<sup>3</sup> Moreover, they display abnormal rom-

bomere segmentation and neuronal migration in the developing hindbrain, resulting in anatomic abnormalities of the cranial nerves, particularly of the V, VI, VII, IX, and X pairs.<sup>3</sup> Therefore, Krox-20 is thought to mediate even hindbrain development.

We report the peculiar clinical features of a family carrying a heterozygous missense EGR2 mutation (Arg381His)<sup>6</sup> and affected by severe CMT1 with a unique combination of cranial nerve deficits in one member.

Patients and methods. Two members of the family were affected: the 67-year-old father and his 33-year-old daughter. The father had gait abnormalities from infancy and progressive wasting and weakness of distal limb muscles, with later involvement of proximal muscles. He became chairbound at age 55. During his 30s, he gradually developed diplopia and strabismus and thereafter progressive bilateral hearing loss. At age 62, he suddenly developed stridor and dyspnea and needed tracheostomy for bilateral vocal cord palsy. At age 67, examination showed weakness of left superior and medial rectus muscles with diplopia on upward and lateral gaze toward right, consistent with a partial palsy of the third cranial nerve. His pupils were normal and he had severe bilateral hearing loss. He still needed the tracheostomy tube, was dysphonic, and had very mild dyspnea. Stance and gait were impossible. Upper limb weakness was mild proximally but very severe distally; he was paraplegic with only incomplete thigh movements. Muscle wasting was severe in forearms, hands, and lower limbs. Deep tendon reflexes (DTRs) were absent. He had severe sensory loss to all modalities with stocking-glove distribution and pes cavus and achilles tendon tightening.

The daughter had a similar history of clumsy gait since

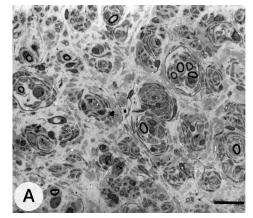
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Supported by Telethon-Italy (grants to A.S., F.T.).

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Presented in part at the ninth meeting of the European Neurological Society (ENS); June 5-9, 1999; Milan, Italy.

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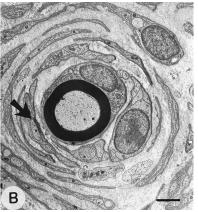


Figure. Daughter's sural nerve biopsy. (A) Semithin section. Severe loss of myelinated fibers, several onion-bulb formations, few thinly myelinated fibers, and a regenerating cluster are seen (toluidine blue; bar =  $20 \mu m$ ). (B) Electron microscopy. A normally myelinated fiber is surrounded by a multilayered onion bulb consisting of Schwann cell cytoplasmic processes often containing unmyelinated axons (arrow) (uranyl acetate and lead citrate; bar =  $2 \mu m$ ).

early childhood and a progressive sensorimotor deficit distally in all limbs. On examination, cranial nerves were normal. She had pes cavus and severe achilles tendon tightening; without special shoes, she needed support to walk. There was distal muscle wasting and weakness along with sensory loss, moderate in upper limbs and severe in lower limbs. DTRs were brisk but ankle jerks were absent.

Nerve conduction studies demonstrated marked slowing of motor conduction velocities, which could be measured only along radial nerves in the father (21 to 28 m/sec) and in upper limb nerves in the daughter (16 to 24 m/sec). In these nerves, distal motor latencies were prolonged (5 to 7 msec) and compound muscle action potential (CMAP) amplitudes were moderately to severely reduced. Apart from the femoral nerve in the daughter, M-responses were absent in lower limb nerves. F-wave response could be obtained only in the daughter's median nerve (latency = 51.2 msec). All sensory action potentials were absent. In both patients, CMAP amplitudes were reduced and latencies were prolonged in the facial and spinal accessory nerves; blink reflex examination revealed prolongation of R1 (16.2 to 20 msec) and R2 (43.1 to 46.2 msec) responses.

Audiometry was performed in the father and showed 60 to 80 dB pantonal sensorineural hearing loss. Brainstem auditory evoked potential (BAEP) studies revealed loss of the early waves and severe bilateral delay of the V wave latency (7.29 to 7.59 msec), which were consistent with the audiometric findings and suggested a cochlear or retrochoclear defect. BAEPs were normal in the daughter and visual evoked potentials were normal in both patients.

Brain MRI was performed in both cases and failed to reveal any abnormality in the brainstem or cranial nerves.

The daughter underwent sural nerve biopsy, which showed severe loss of myelinated fibers and several onion-bulb formations (figure, A). The few remaining fibers were thinly or normally myelinated. On electron microscopy, onion bulbs consisted of several lamellae of Schwann cell cytoplasmic processes often containing unmyelinated axons; onion bulbs were denervated or they surrounded deremyelinated axons or fibers with normally compacted myelin (see figure, B).

In both patients, direct sequencing analysis of *EGR2* showed a heterozygous missense mutation (Arg381His) in the second zinc-finger domain.<sup>6</sup>

**Discussion.** This family has severe CMT1 associated with a dominant heterozygous *EGR2* mutation

in the second zinc-finger domain that probably impairs interactions with DNA. The father showed a unique combination of clinically overt cranial nerve deficits: unilateral partial third nerve palsy, bilateral palsy of the recurrent nerves leading to vocal cord paresis requiring tracheostomy, and bilateral sensorineural hearing loss. Electrophysiologically, both patients showed evidence of demyelination and axonal loss along the VII and XI cranial nerves, and also along the sensory trigeminal nerve fibers (as shown by blink-reflex abnormalities). Audiometric and BAEP findings were consistent with sensorineural hearing loss, although they could not discriminate between a cochlear and retrocochlear defect.

Electrophysiologic evidence of demyelination in cranial nerves is expected in inherited demyelinating neuropathies, such as CMT1 and DSD, characterized by a generalized dysfunction of Schwann cell myelin. Prolongation of BAEP early wave latencies is common in these diseases.7 However, the simultaneous clinical involvement of different cranial nerves observed in our patient is absolutely exceptional in CMT1 and may be related to the role of Krox-20/ EGR2 in brainstem development. Patients with CMT or DSD rarely show clinical cranial nerve involvement. Trigeminal neuralgia (sometimes familial) has been occasionally reported in CMT1 and DSD,8 and weakness of masticatory or facial muscles is rarely observed in DSD.9 Sensorineural hearing loss may occur in CMT1.<sup>10</sup> Even bulbar muscle weakness has been reported as a rare manifestation of CMT1A<sup>10</sup> or DSD.9 Dysphonia due to partial vocal cord paresis and dyspnea due to diaphragm weakness are exceedingly rare.10 The axonal subtype CMT2C is characterized by laryngeal recurrent and frenic nerve involvement<sup>1,2</sup>; these nerves are rather long and progression of a length-dependent severe neuropathy might explain their involvement.<sup>10</sup> However, this mechanism cannot explain either oculomotor nerve palsy, which does not occur in CMT and DSD, or sensorineural hearing loss. In our patient, involvement of multiple cranial nerves seems to be associated with a specific EGR2 function. Consequently, one might expect cranial nerve involvement to occur at the nuclear level. However, because MRI was normal and we could not further localize the acoustic defect, we could not establish whether cranial nerve nuclei were primarily affected. One can hypothesize that *EGR2* mutation causes an underlying nuclear defect that becomes clinically evident after prolonged nerve trunk demyelination and axonal loss.

In the few reported patients carrying *EGR2* mutations, only the two DSD cases, who harbored the same mutation, showed cranial nerve involvement<sup>5,6</sup>: one had slight facial and masticatory muscle weakness and the other only mild facial weakness.

Although the full spectrum of neuropathies associated with *EGR2* mutations has yet to be defined, cranial nerve abnormalities in the setting of a severe demyelinating or hypomyelinating neuropathy should raise the suspicion of an *EGR2* mutation.

**Note added in proof:** We have become aware that Latour et al. reported in an abstract the same *EGR2* mutation in a 9-year-old girl (J Periph Nerv Syst 1999;4:293–294). Interestingly, the patient had strabismus and nystagmus.

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# Abnormalities in CSF concentrations of ferritin and transferrin in restless legs syndrome

**Article abstract**—CSF and serum were obtained from 16 patients with idiopathic restless legs syndrome (RLS) and 8 age-matched healthy control subjects. Patients with RLS had lower CSF ferritin levels  $(1.11 \pm 0.25 \text{ ng/mL})$  versus  $3.50 \pm 0.55 \text{ ng/mL}$ ; p = 0.0002) and higher CSF transferrin levels  $(26.4 \pm 5.1 \text{ mg/L})$  versus  $6.71 \pm 1.6 \text{ mg/L}$ ; p = 0.018) compared with control subjects. There was no difference in serum ferritin and transferrin levels between groups. The presence of reduced ferritin and elevated transferrin levels in CSF is indicative of low brain iron in patients with idiopathic RLS. **Key words:** Restless legs syndrome—Iron—Ferritin—Transferrin—CSF.

NEUROLOGY 2000;54:1698–1700

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Restless legs syndrome (RLS) has been associated commonly with iron deficiency. 1,2 However, iron supplementation even in RLS patients without iron deficiency has been shown to produce improvement in some patients. 1,2 A plausible interpretation of these

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Address correspondence and reprint requests to Dr. Christopher J. Earley, Johns Hopkins Bayview Medical Center, Department of Neurology, 4940 Eastern Avenue, A6C, Room 678, Baltimore, MD 21224; e-mail: cward@jhmi.edu results is that the management of iron in the brain is altered in patients with RLS. This is possibly due to the blood-brain barrier, which allows the brain to maintain its iron status independent of blood levels.<sup>3</sup> To determine whether brain iron status was altered in RLS, we evaluated serum and CSF iron, ferritin, and transferrin concentrations in patients with RLS and control subjects.

**Methods.** We enrolled 16 patients with idiopathic RLS<sup>4</sup> who had periodic leg movements in sleep of more than 15 per hour, a 1-year history of daily RLS symptoms, and a positive clinical response to levodopa. Exclusion criteria were iron deficiency (ferritin < 18 ng/dL), renal/metabolic disorders, neuropathy, brain or spinal cord injuries, chronic inflammatory processes, and chronic pain syn-

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