Original Article
Characteristics of demyelinating Charcot-Marie-Tooth disease with concurrent diabetes mellitus

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Abstract: Purpose: Charcot-Marie-Tooth disease (CMT) is the most common type of inherited peripheral neuropathy and has a high degree of genetic heterogeneity. CMT with concurrent diabetes mellitus (DM) is rare. The purpose of this study is to explore the genetic, clinical and pathological characteristics of the patients with CMT and concurrent DM. Methods: We investigated gene mutations (the peripheral myelin protein 22 gene, myelin protein zero gene, lipopolysaccharide-induced tumor necrosis factor-α factor gene, early growth response gene and the neurofilament light chain gene loci) of a relatively large and typical Chinese family with CMT1 and concurrent DM2. From the literature, we also retrieved all reported families and single cases with CMT and concurrent DM. We comprehensively analyzed the characteristics of total 33 patients with CMT and concurrent DM, and further compared these characteristics with those of patients of diabetic peripheral neuropathy (DPN). Results: Patients with CMT and concurrent DM had some relatively independent characteristics and pathogenic mechanisms. So we designated that kind of characteristic demyelinating CMT which accompanies DM as Yu-Xie syndrome (YXS), a new specific clinical subtype of CMT. Conclusion: CMT is an etiologic factor of DM, even though the intrinsic association between CMT and DM still remains further exploration.

Keywords: Charcot-Marie-Tooth disease, diabetes mellitus, pedigree analysis, Yu-Xie syndrome

Introduction

Charcot-Marie-Tooth disease (CMT), first described by Charcot, Marie, and Tooth *et al.* in 1886, is the most common type of hereditary motor and sensory peripheral neuropathy [1]. Its incidence is about 1/2500. It is a disease with a high degree of genetic heterogeneity [2] and its current molecular biological classification mainly includes CMT1 (including 1A, 1B, 1C, 1D, and 1E), CMT2, CMT3\CMTX and CMT4. CMT1A is the most prevalent type, accounting for about 50% to70% of all demyelinating CMT cases [3-5]. CMT1A is usually caused by duplication at chromosome 17p11.2-12. The typical phenotype of CMT1A is characterized by symmetrical, slowly progressive, distal muscle weakness and wasting, sensory impairment and absent or diminished deep tendon reflexes [6]. Diabetes mellitus (DM) is a common metabolic disorder, characterized by chronic hyper-

glycemia that can be associated with microvascular complications. Both CMT and DM are relatively common, however, coexisting of these two conditions was rarely reported before. In 1989, Ivarsson and Bjerre [7] first reported a family with hereditary motor sensory neuropathy (Charcit-Marie-Tooth disease) with superimposed type I diabetes mellitus. Later on more publications reported coexisting cases of CMT and DM either with single cases [8-10] or family cases [11, 12]. Recently, it has been reported that CMT1A coexisting with DM showed a tendency to worsen the clinical and neurophysiological CMT1A phenotype [13]. With the increased number of these concurrent cases, it deserves us to pay special attention to this group of patients.

In this paper, we report another typical family with CMT and concomitant diabetes mellitus (DM) whose gene mutations were examined.
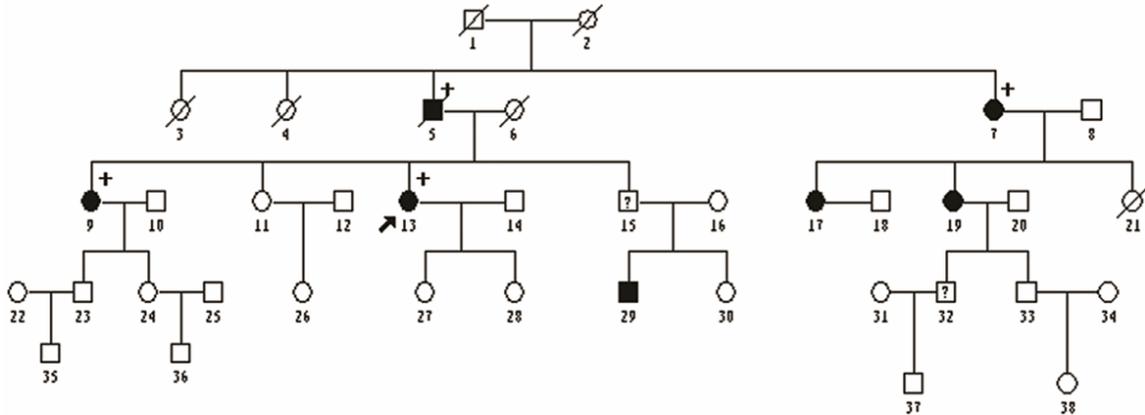
Figure 1. The pedigree of a Chinese family with CMT and concurrent DM. ⬜•⁺ refers to the proband, ■⁺ refers to the dead male patient with the CMT and concurrent DM, ●⁺ refers to female patient with the CMT and concurrent DM, ■ refers to the male patient with the CMT, ● refers to female patient with the CMT, ⬚? refers to the patient with suspected CMT.

We summarized and analyzed their clinical and pathological characteristics and retrieved all reported families and single cases with CMT and concurrent DM in the literature. The purpose of this study is to explore potential correlation between these two symptoms by analyzing the characteristics of this special group of CMT patients.

Materials and methods

Chinese CMT family presentation

F_1 pedigree: A family with CMT and concurrent DM in Zhejiang Province of China was studied. The pedigree showed autosomal dominant inheritance. The general information of the pedigree: 5 generations and 38 people, and 31 people alive currently; 6 patients with clinically diagnosed CMT, of which 4 patients with concurrent type 2 diabetes; 3 patients with suspected CMT, of which one patient with suspected CMT showing congenital skin disease. The family tree is shown in **Figure 1**. Symptoms of female patients in the pedigree were not obviously less severe than those of male patients in the pedigree.

Proband: The patient was a 49-year-old female who began to experience progressive bilateral lower limb weakness at age 39. Because of tapered lower limbs and bilateral foot numbness, she had difficulty to walk stairs. At age 43, she had difficulty to maintain balance for walk and fell easily. She also experienced bilat-eral upper limbs weakness. Her parents did not involve in a consanguineous marriage. Physical examination showed the patient with normal intelligence, step-page gait, and slight atrophy of the thenar and hypothenar muscles. In addition, the patient also showed obvious tapered bilateral lower limbs with atrophied muscles, like a crane-leg. We did not observe pes cavus deformity. But we did observe the patient with reduced grip strength for both hands. The muscle strength of bilateral lower limbs was graded as 3 to 4, and was poor at the distal end. The patient was incapable of dorsiflexion or plantar flexion with both feet. Her muscle tension of four limbs was normal. However, her bilateral knee reflex and ankle reflex were negative. The patient experienced glove-stocking hypoasthesia in the four limbs. Her both feet suffered kinesthesia and could not sense position and vibration. Her fasting glucose levels measured on different days was between 7.6-14.1 mmol/L; and her HgbA1c was 8.1. Electromyogram (EMG) showed neurogenic muscular atrophy, which was more severe in both lower limbs. The conduction velocity of the motion sensation of bilateral median nerves, ulnar nerves, common peroneal nerves, and tibial nerves was decreased significantly (13-28 m/s); and the amplitude was also decreased. The results from other examinations, such as thyroid function, cerebrospinal fluid examination, folic acid and vitamin B12 levels, were normal. Plasma glucose levels could be adjusted to normal range by oral administration of metformin. This patient was diagnosed with CMT type 1 with concurrent DM2.
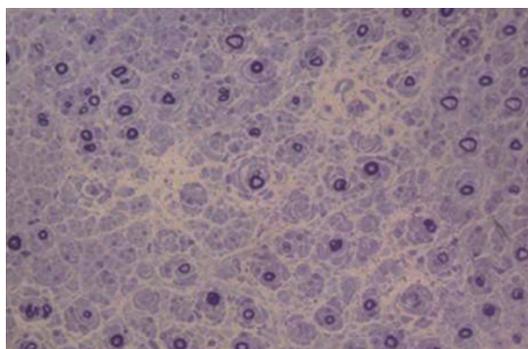
Figure 2. Biopsy from the patient's sural nerve showed decreased myelinated nerve fibers and a large number of hypertrophic "onion bulb" structures (Toluidine blue ×300).

Other patients in the pedigree had similar clinical manifestations. But their symptoms, such as bilateral lower limb weakness and muscle atrophy, were less severe. Hypoesthesia of the lower limbs was mild, and diabetic symptoms were not obvious. Physical signs and auxiliary examination results were similar to those of the proband. The nerve conduction velocity was between 16 to 29 m/s. The oldest patient was 84 years of age and the youngest was 8.

One 50-year-old female patient with suspected CMT experienced combined congenital skin disease. She suffered from evenly distributed small nipple-like gray skin protrusions all over the body; and the texture of the protrusions was relatively firm. Blood samples could not be collected due to skin condition. This patient declined examinations and treatments.

One 28-year-old male patient with suspected CMT did not experience any neurological symptoms or show any positive physical signs. But the EMG result showed decreased conduction velocity of the common peroneal nerve.

One 29-year-old male patient was found to have slight atrophy in both lower limbs and the thenar muscles of both hands (No.15) by physical examination. He was suspected as CMT.

The pathological examination results of nerve biopsy for proband were shown in **Figure 2**. A diagnosis of CMT type 1 was considered.

Genetic examination

Blood samples were drawn from 25 family members in the pedigree. DNA was extracted from peripheral blood leukocytes by standard phenol extraction methods. Five genetic loci of CMT1 (A→E) including the peripheral myelin protein 22 gene (PMP22), myelin protein zero gene (MPZ), lipopolysaccharide-induced tumor necrosis factor-α factor gene(LITAF), early growth response gene (EGR2) and the neurofilament light chain gene (NEFL), were tested successively. For PMP22 gene loci, we not only screened the duplication on chromosome 17p11.2, but also checked the point mutations. The examine method was based on the previous literatures [14-19]. Hotstar Taq DNA polymerase (Qiagen) was used in the PCRs. The PCR products were purified with PCR purification kit (Qiagen) and Exon I (New England Biolabs)-SAP (BioTec, Norway), and sequenced on an ABI 3730XL DNA analyzer (Applied Biosystems). Sequence assembly was conducted with Autoassembler (Applied Biosystems). Assays were repeated in some patients to confirm the result. All 25 family members and 15 healthy individuals signed the informed consent forms. This study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the British Medical Journal (1964 July 18; 2: 177), and was approved by the Medical Ethics Committee of Shanghai Seventh Hospital.

Presentation of other CMT patients from literatures

Families and single cases with CMT and concurrent DM were retrieved from the literatures. Three families were reported in 2006 [11], 2001 [12], and 1996 [20], respectively (F2, F3, and F4 families). Each contained 6, 5, and 3 patients with CMT1 and concurrent DM (case 5-18 in **Table 1**), respectively. Additionally, 15 single cases [8, 10, 21-24] were reported (case 19-33 in **Table 2**), of which 2 patients [8, 21] came from two different CMT family (case 19 and case 20). A total of 33 patients with CMT and concurrent DM were studied. The clinical data (including the medical history), pathological characteristics and gene mutations of these patients were analyzed.

F2 family basic information [11]: 28 people in a Turkish family out of total 69 family members were diagnosed with CMT type 1. The genetic examination results showed large focal amplification of the PMP22 gene. These patients were

Table 1. Clinical and pathological characteristics of patients with CMT and concurrent DM (familial occurrence)

Families Case number	Country inheritance	No. of patients	Type of CMT	Type of DM	Severity of CMT symptoms	Severity of DM symptoms	Onset age of CMT	Onset age of DM	Typical pathological	Genetic variation	Reference
F1 Case 1-4	China AD	4/6	CMT1	DM2	Involvement of all four limbs no pes cavus	Mild No overweight	35-40	Slightly later than the former	DDemyelination, some are hyperplastic, forming onion bulb structures	Unkown	2014 Yu, et al.
F2 Case 5-10	Turkey AD	6/28	CMT1A	DM2	Involvement of all four limbs pes cavus	Mild overweight	35-40	40	same as above	*PMP22* duplication	2006 Filiz Koc, et al
F3 Case 11-15	Turkey AD	5/6	CMT1A	DM2	Involvement of all four limbs pes cavus	Moderate overweight unknown	In their 50s	In their 50s	same as above	*PMP22* duplication	2001 M. Celik, et al.
F4 Case 16-18	Japan AD	3/7	CMT1B	DM2 suspected	Involvement of all four limbs no pes cavus	Moderate overweight unknown	In their 40s	In their 40s	same as above	*MPZ* point mutation	1996 Ohnishi A, et al

Note: In the column "Number of patients", the denominator refers to the number of all the CMT patients in that family, and the numerator refers to the number of CMT patients with concurrent DM. In the column "inheritance", AD refers to autosomal dominant inheritance.

Table 2. Clinical and pathological characteristics of patients with CMT and concurrent DM (single occurrence)

Case number	country	Type of CMT	Type of DM	Severity of CMT symptoms	Severity of DM symptoms	Onset age of CMT	Onset age of DM	Typical pathological changes	Other specific symptoms	Genetic variation	Reference
Case 19	Canada	CMT1A	DM2	Involvement of all four limbs	Moderate	teens	39	Demyelination some are hyperplastic forming onion bulb structures	Charcot ankle	PMP22 duplication	2010 Natatic EP, et al
Case 20	England	CMT1A	DM1	Involvement of all four limbs	Severe	6	32	Demyelination some are hyperplastic forming onion bulb structures	foot ulcer	PMP22 duplication	1997 P. K. Thomas, et al
Case 21-23	USA	CMT1A	DM1	Involvement of all four limbs pes cavus unknown	Severe overweight unknown	Relatively early	13, 26 and middle age	unknown	renal failure ketoacidosis	PMP22 duplication	2008 Soham Sheth et al.
Case 24-30	USA	CMT1A	DM2	unknown	Mile Might be overweight	unknown	Adulthood	unknown	no	PMP22 duplication	2008 Soham Sheth et al.
Case 31	Japan	CMT1	unknown	Involvement of all four limbs pes cavus unknown	Moderate overweight unknown	20	40	Demyelination some are hyperplastic forming onion bulb structures	phrenic nerve palsy dyspnea osteomyelitis	unknown	2002 Rinsho Shinkeigaka
Case 32	Japan	CMT1	DM2	Involvement of all four limbs pes cavus	Relatively severe overweight unknown	40	46	unknown	no	unknown	2003 T. Ota and K. Osawa
Case 33	Ireland	CMT1A	DM2	Severe	Severe	Middle age	53	Demyelination secondary axonal loss	ulceration of both feet	PMP22 duplication	2011 Htet H N Win, et al

diagnosed with CMT type 1A. Six of the 28 patients were diagnosed with DM2. The DM2 onset age of these patients was about 40 years old. However, the CMT onset age of these patients was relatively late, indicating that these 6 patients were older than other patients with simple CMT. Clinical manifestations were progressive four limb weakness (more severe in the lower extremities), muscle atrophy, and numbness. EMG results demonstrated decreased nerve conduction velocity. They all suffered pes cavus deformity. Pathological examination revealed demyelination with some myelin sheath proliferation and onion bulb structures formation.

F3 family [12]: 6 people in a three-generation Turkish family with nearly a dozen people were diagnosed with CMT. Molecular biological examination showed large focal amplification of the PMP22 gene. These patients were diagnosed as CMT type 1A. Five of the six patients had concurrent DM2; and the other young patient may likely progress to DM. The onset ages of both CMT and DM were about 40 years. Clinical manifestations demonstrated progressive four limb weakness (more severe in the lower extremities), muscle atrophy, and hypoesthesia. Pes cavus deformity was observed. EMG examination showed decreased nerve conduction velocity. Sural nerve biopsy revealed demyelination and formation of onion bulb structures.

F4 family [20]: 7 people in a four-generation Japanese family were diagnosed with CMT1, and molecular biological examination showed point mutation (Arg98 → His) in MPZ gene. Those people were diagnosed with CMT type 1B. Three of the seven patients experienced combined DM (maybe DM2). The onset ages of both CMT and DM were about 40 years. Clinical manifestations were progressive limb acratia (more severe in the lower extremities), muscle atrophy, and paresthesia. No pes cavus deformity was observed. EMG showed significantly decreased nerve conduction velocity. Sural nerve biopsy revealed demyelination and formation of abundant onion bulb structures.

In addition, the other two families [8, 21] had 5 patients with CMT type 1A, of which 1 patient complicated with DM as well.

Comparative studies on patients of DPN and CMT with concurrent DM

We retrieved the DPN-related information, and six major references were obtained [25-30]. The clinical and pathological characteristics of 33 patients with CMT and concurrent DM were compared with those of patients with DPN.

Results

The CMT1 Chinese family

CMT1 was considered for the family with CMT and concurrent DM in Zhejiang Province, China. Six genetic loci were detected, including PMP22, MPZ, LITAF, EGR2 and NEFL. Abnormal amplification of PMP22 was not found, and no point mutation was found at any of the five genetic loci. Therefore, currently existing subtypes, including CMT1A, B, C, D, and E, were excluded. However, based on the symmetrical distal muscle weakness, reduced motor and sensory nerve conduction velocities and family history, this family was diagnosed CMT. Thus, their CMT may belong to a new subtype. Further gene mapping could not be performed due to the difficulties of obtaining blood samples.

Biopsy of the sural nerve of family members showed demyelination with partial myelin sheath proliferation and hypertrophic "onion bulb" structures (**Figure 2**).

Basic characteristics of patients with CMT and concurrent DM from literatures

By carefully analyzing the total 33 patients with CMT and concurrent DM, who were from different families and different ethnic groups, we found: (1) The concomitant disease occurred in both male and female patients; (2) The family patients were autosomal dominant inheritance; (3) Clinically, all patients belong to demyelination type. In terms of molecular biological type, CMT1, especially CMT type 1A, is predominant, and the main gene mutation was large focal duplication on PMP22; (4) Similar to its genetic heterogeneity, CMT caused by various gene mutations can be accompanied by DM; (5) Differences may exist in the molecular genetic basis between patients from different ethnic groups. CMT type 1A is predominant in Western patients, but other CMT1 types are common in Asian patients, such as Japanese

Table 3. Comparisons between patients with CMT and concurrent DM and patients with diabetic peripheral neuropathy (DPN)

	Etiology and pathogenesis	Main pathologic changes	Main clinical symptoms	Main physical signs	Genetic variation	Treatment	Prognosis
CMT with concurrent DM	Heredity and life style	Demyelination, some are hyperplastic forming onion bulb structures	Motor and sensory symptoms, such as myasthenia, hypoesthesia	Decreased symmetrical sensory, obvious muscle atrophy	Single gene	Relatively easy, can be controlled by diet and exercise partly	Relatively good
DPN	Metabolic disorders, immunological changes, ischemic damage	Axonal degeneration, demyelination may occur at later stage, hyperplasia and onion bulbstructures are rare	Mainly sensory symptoms; pain is the most common symptom, numbness and hypoesthesia are present; autonomic nervous symptoms are common also	Symmetrical sensory disorder, muscle atrophy is unobvious	Multiple genes; Possibility is high	Relatively difficult, medication is required, the therapeutic effects are unsatisfactory usually	Relatively poor, gangrene may occur and amputation may be required

and Chinese; (6) Unlike most patients with CMT1, the onset age in this group of patients with CMT and concurrent DM was later, often after 40 years old, which is close to the onset age of DM. Therefore, family members with CMT and concurrent DM were generally older than patients with simple CMT; (7) Most DM type was type 2 and the onset age was typically after 35 years old. The diabetic symptoms were not obvious; (8) Only some of the family members with CMT had concurrent DM. DM did not occur in all family members. And no patients had simple DM in these families; (9) Clinical manifestations are the same as those of typical demyelination type, i.e., symmetrical distal limb weakness, muscle atrophy, sensory disturbance, upper and lower extremity involvement (symptoms are worse in the lower extremities), and pes cavus deformity is common; (10) Usually, symptoms of patients with CMT and concurrent DM were more serious than those of patients with simple CMT; (11) Neuropathological changes are demyelination, partial myelin sheath proliferation, and hypertrophic "onion bulb" formations; (12) Body mass index of patients was not necessarily increased. Detailed characteristics are listed in **Tables 1** and **2**.

Comparison between CMT with concurrent DM and DPN

Clinical and pathological characteristics of 33 patients with CMT and concurrent DM were compared with those of patients with DPN. It was found that they were significantly different in causes, pathogenesis, major pathological changes, clinical symptoms, physical signs, results of auxiliary examinations, and prognosis. Detailed comparisons are shown in **Table 3**.

Discussion

CMT is a typical single-gene disorder, more than 30 pathogenic genes have been found so far for this disease [31]. The most common pathogenic genes include PMP22, MPZ, and Cx32. Specific pathogenic mechanisms of various genes have also been clarified to a certain extent. In terms of clinical features, the symptoms are mainly concentrated in the peripheral nervous system, differing from other genetic diseases in which multiple systems are affected. From a genetic perspective, DM is a multigene disorder (especially DM2, with the exception of a few DM1 types), and the involved genetic factors are more complex. In fact, CMT concurrent with DM were rarely reported in previous studies. Only 33 patients were identified in a thorough literature review and information collection. However, there might be more CMT patients who were not examined for DM and have not reported yet.

Ethnic specific genetic difference of CMT

Among the 33 patients with CMT and concurrent DM, 18 patients were identified as members within a family (from four CMT families), 15 patients were sporadic cases (two patients from two different CMT1A families). Among the four families, two Turkish families [11, 12] belong to CMT type 1A, and the mutation was focal duplication of the PMP22 gene. One Japanese family [20] belonged to CMT type 1B, and the mutation was point mutation of the MPZ gene. However, the mutated gene was not identified in the Chinese family; variation of a nucleotide in the MPZ gene had been suspected as the mutation point (A→G, see **Figure 3**), but it was finally identified as polymorphism
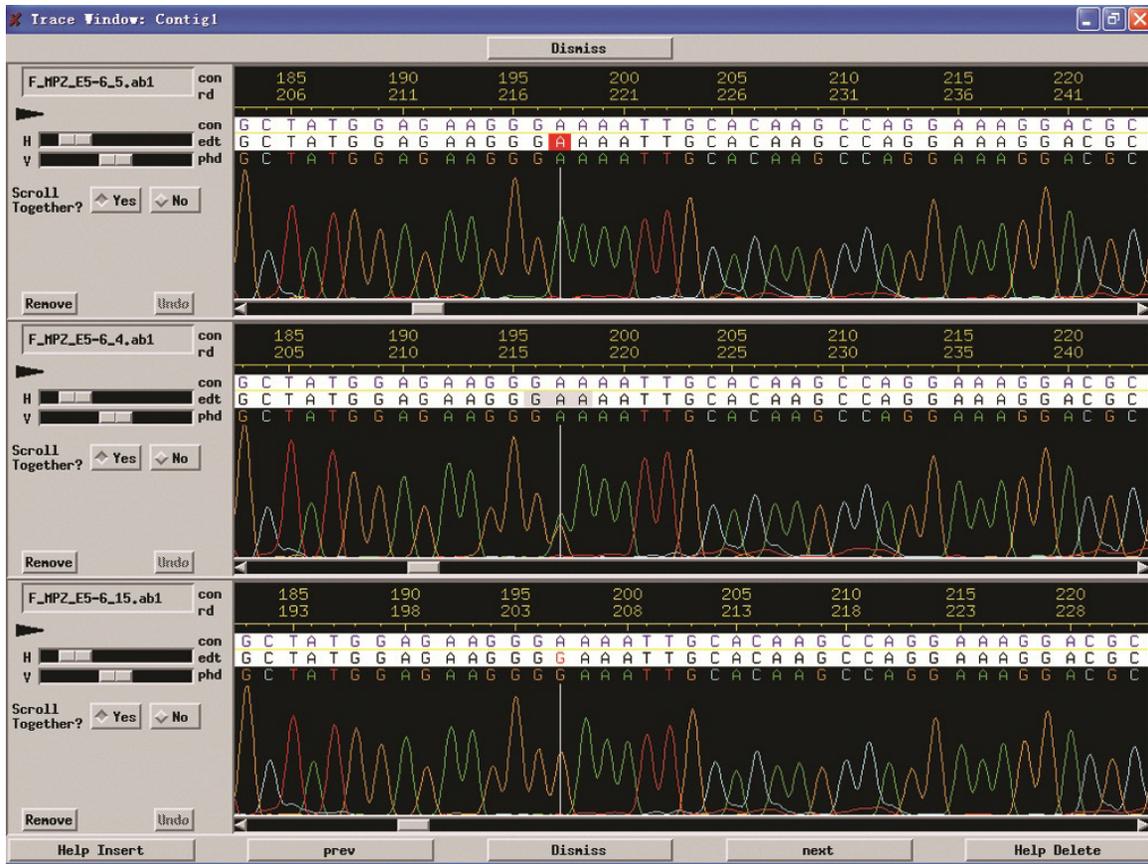
Figure 3. Variation of a nucleotide in the *MPZ* gene had been suspected as the mutation point (A→G) in the Chinese family with CMT and concurrent DM, but it was finally identified as polymorphism and was excluded.

and was excluded. Gene detection methods were clear; and results were verified repeatedly for reliability. However, the diagnosis of CMT type 1 of the Chinese family was supported by genetic characteristics, clinical symptoms, electrophysiological and pathological results. We infer that CMT type 1A is predominant in Turkish patients, and other CMT1 types are more common in Chinese and Japanese patients. Considering the differences in CMTX types among different ethnic groups (e.g., Chinese patients with CMTX1 often manifest as CMT1, and Turkish patients often manifest as CMT2; and X-linked CMT in China is often a *recessively inherited* disorder also different from Turkish patients [32]), we speculated that genetic differences found in this study may be race-specific. Mutations of different gene loci are the biggest difference between different ethnic families, followed by lack of pes cavus deformity in Chinese and Japanese families (data show that CMT patients with focal PMP22

duplication often experience this deformity [24].

Association of DM with CMT

The detailed characteristics of all 33 patients with CMT and concurrent DM are listed in **Tables 1** and **2**. It is important to note that the onset age of patients with CMT and concurrent DM was later, which is different from most patients with simple CMT1. This implies that the incidence of the concurrent symptom may have its own intrinsic reasons. The fact that only some of the CMT patients in the family experienced concurrent DM indicates that DM is associated with CMT, not vice versa. It has been reported that CMT is accompanied by congenital sensorineural hearing loss, which may be caused by single gene mutation [33]. Actually a case was reported in China [34] that CMT combined with sensorineural hearing loss was caused by two single pathogenic genes with different modes of inheritance. The inci-

dence of DM for CMT patients may share similar mechanisms, even though we can not rule out the possibility that concurrence of CMT and DM is a random occasional phenomenon. However, for the four families that we studied here, that possibility of random occurrence is extremely low. Because clinical manifestations were the same as those of typical demyelination type, and the disease-affected areas are relatively extensive; the severity is relatively high. Recent studies showed that symptoms of patients with CMT and combined DM were more severe than those of patients with simple CMT [13, 22]. Our study further confirmed this phenomenon. Neuropathological symptoms indicate that these patients belong to classical CMT type 1. Compared to patients with simple DM2, no obvious increase in BMI was observed with the patients with CMT accompanied by DM2. The BMI of simple DM2 patients is usually significantly increased.

DPN and CMT concurrent with DM

To find special characteristics for the patients of CMT concurrent with DM, we further compared these patients with DPN patients. All data were retrieved from authoritative journals. In terms of etiology, CMT/DM is caused by genetic or environmental factors; while DPN is induced by high blood glucose [27, 28, 30]. We first studied the pathological alterations. CMT/DM mainly shows demyelination with partial myelin proliferation and formation of characteristic "onion bulb" structures. DPN is recognized as axonal disease, i.e., axonal degeneration, and demyelination only occurs at late stage [25, 28]. With regard to clinical symptoms, CMT/DM mainly manifests as symmetrical myodynamia attenuation in the lower extremities, muscle atrophy, and hypoesthesia; however, DPN mainly manifests as pain, paresthesia, hypoesthesia, and autonomic nerve dysfunction [25-27], of which pain in the extremities is the most important and most common symptom that does not occur in CMT/DM. Autonomic nerve dysfunction is also common in DPN and rare in CMT/DM. In terms of treatment, for CMT/DM patients, it is relatively easy to control blood glucose level. However, for DPN patients, even when the blood glucose level is well controlled in a timely manner, it is still quite difficult to alleviate DPN symptoms [25, 27]. And also DPN usually lead to extremities ulceration and amputation [26, 27]. The aforementioned various differences suggest that these two diseases are distinctively different in nature.

Yu-Xie syndrome

In the light of the above results, we found that the patients with CMT and concurrent DM had some relatively independent characteristics and pathogenic mechanisms. We hypothesized that DM in these patients is result from their CMT. And further we designate this combined disease condition as "Yu-Xie syndrome" (YXS), a new specific clinical subtype of CMT. According to our analysis, YXS should demonstrate the following four necessary characteristics:

(1) CMT occurs ahead, DM occurs later or almost at the same time; (2) Clinical manifestations are the similar as those of typical demyelination type (CMT type 1), i.e., symmetrical distal limb weakness, muscle atrophy, sensory disturbance, upper and lower extremity involvement. In addition, some atypical DM symptoms may also appear; (3) Demyelination, partial myelin sheath proliferation, and hypertrophic "onion bulb" structures appear in these patients; (4) The molecular biological type is CMT1.

According to the international classification of DM [35], currently there are 9 genetic syndromes with combined DM; and several of them have nervous system involvement, including Down syndrome, Friedreich ataxia, Huntington chorea, and myotonic dystrophy. We believe YXS should be a new genetic syndrome to be added to this family.

DM2 is a polygenic disorder and its genetic factors are complex. However, the single pathogenic gene of CMT may play a role in the occurrence of DM. Taking into account the molecular biological characteristics of these patients, i.e., CMT caused by a variety of gene mutations can be accompanied by DM, we tend to hypothesize that two factors, CMT-induced lifestyle change and the effects of CMT on gene expression, may explain the occurrence of DM in CMT patients. For example, studies have shown that the serum insulin-like growth factor (IGF) level and its binding protein 2 (IGFBP2) are elevated in patients with CMT type 1A [36], but the causes of this endocrine disorder are not clear. We noticed that we retrospectively obtained our data and results. Thus our hypothesis

should be confirmed in a larger prospective study. One of the possible facts is that people do not perform routine blood sugar level check on CMT patients; and many CMT patients actually may have blood sugar abnormal that doctors did not know. Thus, the YXS hypothesis that we proposed here may help us to more effectively manage the concurrent syndrome of CMT patients. Since DM is a manageable disorder, earlier and effective interventions may help to control the severity of the neuropathy that may subsequently develop.

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Disclosure of conflict of interest

None.

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