THE MODIFYING EFFECT A *PMP22* DELETION IN A FAMILY WITH CHARCOT-MARIE-TOOTH TYPE 1 NEUROPATHY DUE TO AN *EGR2* MUTATION

REMÉNYI Viktória[1], INCZÉDY-FARKAS Gabriella[1, 2], GÁL Anikó[1], BEREZNAI Benjamin[1], PÁL Zsuzsanna[3], KARCAGI Veronika[4], MECHLER Ferenc[5], MOLNÁR Mária Judit[1]
[1]Institute of Genomic Medicine and Rare Disorders, Semmelweis University, Hungary
[2]Zucker Hillside Hospital North Shore - LIJ Health System, Glen Oaks, NY, USA
[3]Department of Neurology, Semmelweis University, Hungary
[4]National Institute of Environmental Health, Department of Molecular Genetics
[5]Department of Neurology, University of Debrecen, Hungary

Background – Mutations of both the *PMP22* and *EGR2* genes cause Charcot-Marie-Tooth (CMT) disease type 1. Deletion of the *PMP22* gene, results in hereditary neuropathy with liability to pressure palsies. More publications exist about the interaction of *PMP22* duplication and other CMT-causing gene mutations. In these cases the intrafamiliar discordant phenotypes draw the attention to the possible role of modifying genes. The gene-gene interactions between the *PMP22* and *EGR2* genes are not well understood.
Case report – We report two brothers with late onset CMT1 due to a c. 1142 G>A (Arg381His) heterozygous substitution in the *EGR2* gene. Additionally, the older brother with the less severe symptoms harbored the *PMP22* gene deletion also.
Conclusion – The coexistence of the two genetic alterations did not aggravate the clinical symptoms. Moreover, the *PMP22* deletion appeared to have a beneficial modifying effect, thus implying potential gene-gene interaction of *PMP22* and *EGR2*. *PMP22* deletion may increase Schwann cells proliferation and compensate the dominant-negative effect of the Arg381His substitution in the *EGR2* gene.

Keywords: *CMT, EGR2 gene mutation, PMP22 deletion, gene-gene interaction, coexistence*

A *PMP22* DELÉCIÓ MÓDOSÍTÓ HATÁSA *EGR2* MUTÁCIÓ MIATT CHARCOT–MARIE–TOOTH 1-ES TÍPUSÚ NEUROPATHIÁS CSALÁDBAN

Reményi V, PhD; Inczédy-Farkas G, MD; Gál A, PhD; Bereznai B, MD, PhD; Pál Z, MD, PhD; Karcagi V, PhD; Mechler F, MD, DSc; Molnár M.J, MD, DSc

Ideggyogy Sz 2014;67(11–12):420–425.

Háttér – A Charcot–Marie–Tooth (CMT) -betegség 1-es típusának hátterében többek között a *PMP22* és az *EGR2* gének mutációi és kópiaszám-változásai is állhatnak. A „Hereditary Neuropathy with Liability to Pressure Palsy" (nyomásos bénulásokra hajlamosító örökletes neuropathia, HNPP) oka a *PMP22* gén deléciója. A *PMP22* gén duplikációjának és más, CMT-t okozó gének mutációinak kapcsolatáról több irodalomban is találhatunk utalást. Ezekben az esetekben az egyes családtagok eltérő klinikai képe hívhatja fel a figyelmet a módosító gének lehetséges szerepére. A *PMP22* és az *EGR2* gének közötti interakciók még nem tisztázottak teljesen.
Esetbemutatás – Férfi testvérpárt mutatunk be, akiknek az *EGR2* gén c. 1142 G>A (Arg381His) heterozigóta patogén mutációja következtében kései kezdetű CMT1 betegség alakult ki. Az idősebb testvérnek enyhébb tünetei vannak, a patogén mutáción kívül még *PMP22* deléciót is azonosítottunk nála.
Megbeszélés – A két patológiás eltérés együttes jelenléte nem súlyosbította a klinikai képet. A *PMP22* deléciónak ebben az esetben inkább jótékony módosító hatását találtuk, mely a *PMP22* és az *EGR2* gének közötti interakcióra utal. A *PMP22* deléció növelheti a Schwann-sejtek proliferációját, így kompenzálhatja az *EGR2* gén c. 1142 G>A (Arg381His) patogén mutációjának negatív hatását.

Kulcsszavak: *CMT, EGR2 génmutáció, PMP22 deléció, gén-gén interakció, együttes jelenlét*

Correspondent: Mária Judit MOLNÁR MD, DSc, Institute of Genomic Medicine and Rare Disorders, Semmelweis University; H-1083 Budapest, Tömő u. 25–29., Hungary. Phone/fax: (36-1) 4591492, e-mail: molnar.mariajudit@med.semmelweis-univ.hu

Érkezett: 2013. december 21. Elfogadva: 2014. február 26.

www.elitmed.hu

Charcot-Marie-Tooth disease (CMT) is a genetically heterogeneous group of hereditary motor and sensory neuropathies. Its estimated prevalence is 1:2500[1]. Charcot-Marie-Tooth disease is characterized by the degeneration or abnormal development of peripheral nerves and is transmitted with different genetic patterns[2]. More than 40 different CMT genes and over 50 loci have been identified so far (www.molgen.ua.ac.be/CMTMutations)[3]. CMT can be divided into major clinical categories, and can further be classified into different subtypes according to the underlying genetic alterations. Harding and Thomas have separated the type 1 and type 2 of CMT based on motor nerve conduction velocity[4]. CMT type 1 primarily affects the myelin sheath and can either be inherited in a dominant, recessive or X-linked (CMT1, CMT3, and CMT4) manner. CMT type 2 primarily affects axons and is either dominant or recessive.

Defects in the *Peripheral Myelin Protein-22* (*PMP22*), *Gap Junction Protein* (*GJB1*), *Myelin Protein Zero* (*MPZ*), and *Mitofusin 2 (MFN2)* genes are the most common genetic causes of hereditary peripheral neuropathies[5]. About 70% of CMT1A (MIM#118220) is caused by a 1.5 Mb tandem duplication of the *PMP22* gene which is located in the 17p11.2-p12 chromosomal region[6]. Unequal crossing over between two highly homologous repeats on chromosome 17p12 can either cause duplication or deletion of the given chromosomal region, resulting in three copies or only one copy of the *PMP22* gene and thus giving rise to CMT1A or hereditary neuropathy with liability to pressure palsies (HNPP) (MIM#162500), respectively[7]. The phenotypic variability is large, duplication or point mutation of the *PMP22* gene may cause not only CMT1A, but Dejerine-Sottas neuropathy (DSN) (MIM#145900), congenital hypomyelinating neuropathy (CHN) (MIM#605253) or Roussy-Lévy syndrome (MIM#180800) also[8–10]. Genetic defects of the *EGR2* can lead to CMT1D (MIM#607678), Dejerine-Sottas neuropathy or congenital hypomyelinating neuropathy. The *EGR2* gene encodes a transcription factor regulating myelination of peripheral and cranial nerves and activating transcription of myelin genes, including *GJB1*, *PMP22*, *MPZ* and *PRX (periaxin)*[11]. The *EGR2* mutations in CMT are generally associated with severe forms of demyelination or dysmyelination.

Disease severity can be highly variable, even among probands with identical mutations even within the same kinship. Although stochastic effects and environmental factors are likely to contribute to phenotype variability[12], anecdotal reports from the literature[13] suggest that mutations in other CMT genes can modify the CMT1A phenotype caused by *PMP22* duplication. Here we report the clinical features of two members of a Hungarian family with CMT due to heterozygous missense *EGR2* mutation apparently modified by *PMP22* gene deletion.

Patients and methods

Here we report the case of two brothers, aged 45 and 49 years. The patients gave written informed consent. This study was carried out according to the Helsinki Declaration of 1975. This study was approved by local ethics committee. Neurophysiological investigations were performed by standard techniques (Dantec Keypoint, Denmark). Nerve conduction studies were assessed for the median, ulnar, tibial and sural nerves. Motor nerve conduction velocity (MCV), distal motor latency (DL) and compound muscle action potential (CMAP) were recorded for the median, ulnar and tibial nerves. Sensory nerve conduction velocity (SCV) and sensory nerve action potential (SNAP) were assessed for the median and sural nerves. Sural nerve biopsy was performed and light and electron microscopy preparations were performed according to standard methods. Blood samples were collected for molecular analysis. *PMP22* gene deletion and duplication was detected by MLPA (Multiplex Ligation-dependent Probe Amplification) was performed using the SALSA MLPA KIT P033-B2 CMT1 (MRC-Holland, Amsterdam, The Netherlands) according to the manufacturer's introduction[14] and confirmed by real-time PCR (ABI 7300)[15]. All coding exons of *GJB1, MPZ* and *EGR2* genes have been investigated. The PCR products were sequenced using the ABI Prism 3500 sequencing machine. The received sequences were compared with the human reference genome (NM_000399.3; NM_000530.6; NM_000166) using the NCBI Blast program. The effect of the detected mutation was analyzed by the PolyPhen-2 prediction software.

Results

CLINICAL PROFILE

Patient 1: The first symptoms of the 45 years old patient appeared at the age of 25. First investigations revealed pes cavus with distal type muscle atrophy and paresis. Mild mitral valve insufficiency was also reported in the patients' history. Clinical investigation at age 45 revealed mild-moderate

Table 1. *The clinical data of the two investigated patients*

Patients	Patient 1	Patient 2
Age/Onset	47/25	51/24
Concomittant diseases	Mitral valve insuffiency	Diabetes mellitus, hypertension, cataract
Muscle atrophy and weakness	Moderate atrophy and paresis in the upper, severe in the lower limbs	Moderate atrophy and paresis in the limbs. Only the distal muscles of the lower limbs were severely affected
Reflexes	Absent tendon reflexes	Absent tendon reflexes
ENG	Severe demyelinating neuropathy. No peroneal and sural response were detected	Severe demyelinating neuropathy predominantly in the lower limbs
Sural nerve biopsy	Segmental demyelinisation with increased peri-, and endoneural connective tissue	Not done
Genetic results	PMP22: norm EGR2: c.1142 G>A (p.Arg381His) mutation	PMP22: deletion EGR2: c.1142 G>A (p.Arg381His) mutation
Barin CT	Not done	Lacunar infarcts in the basal ganglia

Table 2. *The nerve conduction study data of the two patients*

Patients	Patient 1			Patient 2		
	DL (ms)	Amp (mV)	CV (m/s)	DL (ms)	Amp (mV)	CV (m/s)
Right median nerve motor	5.9	4.6	36.3	5.8	4.8	37.6
Right ulnar nerve motor	4.9	4.5	31.2	5.3	4.2	38.0
Right peroneal nerve motor	absent	absent	absent	14.3	0.2	absent
Right sural nerve	absent	absent	absent	absent	absent	absent

Amp: Amplitude; NCV: Nerve Conduction Velocity; DL: Distal Latency

atrophy and weakness predominantly in the distal muscles of the upper limb with very severe atrophy and weakness in the lower limb muscles. He was wheelchair-bound, only a minimal extension of the lower limb could be achieved from a semi-flexed position. Fasciculation could be observed in his shoulder and arm muscles. His deep tendon reflexes were absent. Sensation of pain and light touch was decreased below the wrist and knee joints bilaterally. Proprioceptive sensation including joint position and vibration were impaired below the levels of the ankles.

Patient 2: The first symptoms of the 49-year-old brother started at age 24 with distal type muscle atrophy and weakness in the lower extremities. Over the years the patient suffered from multiple diseases and was treated for cataracts, diabetes mellitus, gout and hypertension. He had no clinical history suggestive of liability to pressure palsies. Neurological examination at the age of 49 revealed pes cavus, atrophy and severe weakness mainly in the distal muscles of the lower extremities, absent deep tendon reflexes, severe sensory deficiency was observed to all sensory modalities below the wrist and knee joints **(Table 1.)**. He is still ambulatory with crutches. The father of the siblings also suffered from similar symptoms, however he refused the offered neurological examination and genetic tests. The mother did not have any neurological symptoms.

NERVE CONDUCTION STUDIES

In case of *Patient 1* neurophysiology could not detect any peroneal and sural nerve response. Motor nerve conduction velocities of the median and ulnar nerve were moderately and severely decreased, respectively. Distal latencies were increased. The amplitudes of the motor response were slightly decreased. In *Patient 2* ENG could not detect a sural nerve response. The peroneal nerve motor response could be detected only at the ankle with very low amplitude. The motor conduction velocities of the median and ulnar nerves were decreased. Amplitudes of motor responses were slightly decreased **(Table 2.)**.

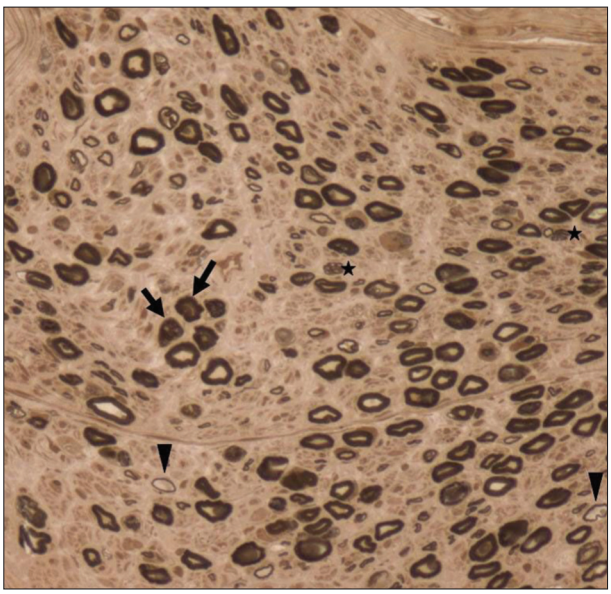

Figure 1. *The sural nerve biopsy of Patient 1 examinated by light microscopy. A mild reduction of myelinated and unmyelinated fibers can be observed. (Paraphenylenediamine staining, × 400)*

Marking: Arrowhead: fibers with thin myelin; Arrow: tomacoulos fibers; Asterisk: small regeneration axon groups

SURAL NERVE BIOPSY

Sural nerve biopsy was taken only from *Patient 1 (only with EGR2 mutation).* In his sural nerve segmental demyelination, increased peri- and endoneural connective tissue could be seen. Semithin cross-sections of the nerve showed a mild reduction of myelinated and unmyelinated fiber density. Myelin degradation products could be observed frequently. Some fibers had thin myelin sheaths. The number of dystrophic axons and small fibers resulting from axonal degeneration and regeneration were increased. Onion bulb formation was rare **(Figure 1.)**. In *Patient 2* (with both *EGR2* and *PMP22* alterations) sural nerve biopsy was not performed.

MOLECULAR GENETIC RESULTS

Genetic analyses revealed the c. 1142 G>A (Arg381His) mutation in the exon 4 of the *EGR2* gene in both patients in heterozygous form. The PolyPhen-2 software predicted this substitution as probably damaging (PSIC score: 0,986). This mutation has previously been reported by Pareyson et al. (Arg381His) also as pathogenic mutation[16]. Genetic testing of the *PMP22* gene detected a deletion in *Patient 2*. The *PMP22* deletion could not be identified in the other sibling. No pathogenic alteration was found in the *GJB1* and *MPZ* genes of our patients.

Discussion

This study reports the coexistence of the *PMP22* deletion and *EGR2* mutation. Based on the phenotype this gene-gene interaction did not have a deleterious effect, since the patient harboring both mutations had a less severe phenotype than his younger brother despite his concomitant diseases (diabetes mellitus) also affecting peripheral nerves. However we can not exclude the effect of environmental factors, although the two brothers have been living in the same household. The discordant phenotype of the brothers suggests the modifying effect of *PMP22* deletion. As far as we know only one case report has been published concerning the coexistence of a *PMP22* deletion and the defect of another gene in CMT patient[17]. In this case the coexistence of the *ABCD1* gene mutation (which results in adrenoleukodystrophy or adrenomyeloneuropathy, but not in CMT) aggravated the clinical symptoms due to *PMP22* deletion. More publications exist about the interaction of *PMP22* duplication and other CMT-causing gene mutations[13, 17]. In these cases the intrafamiliar discordant phenotypes draw the attention to the possible role of modifying genes. In a Dutch report, the interaction of the *PMP22* duplication and the G112S and I92V mutations of the *LITAF* gene resulted in a very severe phenotype[13]. In another family, two brothers had *PMP22* gene duplication on one allele, which they inherited from their father, on the other allele the missense mutation Arg200Gly of the *GJB1* gene, which they inherited from their mother[17]. The younger brother had Dejerine-Sottas syndrome resulting in severe kyphoscoliosis causing respiratory compromise and death at an early age. The older brother with the same genotype had less severe clinical manifestations. This observation suggests that unknown environmental or other stochastic factors may play a role in the clinical expression and progression of this genetically determined disease. This assumption is supported by the different clinical picture of two pairs of homozygotic twins with CMT1A due to *PMP22* duplication[12]. In both families the less-affected twin had a greater degree of palpable nerve enlargement, suggesting either a protective effect of interstitial nerve hypertrophy on axon function or, alternatively, that hypertrophy may have reflected a better ability to

restore lost function through mechanisms such as remyelination. The low prevalence of *PMP22* duplication has been associated by genetic and /or epigenetic modifying factors as well[18]. These cases suggest that the coexistence of different gene variances, and/ or epigenetic and environmental factors can be additive in their effects on the clinical phenotypes.

The Early Growth Response protein 2 *(EGR2)* is a zinc finger transcription factor. It induces expression of several proteins involved in myelin sheath formation and maintenance. It is activated in Schwann cells before the onset of myelination. *EGR2* activates the transcription of several myelin-associated genes, such as *PMP22*, *Cx32 (GJ1B)* and *PRX*[19]. The disease causing Arg381His (R381H) *EGR2* substitution has previously been described in families both with early and late onset CMT and congenital hypomyelinating neuropathy[16, 20]. In one family with early onset CMT one of the patients showed a unique combination of clinically overt cranial nerve deficits[16]. In our cases cranial nerve involvement was not detected. The Arg381His (R381H) substitution of *EGR2* is localized within the alfa-helix of the second zinc finger. The DNA binding sites of the *EGR2* transcription factor are connected to the zinc finger domains and it interacts with the DNA at the consensus *EGR2* binding site[21]. When the transcription factor binds with the DNA the arginine is able to form hydrogen bonds on the G rich strand on the consensus binding site. If the arginine is mutated to histidine, the hydrogen bonds will not be established.

The coexistence of an *EGR2* mutation and another pathogenic Charcot-Marie-Tooth -causing mutation (*GJB1*) has been reported in a family, where the R359W mutation in *EGR2* was shared by the affected daughter and her father[22]. The daughter also had a V136A de novo mutation in the *GJB1* gene. The father, harboring only the *EGR2* mutation, showed a mild CMT phenotype, however his daughter with the coexisting mutations had a more severe phenotype.

The pathogenic mutation detected in our patients is located within the DNA binding domain (DBD) of the EGR2 gene and results in absent DNA binding and transcriptional activity. *Nagarajan* et al discussed the effect of this mutation as a dominant-negativ inhibition of the *EGR2*-mediated expression of these essential myelin proteins[23] leading to demyelination. *PMP22* is involved in controlling myelin thickness and stability[24] and *PMP22* deficiency can increase proliferation of Schwann cells and fibroblast cultures in vitro resulting in axons with abnormally thick myelin (tomacula formation). The tomaculas are formed by excessive myelin folding, which is not compacted[25]. With these biochemical processes we would suppose a much worse condition for *Patient 2.* However the coexisting *PMP22* gene deletion can be one of the other genetic factors to compensate the effect of the deleterious *EGR2* mutation.

In conclusion: this is the first report describing the coexistence of *PMP22* gene deletion and a pathogenic mutation of the *EGR2* gene causing CMT1A. The coexistence of the *PMP22* deletion and *EGR2* mutation did not aggravate the clinical symptoms, since the patient with the double genetic defects had less severe phenotype. Our observation suggests the importance of further investigation of the gene-gene interaction in monogenic disorders such as Charcot-Marie-Tooth 1A for a better understanding of phenotype-genotype correlations.

DECLARATION

Hereby the authors of this manuscript give their signed consent of the data in the manuscript is original and the manuscript is not under consideration elsewhere, none of the manuscript contents have been previously published except in abstract form and all authors have read and approved all versions of the manuscript, its content, and its submission to the Clinical Neuropathology. The authors declare no conflict of interests.

ACKNOWLEDGMENTS

The authors would like to thank both patients for participating in the study, Györgyi Báthori for her technical help and Henrietta Pikó for performing MLPA analysis. The study was supported by the TÁMOP-4-2-1/B-03/1/KMR-2010-001 and BIOINF009-TÉT_10_1_2011_0058 grants.

REFERENCES

1. *Skre H.* Genetic and clinical aspect of Charcot-Marie-Tooth's disease. Clin Genet 1974;6:98-118.
2. *Banchs I, Casasnovas C, Albertí A, et al.* Diagnosis of Charcot-Marie-Tooth Disease. J Biomed Biotechnol 2009; Article ID: 985415 Epub 2009. Oct.8 doi:10.1155/2009/985415
3. *Patzko A, Shy ME.* Update on Charcot-Marie-Tooth Disease. Curr Neurol Neurosci Rep 2011;11:78-88.
4. *Harding AE, Thomas PK.* The clinical features of hereditary motor and sensory neuropathy types I and II. Brain 1980;103:259-80.
5. *Saporta ASD, Sottile SL, Miller LJ, Feely SM, Siskind CE,*

Shy ME. Charcot Marie Tooth (CMT) Subtypes and Genetic Testing Strategies. Ann Neurol 2011;69:22-33.
6. *Nelis E, Van Broeckhoven C, De Jonghe P, Löfgren A, Vanderberghe A, Latour P, et al*. Estimation of the mutation frequencies in Charcot-Marie-Tooth disease type 1 and Hereditary Neuropathy with Liability to Pressure Palsies: A European Collaboration Study. Eur J Hum Genet 1996; 4:25-33.
7. *Pentao L, Wise CA, Chinault AC, Patel PI, Lupski JR*. Charcot-Marie-Tooth type 1A duplication appears to arise from recombination at repeat sequences flanking the 1.5 Mb monomer unit. Nat Genet 1992;2:292-300.
8. *Roa BB, Dyck PJ, Marks HG, Chance PF, Lupski JR*. Dejerine–Sottas syndrome associated with point mutation in the peripheral myelin protein 22 (PMP22) gene. Nat Genet 1993;5:269-73.
9. *Kovach MJ, Lin JP, Boyadjiev S, et al.* An unique point mutation in the PMP22 gene is associated with Charcot-Marie-Tooth disease and deafness. Am J Hum Genet 1999;64:1580-93.
10. *Simonati A, Fabrizi GM, Pasquinelli A*. Congenital hypomyelination neuropathy with Ser72Leu substitution in PMP22. Neuromuscul Disord 1999;9:257-61.
11. *Szigeti K, Wiszniewski W, Saifi GM, et al.* Functional, histopathologic and natural history study of neuropathy associated with *EGR2* mutations. Neurogenetics 2007;8: 257-62.
12. *Garcia CA, Malamut RE, England JD, Parry GS, Liu P, Lupski JR*. Clinical variability in two pairs of identical twins with the Charcot-Marie-Tooth disease type 1A duplication. Neurology 1995;45:2090-93.
13. *Meggouh F, de Visser M, Arts WF, De Coo RI, van Schaik IN, Baas F*. Early onset neuropathy in a compound form of Charcot-Marie-Tooth Disease. Ann Neurol 2005;57:589-91.
14. *Stangler Herodez S, Zagradisnik B, Erjavec Skertget A, Zagorac A, Kokalj Vokac N*. Molecular diagnosis of PMP22 gene duplications and deletions: comparison of different methods. J Int Med Res 2009;37:1626-31.
15. *Aarskog NK, Vedeler CA*. Real-time quantitive polymerase chain reaction. Hum Genet 2000;107:494-8.
16. *Pareyson S, Taroni F, Botti S, et al.* Cranial nerve involment in CMT disease type 1 due to early growth response 2 gene mutation. Neurology 2000;54:1696-8.
17. *Hodapp JA, Carter GT, Lipe H, Michelson SJ, Kraft GH, Bird T*. Double Trouble in Herediter Neuropathy. Arch Neurol 2006;63:112-7.
18. *Abe A, Numakura C, Kijima K, Hayashi M, Hashimoto T, Hayasaka K*. Molecular diagnosis and clinical onset of Charcot-Marie-Tooth disease in Japan. J Hum Genet 2011;56:364-8.
19. *Warner LE, Svaren J, Milbrandt J, Lupski JR*. Functional consequences of mutations in the early growth response 2 gene (EGR2) correlate with severity of human myelinopathies. Hum Mol Genet 1999;8:1245-51.
20. *Vanderberghe N, Upadhyaya M, Gatignol A, et al.* Frequency of mutations in the early growth response 2 gene associated with peripheral demyelinating neuropathies. Online mutation report. J Med Genet 2002;39:e81. (http://www.jmedgenet.com/cgi/content/full/39/12/e81)
21. *Yoshihara T, Kanda F, Yamamoto M, et al.* A novel missense mutation in the early growth response 2 gene associated with late-onset Charcot-Marie-Tooth disease type 1. Neurol Sci 2001;184:149-53.
22. *Chung KW, Sunwoo IN, Kim SM, et al.* Two missense mutations of EGR2 R359W and GJB1 V136A in Charcot-Marie-Tooth disease family. Neurogenetics 2005;6:159-63.
23. *Nagarajan R, Svaren J, Le N, Araki T, Watson M, Milbrandt J*. EGR2 mutations in inherited neuropathies dominant-negatively inhibit myelin gene expression. Neuron 2001;30:355-68.
24. *D'Urso D, Schmalenbach C, Zoidl G, Prior R, Müller HW*. Studies on the effects of altered PMP22 expression during myelination in vitro. J Neurosci Res 1997;48:31-42.
25. *Li J, Parker B, Martyn C, Natarajan C, Guo J*. The PMP22 Gene and Its Related Diseases. Mol Neurobiol 2012 December 7. Epub ahead of print