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Report

Mutations in Two Genes Encoding Different Subunits of a Receptor Signaling Complex Result in an Identical Disease Phenotype

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Polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL), also known as "Nasu-Hakola disease," is a globally distributed recessively inherited disease leading to death during the 5th decade of life and is characterized by early-onset progressive dementia and bone cysts. Elsewhere, we have identified PLOSL mutations in *TYROBP* (*DAP12*), which codes for a membrane receptor component in natural-killer and myeloid cells, and also have identified genetic heterogeneity in PLOSL, with some patients carrying no mutations in *TYROBP*. Here we complete the molecular pathology of PLOSL by identifying *TREM2* as the second PLOSL gene. TREM2 forms a receptor signaling complex with TYROBP and triggers activation of the immune responses in macrophages and dendritic cells. Patients with PLOSL have no defects in cell-mediated immunity, suggesting a remarkable capacity of the human immune system to compensate for the inactive TYROBP-mediated activation pathway. Our data imply that the TYROBP-mediated signaling pathway plays a significant role in human brain and bone tissue and provide an interesting example of how mutations in two different subunits of a multisubunit receptor complex result in an identical human disease phenotype.

Since *TYROBP* encodes a cell-surface receptor element that interacts with many different proteins depending on the cell type, we used a genetic approach to search for genes involved in polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL [MIM 221770]), also known as "Nasu-Hakola disease" (Nasu et al. 1973; Paloneva et al. 2001; also see the GeneTests–GeneClinics Web site). We initially analyzed two informative families showing exclusion of linkage to the PLOSL locus located on chromosome 19q13.1 (Pekkarinen et al. 1998*a*, 1998*b*), for segregation of the marker haplotypes flanking genes that encode the polypeptides interacting with TYROBP. These genes included those for TYROBP-associated receptors SIRPBETA1 (chromosome 20p13) (Dietrich et al. 2000), TREM1 (chromosome 6p21.2), TREM2 (chromosome 6p21.2) (Bouchon et al. 2000), LY95 (NKp44, chromosome 6p22.1) (Vitale et al. 1998), MDL1 (chromosome 7q33) (Bakker et al. 1999), CD94 (chromosome 12p13.3) (Lanier et al. 1998*b*), KIR2DS2 (chromosome 19q13.4) (Lanier et al. 1998*a*), and NKG2C (chromosome 12p13.1) (Lanier et al. 1998*b*). Furthermore, haplotypes of chromosomal regions containing genes for the intracellular protein tyrosine kinases (PTKs) SYK (chromosome 9q22.1) and ZAP70 (chromosome 2q11.2) (Lanier et al. 1998*a;* McVicar et al. 1998) of the downstream signal-transduction pathway were analyzed for cosegregation. For haplotype construction, we selected two or three polymorphic markers flanking each candidate gene. We ge-

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notyped the following polymorphic markers: *D6S1616, D6S1575,* and *D6S1549,* for *TREM1, TREM2,* and *LY95; D20S198* and *D20S906,* for *SIRBETA1; D7S661* and *D7S2513,* for *MDL1; D12S336,* for *CD94; D19S926* and *D19S891,* for *KIR2DS; D12S77* and *D12S1697,* for *NKG2C; D9S1836* and *D9S1820,* for *SYK* and *D2S2222;* and *D2S2175,* for *ZAP70.* The position of the genes and markers were determined by Ensembl, version 3.26.1 (see the Emsembl Human Web site), and the UCSC Human Genome Browser (August 6, 2001, draft assembly [see the UCSC Human Genome Project Working Draft Web site]). Information on the sequence of the primers is available at the UCSC Human Genome Browser (see the UCSC Human Genome Project Working Draft Web site). Genotyping was performed as described elsewhere (Wessman et al. 2002). The genotyped families originated from Sweden (Nylander et al. 1996) and Norway (Edvardsen et al. 1983), and each had two affected family members (Pekkarinen et al. 1998*a;* Paloneva et al. 2000).

The only chromosomal region showing complete cosegregation with PLOSL was the 6p21-p22 region covered by the markers *D6S1616, D6S1575,* and *D6S1549* (fig. 1). This 10-cM DNA region contains genes for *TREM1, TREM2,* and *LY95.* The patients in the Swedish and Norwegian families were homozygous for different haplotypes, implying two independent mutations. Sequence analysis of the genomic DNA of the patients revealed mutations only in *TREM2* (for primer sequences, see table 1). The Swedish family had a homozygous G-to-A mutation at position 233 (233G→A), changing tryptophan 78 to a translation termination codon (W78X). This same mutation also was found in another Swedish family, which had three affected family members, but DNA for sequencing was available from only one patient. In the Norwegian family, a 558G→A mutation was found, resulting in conversion of lysine 186 to asparagine (K186N) (fig. 2). Neither of these mutations was found in a control panel of 100 Scandinavian DNA samples.

Since our sequence analyses of *TYROBP* from one American (whose family originates from Slovakia [Bird et al. 1983]), from one Bolivian, and from two Italian sibs, all of whom have PLOSL, had not revealed mutations, we amplified and sequenced the exons and intron-exon boundaries of *TREM2* from the genomic DNA of these patients. All had mutations in *TREM2:* the American patient was homozygous for a 401A→G substitution, resulting in conversion of the aspartic acid residue to glycine, at position 134 (D134G). The two Italian patients were homozygous for a conversion of nucleotide T to nucleotide C, in the splice-donor consensus site at the second position of intron 3 (482+2T→C), whereas their two unaffected sibs were homozygous for the normal allele. In the Bolivian patient, a homozygous 132G→A mutation changed tryptophan at position 44 to a translation stop codon (W44X). None of the mutations was observed in a control panel of 100 white individuals. The positions of the identified TREM2 mutations are shown in figure 2.

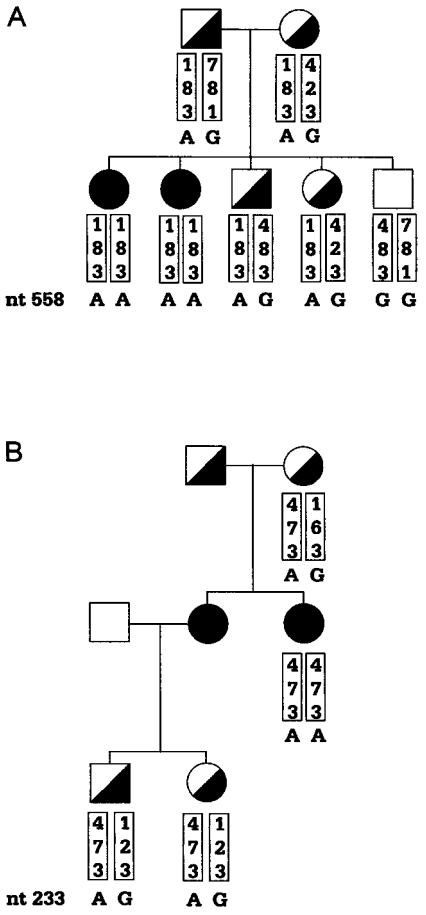

Figure 1 Pedigrees, haplotypes, and TREM2 mutations in the Norwegian (*A*) and Swedish (*B*) families with PLOSL. Black symbols denote patients with PLOSL; half-black symbols denote heterozygous carriers of a mutated *TREM2* allele; white symbols denote individuals who carry two wild-type alleles of *TREM2.* The 10-cM haplotypes were constructed by genotyping the following markers in both families: *D6S1616-D6S1575-D6S1549* (from top to bottom in the figure). nt = position of mutated nucleotide. *A,* Haplotype 1-8-3 and 558G→A mutation, showing cosegregation with PLOSL in the Norwegian family. Haplotype 4-8-3 in the male carrier probably results from a recombination. *B,* Haplotype 4-7-3 and 233G→A substitution, cosegregating with PLOSL in the Swedish family.

The 230-amino-acid TREM2 polypeptide belongs to the immunoglobulin superfamily (Ig-SF) and is predicted to consist of a 13-amino-acid signal peptide followed by a 154-amino-acid extracellular domain encoded by exons 2 and 3, with two cysteines potentially involved in generating an intrachain disulfide bridge of the Ig-SF V–type fold. The 33-amino-acid transmembrane domain is followed by a short, 30-amino-acid long cytoplasmic domain (Bouchon et al. 2000). On the cell membrane

of macrophages and dendritic cells, TREM2 is bound noncovalently to a disulfide-bonded TYROBP homodimer (Campbell and Colonna 1999; Bouchon et al. 2001*b*). This interaction is mediated by oppositely charged amino acids in the transmembrane domains of these proteins; one of these amino acids is a positively charged lysine in TREM2, and the other is a negatively charged aspartic acid in TYROBP. The interaction between TREM2 and an unidentified ligand results in the phosphorylation of tyrosines in the intracellular tyrosine-based activation motif (ITAM) of TYROBP. Phosphorylated ITAM binds the cytosolic PTKs SYK and ZAP70, and this interaction leads to an increase in intracellular Ca^{2+} concentration and to subsequent cellular activation (Lanier and Bakker 2000).

The mutations in the Bolivian (W44X) and Swedish (W78X) patients are predicted to result in the generation of a truncated protein lacking the transmembrane and cytoplasmic domains. In the Italian patients, the homozygous mutation of the splice donor site probably results in the skipping of exon 3 from the mature mRNA, also leading to a truncated protein. The mutation in the Norwegian family with PLOSL changes the positively charged lysine to asparagine in the transmembrane domain of TREM2. This has been shown to disrupt the association with (McVicar et al. 1998; Bakker et al. 1999), as well as the cell-surface expression of, TYROBP (Lanier et al. 1998*b;* Smith et al. 1998). Thus, all these PLOSL mutations are likely to result in complete loss of function of TREM2. The clinical phenotype of these patients with PLOSL was identical with that of those carrying mutations in *TYROBP* (table 2).

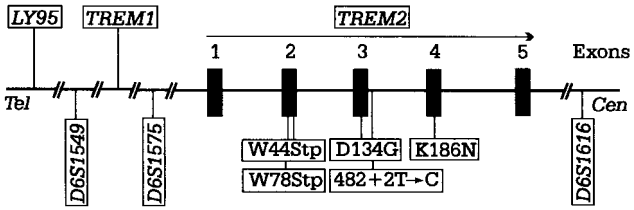

Figure 2 Schematic presentation of the identified PLOSL mutations in *TREM2*. The positions of other loci for TYROBP-associated cell-surface receptors, *TREM1* and *LY95*, as well as of the polymorphic "*D*" markers used in the segregation analysis, are indicated.

To gain some insight into the peculiar tissue manifestations of PLOSL in the brain and bone, we compared the levels of the *TREM2* steady-state transcripts with those of *TYROBP* in human tissues and cell lines rele-

Table 1

Genomic and cDNA Primer Sequences Used to Amplify *TYROBP, TREM1, TREM2,* and *ACTB*

	PRIMER[a] (5′→3′)	
FRAGMENT	Forward	Reverse
TYROBP:		
Exon 1	tggggacggaggtgaagttt	cccatcccaacacccacttt
Exon 2	gcctgtgggtttctcccaga	ggcagggaggtttggaaagg
Exon 3	ccgtctctcccacacccttt	cctccattaccatccctttgga
Exon 4	gggctgggtaaactcccaga	cccagcccctcttcacacat
Exon 5	gcagaggagaaggggaaca	agtattggggagcggtctgg
Intron 1	gtggtgagttaggggcttcc	tctgcacaacttgtcctgtgg
TYROBP by quantitative RT-PCR	atgggggacttgaaccc	tcatttgtaatacggcctctgtg
TREM1:		
Exon 1	acttaactgagaagtgagtcttggtctc	gcagtagtatatttgctgtcccatagtag
Exon 2	atatgggtggttggacaagaaa	agacagactgctgggaatcct
Exon 3	ctcatccacattttcatccatacatc	gacatttctacccagactaatgtgact
Exon 4	gcaaggatctaagcagaggaga	tgtttggggctgtaacttcttt
TREM2:		
Exon 1	caccgccttcataattcacc	gactcctcctcccctctgtc
Exon 2	agtgggtggttctgcacac	tccttcagggcaggattttt
Exon 3	gctctagttgccttgtaatttgtagtt	agtgtaatgacctgatccacataggac
Exons 4 and 5	agcaaaatctcttgtctttttctcatc	cctagaactcaagtctcttgactatgg
Exon 4 seq	tcttccttcacgtgtctctcag	cccattccctgagagaagatt
Exon 5 seq	cctcaaggagcaaaatctcttgt	ccagggtatcagctccaaac
TREM2 probe	atggagcctctccggctgct	tcacgtgtctctcagccctg
TREM2 by quantitative RT-PCR	atggagcctctccggctgct	tcacgtgtctctcagccctg
ACTB:		
ACTB by quantitative RT-PCR	tcacccacactgtgcccatctacga	cagcggaaccgctcattgccaatgg

[a] Except in the cases of exons 4 and 5 of *TREM2* that were sequenced by primers with the designation ending with "seq," PCR primers were used for sequencing.

Table 2

Comparison of PLOSL Manifestations in Patients with Mutations in Either *TREM2* or *TYROBP*

	TREM2[a]							
SYMPTOM(S)	I:1	I:2	II:1	III:1	IV:1	IV:2	V:1	*TYROBP*[b]
Bones (3rd decade):								
Skeletal pain	−	+	+	+	+	+	+	+
Bone cysts or fractures	+	+	+	+	+	+	+	+
CNS (4th–5th decades):								
Frontal-lobe syndrome[c]	+	+	+	+	+	+	+	+
Progressive dementia	+	+	+	+	+	+	+	+
Other disturbances of higher cortical functions[d]	+	+	−	+	NA	+	+	+
Convulsions	+	−	+	+[e]	+	NA	−	+
Primitive reflexes	+	−	+	+	NA	NA	+	+
Diffuse slowing in the electroencephalogram	−	+	+	+	−	NA	−	+
Brain atrophy[f]	+	+	+	+	+	+	+	+

[a] Roman numerals denote the nationality of the family: I = Italian; II = U.S.; III = Bolivian; IV = Norwegian; V = Swedish. The arabic numerals denote the individual tested. + = present; − = absent; NA = data not available.

[b] Data are based on reports by Hakola (1972, 1990), Hakola and Partanen (1983), Hakola and Puranen (1993), and Paloneva et al. (2000, 2001).

[c] Euphoria and loss of social inhibitions.

[d] Agnostic-aphasic-apraxic symptoms.

[e] Convulsions appeared after neurosurgery.

[f] Confirmed by autopsy, computed tomography, or, magnetic-resonance imaging.

vant to the clinical phenotype, using northern-blot analyses. In the CNS, the signal-intensity levels of *TREM2* transcripts closely followed those of *TYROBP,* being strongest in the basal ganglia (putamen, caudate nucleus, and substantia nigra), corpus callosum, medulla oblongata, and spinal cord. This would suggest regional coexpression of these two genes encoding interactive proteins in the CNS. In contrast to the strong steady-state mRNA signal intensities of *TYROBP* in hematological cells and tissues, we detected *TREM2* signals only in lymph nodes (fig. 3).

The characteristic bone cysts in the patients with PLOSL may reflect chronic dysfunction of osteoclasts. To characterize the expression of *TREM2* and *TYROBP* in bone, we performed quantitative RT-PCR analysis of mRNA in cells differentiating along the osteoclastic lineage. We stimulated monocytes by use of either pseudosynovial fluid obtained from total-hip arthroplasties or a combination of cytokines (comprising macrophage colony–stimulating factor [R&D Systems], receptor activator of NF-κB ligand [Alexis Biochemicals], and interleukin-1β [R&D Systems]). With these inductors, multinuclear tartrate-resistant acid phosphatase– and cathepsin K–positive osteoclastic cells can be generated from peripheral blood monocytes (Kim et al. 2001). The relative amount of *TYROBP* transcripts was ~200 times higher than that of *TREM2,* but stimulation increased the expression of both *TYROBP* and *TREM2* (fig. 4). This would suggest that osteoclasts, potentially involved in the pathogenesis of PLOSL, express both *TREM2* and *TYROBP.*

TREM2 polypeptide has a structure similar to that of TYROBP-associated TREM1 and LY95, these proteins constituting a superfamily of activating cell-surface receptors (Daws et al. 2001). TREM1 is strongly up-regulated in cells that mediate acute inflammatory responses to bacterial infection (i.e., neutrophils and monocytes) (Bouchon et al. 2001*a*), whereas TREM2 is expressed on macrophages and monocyte-derived dendritic cells, suggesting that TREM2 plays a role in chronic, rather than in acute, inflammation (Bouchon et al. 2000). This observation would agree well with the late onset and slow progression of PLOSL, which potentially results from chronic inflammation in the CNS and bone.

We have identified mutations in all 39 patients with PLOSL who were available to us; 31 (79%) were found to carry a mutation in *TYROBP,* and 8 (21%) were found to carry a mutation in *TREM2.* All of our 25 Finnish patients have the same founder mutation in *TYROBP,* a 5.3-kb deletion encompassing exons 1–4, designated "$PLOSL_{Fin}$" (Paloneva et al. 2000). Other patients carrying *TYROBP* mutations are from Sweden ($PLOSL_{Fin}$, one family) (Paloneva et al. 2000), Norway ($PLOSL_{Fin}$, one family) (Paloneva et al. 2000; Tranebjærg et al. 2000), Japan ($PLOSL_{Jpn}$, 141delG, one family) (Paloneva et al. 2000), and Brazil (a large deletion encompassing exons 1–4, one family) (J.P., unpublished data). Families with mutations in *TREM2* originate from the United States, Norway, Sweden, Italy, and Bolivia. The molecular pathogenesis of PLOSL seems to be explained by these two genes.

We are aware of one earlier example of a human disease resulting from defects in different components of the same signaling pathway. Autosomally dominant holoprosen-

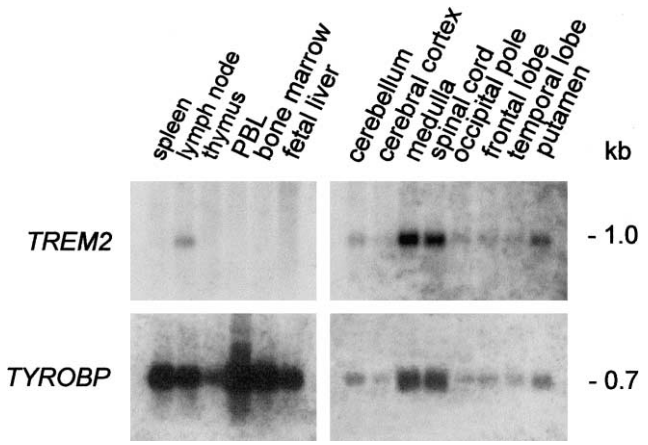

Figure 3 Northern-blot analysis of human tissues, with radiolabeled human *TREM2* and *TYROBP* cDNAs used as probes. We hybridized human multiple-tissue northern blots (Clontech), with each lane containing 2 μg of poly(A)$^+$ RNA, and a multiple-tissue mRNA expression array (Clontech) (J.P., unpublished data), using a [^{32}P]-labeled *TREM2* cDNA probe, according to the manufacturer's instructions. We generated the probe, corresponding to the transcribed region of *TREM2,* by PCR, from a cDNA clone (GenBank accession number BF343916) obtained from the IMAGE Consortium. We labeled and purified the probe by using the Rediprime II Random Prime Labelling System (Amersham Pharmacia Biotech) and the QIAquick Nucleotide Removal Kit (Qiagen) and performed the hybridizations by using ExpressHyb hybridization solution, according to the manufacturer's (Clontech) protocol. A strong steady-state *TYROBP* mRNA signal is observed in hematological cells and tissues such as peripheral blood leukocytes (PBL) and spleen, whereas *TREM2* can be detected only in lymph nodes. The intensities of the steady-state mRNA signals of *TREM2* and *TYROBP* in different parts of the CNS are similar. In the CNS, relatively strong northern-blot signals can be detected in the basal ganglia (putamen and caudate nucleus), medulla, spinal cord, and corpus callosum. *TYROBP* northern-blot data have been published elsewhere (Paloneva et al. 2000).

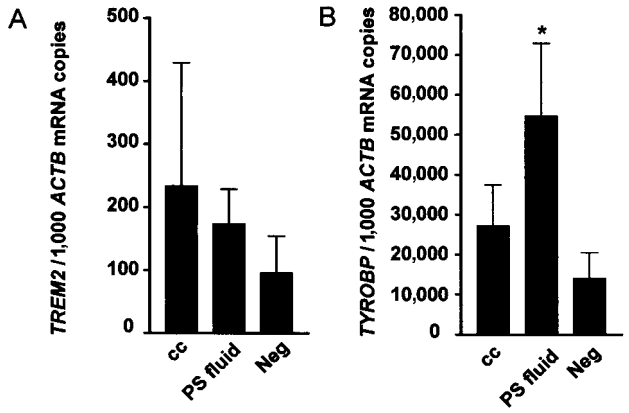

Figure 4 Quantitative RT-PCR analysis of the expression of *TREM2* (*A*) and *TYROBP* (*B*). Monocytes were stimulated with either a cytokine combination (comprising M-CSF, RANKL, and IL-1β) (cc) or pseudosynovial (PS) fluid, for 24 h, along the osteoclastic lineage. Human monocytes from healthy individuals were isolated from buffy-coat cells over Ficoll-Paque (Amersham Pharmacia Biotech). Mononuclear cells were collected, washed with PBS, and resuspended in serum-free macrophage medium (GIBCO) with antibiotics. Approximately 10–15 × 10^6 cells/well were allowed to adhere to six-well plates, for 1 h at 37°C. Nonadherent cells were washed away with PBS, and mononuclear cells were stimulated, for 24 h, with either cytokines (i.e., M-CSF, RANKL, and IL-1β) or PS fluid. Stimulations were performed four times, in duplicate. Total RNA was isolated by use of TRIzol reagent, according to the manufacturer's instructions (GibcoBRL/Life Technologies). The RNA concentration was measured spectrophotometrically, and the quality was ascertained by ethidium bromide agarose gel. Three micrograms of the RNA was treated with DNase, and 2 μg of RNA was transcribed to cDNA (SuperScript Preamplification System; GibcoBRL). The number of copies of *TYROBP* and *TREM2* in stimulated cells was determined by quantitative RT-PCR amplification from 200 ng of cDNA in LightCycler SYBR Green I PCR mix, by a LightCycler PCR machine (Roche/Molecular Biochemicals). The identity of the product was verified by melting-curve analysis. Serial dilutions of human *TREM2* cDNA (GenBank accession number BF343916) and of *TYROBP* cDNA (GenBank accession number AA481924), cloned in a plasmid vector, were used to determine the copy number of the amplicon per 1,000 copies of *ACTB* (*β-actin*) cDNA (GenBank accession number X00351). Each individual sample was amplified at least twice for both genes. Statistical analyses were performed by one-way ANOVA with Bonferroni's multiple-comparison test (GraphPad Prism, version 3.00 for Windows; GraphPad Software). The values are expressed as the mean ± SEM of copies per 1,000 *ACTB* mRNA. Neg = negative controls. *A,* Expression of *TREM2,* which is increased in both the cc-stimulated (234 ± 195 copies of mRNA) and PS fluid–stimulated (174 ± 55 copies of mRNA) monocytes, compared with that in the negative controls (96 ± 58 copies of mRNA). However, the difference remained statistically nonsignificant ($P > .05$). *B,* Expression of *TYROBP,* which also is increased in cc-stimulated (27,190 ± 10,270 copies of mRNA; $P > .05$) and PS fluid–stimulated (54,740 ± 18,220 copies of mRNA; $P < .05$, denoted by an asterisk [*]) cells, compared with that in the negative controls (14,210 ± 6,290 copies of mRNA).

cephaly results from mutations in genes encoding the signaling molecule, SHH, and its receptor, PTCH, in the sonic hedgehog signaling pathway (Ming et al. 2002).

Interestingly, patients with PLOSL who are homozygous for mutations in either *TREM2* or *TYROBP* display identical CNS and bone manifestations (table 2)—and no immunological symptoms (Paloneva et al. 2000). This indicates a remarkable capacity of the human immune system to compensate for the loss of TYROBP-mediated activating signals. Our findings suggest either significant functional redundancy or the presence of additional cell-surface molecules capable of replacing the inactive TYROBP-TREM2 complex in cells of innate immunity.

Although we have now identified the signaling pathway responsible for PLOSL, the reason for the peculiar tissue specificity of the symptoms of the patients remains unexplained. The findings in patients with PLOSL should motivate further characterization of the cell- and tissue-

specific function of the TREM2-TYROBP signaling complex in the CNS and bone.

Acknowledgments

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Electronic-Database Information

Accession numbers and URLs for data presented herein are as follows:

Ensembl Human, http://www.ensembl.org/Homo_sapiens/
GenBank, http://www.ncbi.nlm.nih.gov/Genbank/index.html (for *TREM2* cDNA [accession number BF343916], *TYROBP* cDNA [accession number AA481924], and *ACTB* cDNA [accession number X00351])
GeneTests–GeneClinics, http://www.geneclinics.org/ (for PLOSL)
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for PLOSL [MIM 221770])
UCSC Human Genome Project Working Draft, http://genome.ucsc.edu/ (for UCSC Human Genome Browser)

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Erratum

In the September 2002 issue of the *Journal*, in the report "Mutations in Two Genes Encoding Different Subunits of a Receptor Signaling Complex Result in an Identical Disease Phenotype," by Paloneva et al. (71:656–662), the nucleotide of the Norwegian *TREM2* mutation is incorrect. In the Norwegian family, a 558G→T mutation was found (not 558G→A, as was incorrectly presented in the report). The mutation results in conversion of lysine 186 to asparagine (K186N), and the conversion is correctly presented in the report. The authors apologize for the error.