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ORIGINAL ARTICLE

Cornelius F. Boerkoel · Hiroshi Takashima
Carlos A. Bacino · Donna Daentl · James R. Lupski

EGR2 mutation R359W causes a spectrum of Dejerine-Sottas neuropathy

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Abstract Heterozygous mutations in the early growth response gene 2 (*EGR2*), which encodes a zinc-finger transcription factor that regulates the late stages of myelination, cause myelinopathies including congenital hypomyelinating neuropathy, Dejerine-Sottas neuropathy (DSN), and Charcot-Marie-Tooth disease type 1. We screened 170 unrelated neuropathy patients without mutations involving the peripheral myelin protein 22 gene (*PMP22*), the myelin protein zero gene (*MPZ*), or the gap junction protein ß1 gene (*GJB1*) and identified two DSN patients with the heterozygous mutation R359W in the α-helix domain of the first zinc-finger of EGR2. We now report that this mutation is a recurrent cause of DSN, and that expressivity ranges from that typical for DSN to a more rapidly progressive neuropathy that can cause death by age 6 years. Furthermore, in contrast to patients with typical DSN, patients with the *EGR2* R359W mutation have more respiratory compromise and cranial nerve involvement.

Keywords Transcription factor mutations · Inherited neuropathy · Recurrent mutation · Facial nerve palsy

Introduction

Dejerine-Sottas neuropathy (DSN, MIM 145900) is a severe demyelinating neuropathy described originally as a hypertrophic neuropathy of childhood [1]. This disorder is indistinguishable clinically from severe Charcot-Marie-Tooth disease type 1 (CMT1, MIM 118200) [2]. It manifests usually with hypotonia and/or delayed motor development within the first 2 years of life [3, 4]. The electrophysiology of DSN is characterized by extremely slow nerve conduction velocities (NCVs, <6–12 m/s) [3, 4] and the histopathology by features of demyelination (onion bulbs and axonal loss) and hypomyelination (thin myelin sheaths) [5, 6].

As observed with CMT1 and congenital hypomyelinating neuropathy (CHN, MIM 605253), DSN is genetically heterogeneous [2]. Altered dosage of the peripheral myelin protein 22 gene (*PMP22*), heterozygous dominant mutations in *PMP22* or the myelin protein zero gene (*MPZ*), recessive mutations in *PMP22* or periaxin (*PRX*), and homozygosity for dominant CMT1-associated *MPZ* mutations can cause DSN [7, 8, 9, 10, 11, 12, 13, 14, 15, 16].

Warner et al. [17] and Timmerman et al. [18] have recently shown that mutations in *EGR2* (MIM 129010) cause CMT1, CHN, and DSN. The R359W mutation in the α-helix domain of the first zinc-finger of EGR2 was initially reported as a *de novo* heterozygous dominant negative mutant allele associated with DSN [18]. We now report two additional DSN patients with this R359W mutation and suggest that it is the most-common neuropathy-associated *EGR2* mutation and consistently causes DSN.

C.F. Boerkoel · H. Takashima · C.A. Bacino · J.R. Lupski (✉)
Department of Molecular and Human Genetics,
Baylor College of Medicine, One Baylor Plaza, Room 609E,
Houston, Texas 77030, USA
e-mail: jlupski@bcm.tmc.edu
Tel.: +1-713-7986530, Fax: +1-713-7985073

J.R. Lupski
Department of Pediatrics, Baylor College of Medicine,
One Baylor Plaza, Houston, Texas 77030, USA

D. Daentl
Shriners Hospital of Northern California,
2425 Stockton Boulevard, Sacramento, California 95817, USA

Materials and methods

Human subjects

All patients referred to this study by their primary physician or neurologist received appropriate counseling and gave informed consent approved by the Institutional Review Board of Baylor College of Medicine. We isolated DNA from the peripheral blood of each patient and established lymphoblastoid cell lines.

The cohort contained patients diagnosed with CMT and related neuropathies from 170 different families. The distribution of clinical diagnoses was 126 families with CMT type 1, 1 family with pathological findings diagnostic of CMT4B, 2 with hereditary

Table 1 Primer pairs used for amplifying the *EGR2* coding region

Primer name	Primer pairs
Exon 1 F	CAGCAACTTGTTTGCTACTTTTATTTCTG
R	GTCTTCAAAGCCAGTGCAGTCAGC
Exon 2a F	AATTTCCCCACCTTTTGGAC
R	GCAGAAGGGTCCTGGTAGAG
Exon 2b F	AGCTTCAACCACAGCCTCAT
R	CTGCTGCTGAGCTGCTACC
Exon 2c F	CAGACTATCCTGGATTCTTTCCAT
R	GCTTATGCCCAGTGTGGATT
Exon 2d F	ATTCTGAGGCCTCGCAAGTA
R	GTTTGTTGTGCAGCTCCAGTG

neuropathy with pressure palsy, 8 with Dejerine-Sottas syndrome, 20 with CHN, and 13 with CMT type 2. The referring physician assigned these diagnoses to each proband, although when available we confirmed the diagnosis by review of accompanying clinical information and objective laboratory studies, e.g., NCVs and nerve histopathology. Each proband from these families had previously tested negative for the CMT1A duplication and HNPP deletion, as well as for mutations in the coding regions of *PMP22*, *MPZ*, and *GJB1*.

Mutation screening

We screened the human CITB-978SK-B and CITB-HSP-C BAC libraries with an overgo primer probe for *EGR2* and isolated three BACs (19J19, 45E19, 221A15) containing both coding exons of *EGR2*. We used these to sequence the intron between the two exons of *EGR2* to obtain additional intronic sequence for optimal design of polymerase chain reaction (PCR) primers [17].

We identified both coding exons by aligning the BAC sequence with the human *EGR2* cDNA and designed primers for PCR amplification of exons and intronic splice junctions with the Primer v3 program (http://www-genome.wi.mit.edu/cgi-bin/primer/primer3_www.cgi) (Table 1). All forward primers had a -21 M13 primer tail (TGTAAAACGACGGCCAGT) and all reverse primers a M13 reverse tail (CAGGAAACAGCTATGACC). Using 50 ng of patient genomic DNA, the above primers, and Qiagen HotStarTaq, we amplified the coding region of *EGR2* as follows: 15 min at 95°C, 40 cycles of amplification (95°C for 30 s, 55°C for 30 s, 72°C for 1 min), and 7 min at 72°C. Amplification of 2a, 2b, and 2d required the addition of Qiagen Q buffer to 20%. Using a 96-PCR purification kit (Qiagen), we purified PCR products amplified from the genomic DNA of patients, relatives, and control chromosomes, and sequenced the products with dye-primer chemistry (Applied Biosystems) with an ABI377 automated sequencer (Applied Biosystems). We aligned resulting sequences and evaluated mutations with the Sequencher sequence alignment program (ACGT Codes). We numbered the *EGR2* cDNA sequence beginning with the adenine of the presumed initiating methionine and described mutations according to den Dunnen and Antonarakis [19].

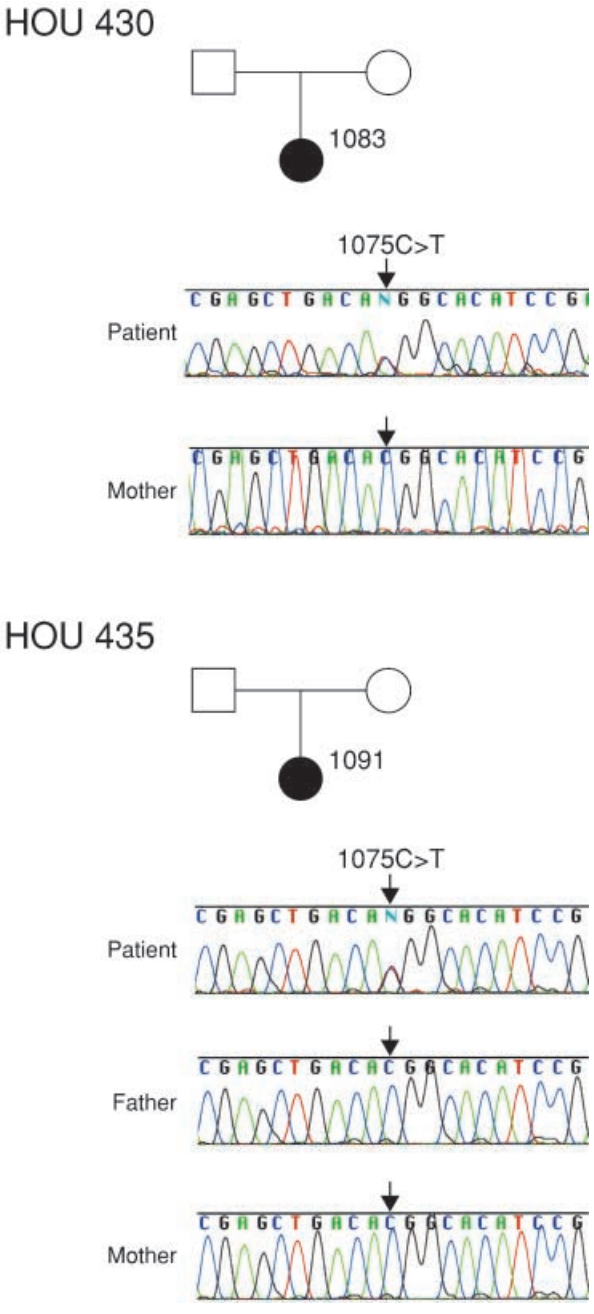

Fig. 1 Chromatograms of *EGR2* alterations identified in patient 1083 from family HOU430 and 1091 from family HOU435. Each had the heterozygous transition 1075C>T causing R359W. The father of 1083 was not available. *Black symbols* indicate Dejerine-Sottas neuropathy

Results

EGR2 mutation analysis in neuropathy patients

By direct sequencing, we screened each coding exon of *EGR2* for mutations in 170 unrelated peripheral neuropathy patients who had tested negative for mutations involving *PMP22*, *MPZ*, or *GJB1*. Patients 1083 and 1091 respectively of families HOU430 and HOU435 were heterozygous for transition 1075C>T. Base 1075C lies in a CpG dinucleotide, a known transition mutation hotspot secondary to the susceptibility to methylation-mediated deamination [20, 21]. By conceptual translation, 1075C>T causes the missense mutation *R359W* (Fig. 1). Consistent with 1075C>T being a *de novo* dominant mutation, we did not observe this mutation in either parent of patient 1091 (Fig. 1), in the mother of patient 1083 (the father was not available, Fig. 1), or in 168 control chromosomes.

Table 2 Clinical features of patients with myelinopathy secondary to *EGR2* mutation R359W (*NA* not available, *MF* myelinated fibers, *OBF* onion bulb formation)

Family Patient	HOU430 1083	HOU435 1091	Timmerman et al. [18]	Taroni et al. [31]
Sex	F	F	M	NA
Inheritance pattern	Sporadic	Sporadic	Sporadic	Sporadic
Age at onset	Birth	4–5 months	Birth	Infancy
Current age (years)	Deceased (6)	22	Deceased (16)	NA
Cause of death	Respiratory failure	Not applicable	Respiratory failure	NA
Motor involvement	Distal dominant, severe	Distal dominant, severe	Distal dominant, severe	Distal dominant, severe
Age of walking (years)	Never	1.3	3	NA
Cranial nerve involvement	Yes	Yes	Yes	NA
Sensory loss	Severe	Severe	Normal	NA
Sensory ataxia	Yes	Yes	Yes	NA
Dysesthesia	None	None	NA	NA
Foot deformity	Pes cavus	Pes cavus	NA	NA
Motor nerve conduction velocity	Undetectable	≤8 m/s	8 m/s	≤8 m/s
Peripheral nerve histopathology	Sever loss of MF, OBF	Severe loss of MF, OBF	Severe loss of MF, OBF	Severe loss of MF, OBF

Phenotype of patients with *EGR2* mutation R359W

Patient 1083 presented with hypotonia and hip dysplasia immediately after birth; she gained minimal use of her hands and feet during the first 6 months of life and then gradually losing motor function, she developed paralysis distal to the knees and elbows by 2 years of age (Table 2). On examination at 2 years of age, she had moderate bilateral facial weakness, inability to close her eyes fully, a mask-like lower face, poor soft palate elevation and nasal speech, severe distal dominant muscle weakness and atrophy, hypotonia, areflexia, and decreased pain sensation in the extremities. By electrophysiology, she had undetectable motor conduction velocities of the facial and right median, tibial, and proximal common peroneal nerves, and absent sensory conduction velocities of the right median and sural nerves. A sural nerve biopsy performed at that time demonstrated a marked decrease of myelinated fibers, evidence of demyelination and remyelination, and onion bulb formations. With progression of her disease, she had increasing difficulty swallowing and breathing; she eventually received most of her food through a gastric tube and died of respiratory failure at 6 years of age. No other family members had a peripheral neuropathy.

Patient 1091 had difficulty grasping objects and strabismus secondary to lateral recti weakness by 4–5 months of age. On examination at 3 years of age, she had strabismus despite two prior corrective eye surgeries. In the upper extremities, she had severe distal muscle weakness and atrophy, areflexia, and decreased pain and temperature sensation; in the lower extremities, she had less-severe distal muscle weakness and atrophy, hyporeflexia, and intact sensation. By 8 years of age, her lower extremity weakness had progressed; she could no longer walk on her heels, could not run as well, and had lower extremity areflexia, reduced sensation, and nerve hypertrophy. As a complication of her hand involvement, she developed bilateral fixed contractures of the fourth and fifth fingers by 15 years of age. The more-severe involvement of her upper extremities was reflected by her electrophyisology studies at 3 years of age: undetectable median and ulnar nerve conduction velocities but tibial nerve conduction velocities of 8 m/s. A sural nerve biopsy at 3 years of age showed a marked decrease in the size and number of myelinated fibers, evidence of demyelination and remyelination, and onion bulb formations. She also developed a severe thoracolumbar scoliosis and required an anterior and posterior spinal fusion at 15 years of age. Currently, at age 22 years, she follows a rigorous physical exercise program, including weight lifting and walking on a treadmill; this routine has markedly slowed deterioration of her strength and endurance. Although she had pneumonia several times in early childhood and has restrictive lung disease from her thoracolumbar scoliosis, her respiratory function has deteriorated little since her spinal fusion.

Both patients 1083 and 1091 had normal intellectual development. Patient 1091 has completed university. Neither patient exhibited central nervous system involvement on physical examination; in addition magnetic resonance imaging of patient 1083 revealed a normal brain.

Discussion

EGR2 is a Cys_2/His_2 zinc-finger transcription factor that is an orthologue of murine Krox20. Expression of *Krox20* in Schwann cells correlates with the later stages of myelination, and in vitro studies have shown that Krox20/EGR2 induce the expression of several proteins involved in myelin sheath formation and maintenance [22]. Consistent with these observations, *Krox20*$^{-/-}$ mice display a block in Schwann cell differentiation [23, 24].

In Krox20 the arginine residue corresponding to R359 of EGR2 is essential for DNA recognition and specificity

[25, 26]. Therefore mutation R359W was predicted to interfere with DNA binding, and Warner et al. [27] have shown that this mutation decreases DNA binding. From their in vitro studies, Warner et al. [27] conclude that R359W is a dominant negative or gain-of-function mutation that interferes with normal functioning of the wildtype *EGR2* product. This deduction is consistent with the *Krox20*$^{+/-}$ mice in which heterozygosity for a loss-of-function mutation does not cause disease.

EGR2 mutations cause a continuum of peripheral neuropathy ranging from severe CHN to typical CMT1 [2]. In addition to the R359W mutation, four other dominant neuropathy-causing alleles have been reported for *EGR2*: D355V, R381H, R409W, and the complex allele S382R+D383Y. Like R359W, each of these mutations lies within a zinc-finger and has been shown [27] or is predicted to affect the binding of EGR2 to DNA. The patients in the family segregating the R409W mutation exhibited typical autosomal dominant CMT1, with disease onset in the 2nd to 3rd decade of life and NCVs ranging from 26 to 42 m/s [17]. The patient with the *de novo* heterozygous D355V mutation developed symptoms late in the 1st decade of life and had NCVs of <19 m/s [28]. A father and daughter with the R381H mutation had a history of gait abnormalities from infancy and NCVs of 16–28 m/s; the father also had severe cranial nerve involvement and paraplegia [29]. Another unrelated girl with R381H presented with congenital hypotonia and Duane syndrome (limitation of abduction and adduction of the globe with narrowing of the palpebral fissure on adduction and widening on abduction) [30]. The patient heterozygous for the complex *de novo* mutation S382R+D383Y had infantile hypotonia, delayed gross motor development, and NCVs of ≤8 m/s [17]. The cause of this variable expressivity has not been defined, but initial studies of DNA binding and reporter gene activation by mutant EGR2 proteins suggest that the severity of the phenotype correlates with mutant EGR2 inhibition of wildtype EGR2 DNA binding and gene activation [27].

Patients with the R359W mutation, most closely resemble patients with the R381H mutation excepting that patients with the R359W mutation generally develop severe disease earlier, have more pronounced respiratory compromise, and have a faster disease progression. The phenotype observed with the R359W mutation is most consistent wit DNS although the clinical presentation ranged from that similar to CHN to that of severe CMT1 (Table 2).. This variable expressivity, which is similar to that observed among patients with myelinopathy-causing mutations in other genes, has not been delineated, although plausible explanations include the effects of modifier genes and differences in genetic background. Awareness of this variable expressivity is of great importance for counseling families regarding the prognosis of the patient and for counseling surviving patients regarding the possible outcomes in their children.

To date, R359W is the most-common neuropathy-causing *EGR2* mutation. Of nine unrelated patients reported with dominant *EGR2* mutations, four have the 1075C>T transition causing R359W [18, 31], two the 1142G>A transition causing R381H [29, 30], one the 1225C>T transition causing R409W [17], one the transversions 1146T>G and 1147G>T (S382R+D383Y) [17], and one the transversion 1064A>T (D355V) [28]. All the transitions occur at CpG dinucleotides. Methylation of mammalian DNA occurs on cytosines primarily in CpG dinucleotides. Spontaneous deamination of the unstable 5-methylcytosine to thymine is a common mutation mechanism [21] and accounts for a third of germline point mutations causing human disease [20] and for 78% of the heterozygous dominant neuropathy-causing mutations reported in *EGR2*. By comparison to the other dominant heterozygous *EGR2* transition mutations, the increased frequency of mutation of 1075C may arise because 1075C is methylated more frequently or is repaired less efficiently following spontaneous deamination of its 5-methylcytosine derivative to thymidine.

EGR2 mutations are a relatively frequent cause of DSN in diverse populations. Of 20 unrelated DSN patients in our cohort, 2 had the heterozygous R359W *EGR2* mutation; by comparison, 4 and 3 of the 20 patients had de novo heterozygous causative mutations in *MPZ* [13, 32] and *PMP22* ([12]; unpublished data), respectively, and 3 recessive *PRX* mutations [16]. Of the 4 patients with R359W *EGR2* mutation, 1 was Ashkenazi Jewish, 1 Indian-Scottish-Irish, and 1 German-English; this suggests the *EGR2* mutation R359W is likely a significant cause of DSN in many populations.

The identification of myelinopathy-causing mutations in *EGR2* previously led to the proposal that genes regulated by EGR2 play a critical role in myelination, and mutations in those genes also cause myelinopathies. Consistent with this claim, J. Milbrandt et al. (personal communication) have shown that EGR2 regulates expression of the two neuropathy-associated genes *MPZ* and *PRX*. Thus it appears that the pathway of EGR2 and the downstream genes that it regulates are a major cause of demyelinating peripheral neuropathies among patients without alterations in *PMP22* dosage.

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