*Am. J. Hum. Genet. 68:269–274, 2001*

# Report

## A Second Locus for an Axonal Form of Autosomal Recessive Charcot-Marie-Tooth Disease Maps to Chromosome 19q13.3

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**Autosomal recessive Charcot-Marie-Tooth disease (CMT) represents a heterogeneous group of disorders affecting the peripheral nervous system. The axonal form of the disease is designated as "CMT type 2" (CMT2), and one locus (1q21.2-q21.3) has been reported for the autosomal recessive form. Here we report the results of a genomewide search in an inbred Costa Rican family (CR-1) affected with autosomal recessive CMT2. By analyzing three branches of the family we detected linkage to the 19q13.3 region, and subsequent homozygosity mapping defined shared haplotypes between markers D19S902 and D19S907 in a 5.5-cM range. A maximum two-point LOD score of 9.08 was obtained for marker D19S867, at a recombination fraction of .00, which strongly supports linkage to this locus. The epithelial membrane protein 3 gene, encoding a PMP22 homologous protein and located on 19q13.3, was ruled out as being responsible for this form of CMT. The age at onset of chronic symmetric sensory-motor polyneuropathy was 28–42 years (mean 33.8 years); the electrophysiological data clearly reflect an axonal degenerative process. The phenotype and locus are different from those of demyelinating CMT4F, recently mapped to 19q13.1-13.3; hence, the disease affecting the Costa Rican family constitutes an axonal, autosomal recessive CMT subtype (ARCMT2B).**

Charcot-Marie-Tooth disease (CMT [MIM 118200]) is part of a complex group of clinically and genetically heterogeneous hereditary motor and sensory neuropathies (HMSN) (Dyck et al. 1993; Lupski 1999). On the basis of electrophysiological criteria, CMT is divided into CMT type 1 (CMT1, the demyelinating form), characterized by a motor median nerve conduction velocity (NCV) <38 m/s, and CMT type 2 (CMT2, the axonal form), with a normal or slightly reduced NCV. At least nine different genes and loci, as well as an increased phenotypic variability, have been associated with an inherited motor and/or sensory axonal phenotype (Vance 2000). Common types of CMT2 with similar phenotypes have been mapped to chromosome 1p36 (CMT2A [MIM 118210]) and to chromosome 7p15 (CMT2D [MIM 601472]) (Ben Othmane et al. 1993*b*; Ionasescu et al. 1996). Recently, mutations in the neurofilament-light gene (NEFL [MIM 162280]), located on chromosome 8p21, were identified for the CMT2E form (Mersiyanova et al. 2000). For patients with only slightly decreased NCV, mutations in the genes encoding connexin 32 (Cx32 [MIM 304040]) and myelin protein zero (MPZ [MIM 159440]) have been reported as well (Timmerman et al. 1996; Birouk et al. 1998; Marrosu et al. 1998; Senderek et al. 2000). For the Thr124Met MPZ mutation, a distinct CMT2 phenotype with pupillary anomalies and deafness has been reported in several studies (Chapon et al. 1999; De Jonghe et al. 1999).

Both the autosomal recessive demyelinating form (CMT4) and the autosomal recessive axonal form

Received September 18, 2000; accepted for publication November 6, 2000; electronically published December 7, 2000.

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0002-9297/2001/6801-0031$02.00

(ARCMT2) are less frequently observed. Two recently discovered disease-causing genes and several loci have been reported for autosomal recessive demyelinating CMT4: the myotubularin-related protein-2 (MTMR2 [MIM 603557]) gene has been located on chromosome 11q22 (Bolino et al. 2000) and, on chromosome 8q24, the N-myc downstream regulated gene 1 (NDRG1 [MIM 605262]) was identified as being responsible for HMSN-Lom (Kalaydjieva et al. 2000 [MIM 601455]); further loci were described on chromosome 8q13-21.1 (Ben Othmane et al. 1993*a*); 11p15 (Ben Othmane et al. 1999); 5q23-33 (LeGuern et al. 1996); 10q21-22, which has mutations in the early growth response gene 2 (EGR2 [MIM 129010]) (Warner et al. 1998); and 10q23 (Rogers et al. 2000). For the autosomal recessive inherited axonal ARCMT2, one locus was mapped on 1q21.2-q21.3; the MPZ gene was ruled out as a candidate (Bouhouche et al. 1999).

Here we report linkage to chromosome 19q13.3 of an autosomal recessive CMT disease with the axonal phenotype (ARCMT2) that affects three branches of a large consanguineous family (CR-1) in Costa Rica. The family, which is of predominantly Spanish ancestry, originates from a single town in the province of Alajuela, Republic of Costa Rica. Among the 31 family members analyzed, 18 were classified as affected with the disease (fig. 1). Informed consent was obtained from each participant. For one patient (B-5.3) no data were available. At the date of examination the ages of the patients were 32–49 years (mean 39.3 years), with a disease duration of 2–15 years (mean 5.5 years). Age at onset of disease was 28–42 years (mean 33.8 years).

Clinically, all patients presented with symmetrical weakness of the plantar extensor and flexor muscles of the ankles. The clinical and electrophysiological features of 6 of the 17 patients could be analyzed in more detail. Four out of the six patients presented with distal weakness in the upper extremities, ranging from slight paresis to severe involvement of the small hand muscles. Distal atrophy of the plantar muscles was present in five patients, three of whom also showed atrophy of the small hand muscles. Ankle jerks were weak in one patient and absent in all others; three patients even presented with areflexia. All patients showed sensory deficit in a symmetrical "stocking-glove" pattern. Five patients presented with distal hypaesthesia and hypalgesia and a decreased sense of vibration and position in the lower extremities, and in three patients the upper extremities were also affected. In one patient only, the senses of vibration and position were decreased in the upper and lower extremities. In all patients, motor-nerve conduction velocity (MCV) of the median and the ulnar nerves was normal or slightly reduced, with ranges of 28.8–54.5 m/s (mean 43.9 m/s) for the median nerve and 40.0–64.7 m/s (mean 53.2 m/s) for the ulnar nerve. In one patient, MCV of the median and ulnar nerves was not detectable. MCV of the tibial nerve could be detected in only three of six patients and was 35–40.7 m/s (mean 37.9 m/s). MCV of the peroneal nerve could be detected in only two patients, with values of 30.6 m/s and 32.7 m/s. In one patient, sensory nerve action potentials (SNAPs) of the median and ulnar nerves could be detected. In this patient, sensory nerve conduction velocity of the median (42.4 m/s) and ulnar (40 m/s) nerves was slightly reduced. SNAPs of sural nerves were not detectable in any patient. Neurographically, amplitudes were decreased in affected nerves, and motor and sensory nerve potentials did not show temporal dispersion. Electromyography of the right anterior tibial muscle showed an increased number of polyphasic motor-unit potentials in all patients and increased amplitudes of the motor-unit potentials (4.7–6.0 mV) in four of six patients. These electrophysiological data clearly reflect an axonal degenerative process. A sural nerve biopsy was not performed.

Initially, SSCP analysis of the MPZ, PMP22, and EGR2 genes failed to reveal a mutation, and the various loci known to be linked to the different hereditary motor and sensory neuropathies could also be excluded after linkage analysis with microsatellites from the respective regions (LOD score $<-2$, data not shown). Finally, a genomewide screening was performed with fluorescent microsatellite markers at a resolution of 10 cM. The coordinates of the markers were taken from the Généthon human linkage map. The order was confirmed through use of the haplotypes generated in this study and the program CRI-MAP, version 2.41, with the "ALL" option chosen (Documentation for CRI-MAP Version 2.4 Web site; also see Green 1992). The PCR products were pooled, loaded onto 5% polyacrylamide gels, and separated on an ABI 377 DNA sequencer (PE Biosystems); the data were analyzed with GENESCAN (version 2.1) and GENOTYPER (version 1.1; PE Biosystems) software.

On the basis of the segregation pattern observed in this family, we performed linkage calculations under assumptions of autosomal recessive inheritance, a disease-gene frequency of .0001, and uniform marker-allele frequencies. Given the late age at onset of the disease, individual B-4.4 (41 years old) was analyzed under the assumption of 90% penetrance. All other healthy members of the family were analyzed under the assumption of 99% penetrance, because their ages were >50 years. The family was divided into three branches in order to make the linkage analysis possible. All three branches were analyzed, with PEDCHECK software, for Mendelian incompatibilities of the genotypes (O'Connel and Weeks 1998), and two-point LOD scores were calculated with the LINKAGE software package, version 5.2 (Lathrop et al. 1985; Ott 1991; Cottingham et al. 1993).

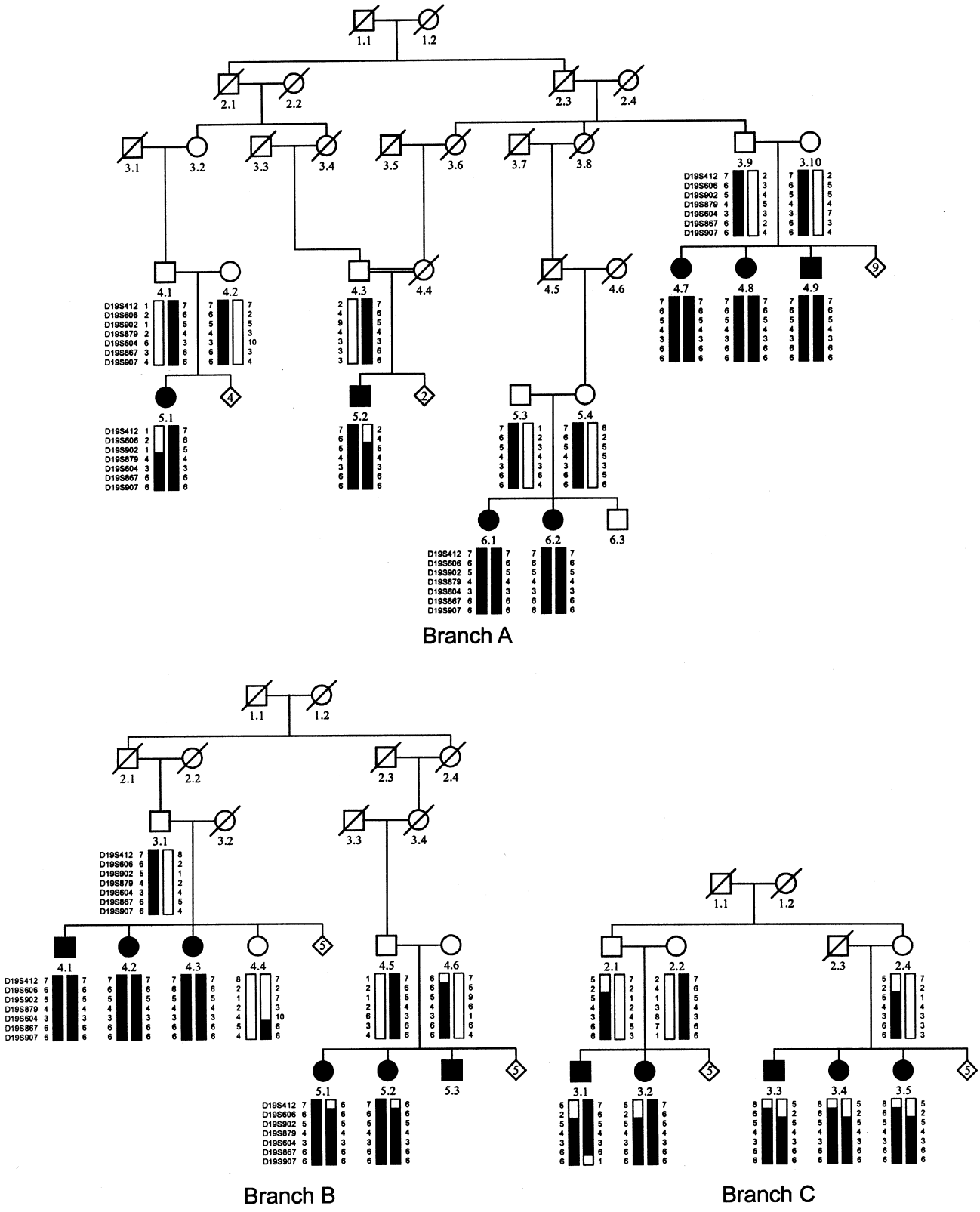


**Figure 1** Pedigree and haplotype analysis of markers from chromosome 19q13 in members of family CR-1, from Costa Rica, with ARCMT2B. Haplotypes segregating with the disease are given in black. Although the exact genealogical connection is not shown, because of the complexity of the family structure, branches A, B, and C have common ancestors. Healthy members of the families, not used for linkage analysis, are summarized to the right of the nuclear families, showing the number of individuals in each case.

**Table 1**

**Two-Point LOD Scores for the Autosomal Recessive CMT Locus in the Costa Rican ARCMT2 Family with Markers from Chromosome 19q13**

| Marker | Distance (cM)[a] | LOD Score at $\theta$ =[b] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | .0 | .001 | .01 | .05 | .1 | .2 | .3 | .4 | $Z_{max}$ | $\theta_{max}$ |
| D19S412 | 69.9 | 1.84 | 3.73 | 5.49 | 6.06 | 5.60 | 4.07 | 2.35 | .83 | 6.07 | .042 |
| D19S606 | 76.2 | 3.70 | 4.85 | 5.66 | 5.64 | 5.04 | 3.51 | 1.95 | .65 | 5.79 | .024 |
| D19S902 | 76.2 | 4.69 | 5.63 | 6.42 | 6.37 | 5.72 | 4.09 | 2.36 | .84 | 6.54 | .023 |
| D19S879 | 78.9 | 7.61 | 7.60 | 7.44 | 6.72 | 5.81 | 3.96 | 2.18 | .72 | 7.61 | .000 |
| D19S604 | 79.0 | 7.17 | 7.15 | 7.00 | 6.33 | 5.48 | 3.76 | 2.12 | .78 | 7.17 | .000 |
| D19S867 | 81.2 | 9.08 | 9.07 | 8.88 | 8.09 | 7.08 | 5.02 | 2.97 | 1.16 | 9.08 | .000 |
| D19S907 | 81.7 | 2.65 | 5.93 | 6.75 | 6.64 | 5.91 | 4.13 | 2.31 | .76 | 6.85 | .022 |

[a] According to the Généthon linkage map.
[b] Cumulative LOD scores were obtained from the analysis of the three family branches.

The LOD scores for the three branches were summed. Finally, linkage to markers on chromosome 19q13.3 was identified. Maximum two-point LOD scores ($Z_{max}$) were obtained for marker D19S867 ($Z_{max}$ = 9.08; table 1). This marker, as well as D19S879 and D19S604, segregated fully with the disease in the family. Key recombination events were observed between markers D19S902 and D19S879 in patient A-5.1 , and between D19S907 and D19S867 in patient C-3.1 (fig. 1). These recombination events locate the interval of interest between D19S902 and D19S907, with a length of 5.5 cM (fig. 2). All patients are homozygous for the same haplotype in this critical region.

The interval defined in this Costa Rican family with ARCMT2 is different from the one recently described in a Lebanese family with CMT4F (Delague et al. 2000). The interval in the Lebanese family is located between D19S220 and D19S412, at least 6.3 cM proximal to the one reported here. Ancestral recombination events observed in the haplotype analysis of several individuals also support the exclusion of that interval (fig. 1). Two genes associated with autosomal recessive CMT are in the immediate neighborhood, and this genetic heterogeneity is in accordance with the different phenotypes—myelinopathy versus axonal type—in both families. Considering that this is the second autosomal recessive CMT type 2 locus, we propose the terms "ARCMT2A" for the locus on chromosome 1q21.2-21.3, described by Bouhouche et al. (1999), and "ARCMT2B" for the locus described in the present study.

The epithelial membrane protein-3 (EMP3, MIM 602335) has been mapped to chromosome 19q13.3 (Liehr et al. 1999). EMP3 is a member of the four-transmembrane-domain gene family that also includes the peripheral myelin protein 22 (PMP22 [MIM 601097]; Taylor and Suter 1996). Given its position and the fact that PMP22 is involved in peripheral polyneuropathies (Lupski 1999; Nelis et al. 1999*a*, 1999*b*), EMP3 was considered as a candidate gene for the ARCMT2 disease reported in the present study. The function of this protein is unknown, but, on the basis of the available data for PMP22, it could be involved in cell proliferation and cell-cell interactions (Taylor and Suter 1996). The complete sequence of the EMP3 cDNA (GenBank accession number X94771) was compared with that of the genomic clone AC020955 (GenBank), using BLAST to determine the intron-exon structure. The four coding exons of EMP3 were PCR-amplified with the following intronic primers: exon 1, forward (5′-CAACCTCTTGAGACTCCGTC-3′) and reverse (5′-GGACAGAGTGAGACCCTTGT-3′); exon 2, forward (5′-CCTCTCCTTTCCTAACCCTG-3′) and reverse (5′-GGTTCCCAATTC-

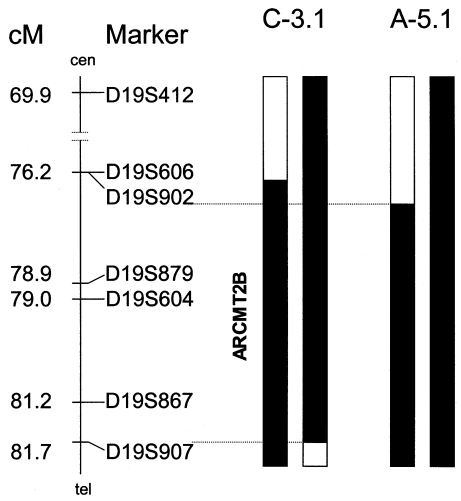


**Figure 2** Critical region of ARCMT2B on chromosome 19q13.3. Key recombinations are shown in individuals C-3.1 and A-5.1, defining the ARCMT2B interval identified in the Costa Rican family. The gene that causes this form of CMT is located in a 5.5-cM region between D19S902 and D19S907. The linkage map of markers from chromosome 19 and genetic distances (in centimorgans) are assigned based on information from the Généthon human linkage map. Blackened regions in chromosomal representations indicate haplotypes related to the disease, and unblackened regions indicate haplotypes not related to the disease.

TCAGTCCC-3′); exon 3, forward (5′-AACTCTGGAC-CCACGGTGAT-3′) and reverse (5′-CCCACTCCCTTC-TGCTCAAT-3′); and exon 4, forward (5′-GGGAAATG-TAGTCTTGAGGG-3′) and reverse (5′-GAAGGAAG-ATCAAGGCAGAG-3′). PCR products from two obligate carriers (B-4.5 and B-4.6), a patient (B-5.2), and a healthy control were tested through use of a denaturing HPLC system (WAVE, Transgenomics) at various separation temperatures (Kuklin et al. 1997–98). In addition, amplified products from a healthy control, an obligate carrier (B-4.5), and a patient (B-5.2) were sequenced on both strands with a BigDye Terminator Cycle Sequencing Kit on an ABI 377 DNA sequencer (PE Biosystems), according to standard protocols.

None of the analyzed individuals presented heteroduplexes in the denaturing high-performance liquid chromatography system, and the subsequent sequence analysis of the four coding exons revealed no variation from the cDNA sequence reported elsewhere (Taylor and Suter 1996). Similarly, the adjacent intronic sequences were identical between the healthy control and patient B-5.2, thus excluding the possibility of a splice-site mutation. Therefore, EMP3 was ruled out as a candidate gene for ARCMT2B. No other obvious candidate genes for a motor and sensory neuropathy with axonal implications were identified. Further refinement of the interval defined in the present study may reduce the number of positional candidate genes that need to be analyzed for the presence of mutations in order to identify the causative gene.

## Acknowledgments

We thank the members of the family for their cooperation in this study. We also thank Siegred Cover, Mireya Matamoros, Maricruz Pacheco, Gerardo Jiménez, and Jorge E. Morera for their help with field work, Gudrun Nuernberg for excellent technical assistance, and Johannes Becker-Follmann and Franz Rueschendorf for their important advice. We thank Arif Ekici for help with computer processing of the pedigree data. Support from the Vicerrectoría de Investigación, University of Costa Rica, is gratefully acknowledged (project 742-98-241). A.L. is a recipient of a scholarship from the Deutscher Akademischer Austauschdienst and received travel support from the Boehringer Ingelheim fund. B.M. is a recipient of a fellowship from the Agencia Española de Cooperación Internacional. This project was sponsored by grants from the Deutsche Forschungsgemeinschaft and Deutsche Gesellschaft für Muskelkranke (to B.R.) and by the ELAN funds (to D.H.). The Gene Mapping Centre is supported by a grant from the German Human Genome Project (to A.R.)

## Electronic-Database Information

Accession numbers and URLs for data in this article are as follows:

BLAST at the National Center for Biotechnology Information, http://www.ncbi.nlm.nih.gov/BLAST/ (for BLAST program)

Documentation for CRI-MAP Version 2.4, http://www.cmbi.kun.nl/tutorials/bioinf/CRI-MAP.doc.html

GenBank, http://www.ncbi.nlm.nih.gov/Genbank/ (for cDNA sequence [accession number X94771] and genomic DNA [accession number AC020955])

Généthon, http://www.genethon.fr/ (for human linkage map)

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for CMT [MIM 118200], CMT2A [MIM 118210], CMT2D [MIM 601472], HMSN-Lom [MIM 601455], NEFL [MIM 162280], Cx32 [MIM 304040], MPZ [MIM 159440], MTMR2 [MIM 603557], NDRG1 [MIM 605262], EGR2 [MIM 129010], EMP3 [MIM 602335], and PMP22 [MIM 601097])

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