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한국인 근긴장성 이영양증 제1형 환자의 분자유전학적 및 임상적 특성

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Molecular and Clinical Characteristics of Myotonic Dystrophy Type 1 in Koreans

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Background : Myotonic dystrophy type 1 (DM1) is an autosomal-dominant muscular dystrophy caused by expansion of cytosine-thymine-guanine (CTG) trinucleotide repeats in the myotonic dystrophy protein kinase (*DMPK)* gene. The clinical features of DM1 are multisystemic and highly variable, and the unstable nature of CTG expansion causes wide genotypic and phenotypic presentations. The aim of this study was to characterize the molecular and clinical spectra of DM1 in Koreans.

Methods : The CTG repeats of 283 Korean individuals were tested by PCR fragment analysis and Southern blot. The following characteristics were assessed retrospectively: spectrum of CTG expansions, clinical findings, genotype-phenotype correlation, anticipation, and genetic instability.

Results : One-hundred twenty-four patients were confirmed as DM1 by molecular tests, and the CTG expansions ranged from 50 to 2,770 repeats (median 480 repeats). The most frequent clinical features were myotonia, muscular weakness, and family history. Patients with muscular weakness or dysfunction of the central nervous system harbored larger CTG expansions than those without each symptom (P<0.05). The age of onset was inversely correlated with the size of the CTG expansion (γ=-0.422, P<0.001). The instability of CTG expansion representing as the maximum difference between sibships was observed from 50 to 700 repeats in nine families. Clinical anticipation and the increase in CTG repeat were significantly higher in maternally transmitted alleles (P=0.002).

Conclusions : Molecular genetic tests are not only essential for diagnosis, but also helpful for suggesting the spectrum and relationship between genotype and phenotype in Korean DM1 patients. *(Korean J Lab Med 2008;28:483-92)*

Key Words : *Myotonic dystrophy type 1, DMPK gene, CTG, Trinucleotide repeat expansion, Polymerase chain reaction, Southern blot, Anticipation, Instability, Age of onset, Korean*

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INTRODUCTION

Myotonic dystrophy type 1 (DM1) is the most common

muscular dystrophy in adults. Two important characteristics of this disease are myotonia and multisystemic involvement, and the clinical diagnosis is based on the findings of myotonia, muscle atrophy, weakness, cataract, and other systemic manifestations such as cardiac arrhythmia and endocrine dysfunction [1]. Although myotonia is a representative feature of DM1, other various myotonic disorders are encountered in the clinic and their differential diagnosis is sometimes difficult, especially in the case of early manifestation. Further investigative tools are available such as muscle biopsy, electromyography, and laboratory tests for endocrine dysfunctions, but the variable clinical features of DM1 make molecular tests important for accurate diagnosis.

DM1 results from the unstable expansion of cytosine-thymine-guanine (CTG) trinucleotide repeats in the 3' untranslated region of myotonic dystrophy protein kinase (*DMPK*) gene on chromosome 19q13.3 [2]. The repeat length is polymorphic in the normal population, but expansion exceeding 50 repeats causes the disease. In the pathogenesis of DM1, expansion in the noncoding region is thought to interfere with transcription, RNA processing, or translation [3, 4]. The size of the CTG repeat in the *DMPK* gene can be estimated by a PCR analysis for sizes up to 100 repeats, and by a Southern blot analysis for over 100. The overall detection rate was reported 100% by these two methods, hence molecular analysis is essential for definite diagnosis.

The overall worldwide prevalence of DM1 is estimated to be approximately 5 to 20 out of every 100,000 people [5]. Although DM1 is not a rare neuromuscular disorder in Korean population, previous studies have analyzed relatively small numbers of patients with focus on the clinical characteristics. The purpose of this study was to analyze the molecular and clinical characteristics of DM1 patients and to establish possible relationships between the molecular aberrations and disease phenotypes in Koreans.

MATERIALS AND METHODS

1. Patients and clinical parameters

From August 1996 through March 2008, 283 individuals including 152 males, 128 females, and 3 fetuses were referred for molecular diagnosis of DM1. There were 217 unrelated patients and 66 of their family members. As controls, 47 healthy Koreans were also analyzed for the distribution of normal, polymorphic CTG repeat length. After molecular diagnosis, each patient was retrospectively reviewed for clinical manifestations including age of onset, family history, clinical myotonia, presence of muscle weakness and muscle atrophy, and involvement of other organs represented by cataract, cardiac abnormalities, dysfunction of central nervous system (CNS) or developmental delay, frontal baldness, and endocrine abnormalities. Other functional and laboratory tests included serum creatine kinase (CK), electromyography, and muscle biopsy pathology. Age and clinical description of each patient were reported in this study as those at the time of blood sampling.

2. Molecular analysis

1) DNA extraction

Informed consent was obtained from each subject and then peripheral blood was drawn into an EDTA tube. Genomic DNA was extracted from whole blood using the PureGene DNA Isolation kit (Gentra Systems, Minneapolis, MN, USA).

2) PCR and fragment analysis

The CTG repeat region in the *DMPK* gene was amplified by PCR to determine the sizes of normal or minimally expanded trinucleotide repeats (less than 500 bp). Primers were 102-F (5'-FAM-GAA CGG GGC TCG AAG GGT CCT TGT AGC-3') and 101-R (5'-CTT CCC AGG CCT GCA GTT TGC CCA TC-3'). The PCR reactions were performed in a 25 μL reaction mixture containing 0.2 mM dNTPs, 100 ng of DNA, 10 pmols of each primer, and 2.5 U of Expand Long Taq polymerase (Roche Diagnostics, Mannheim, Germany). Cycling profiles were as follows: 2 min at 94℃, 10 cycles of 10 sec at 94℃, 30 sec at 65℃, and 2 min at 68℃; followed by 20 cycles of 10 sec at 94℃, 30 sec at 65℃, and 2 min plus cycle elongation of 20 sec for each cycle at 68℃; and 7 min at 68℃. The fragment was analyzed by ABI PRISM 3100 Genetic Analyzer with the GeneMapper ID 3.5 software (Ap-

plied Biosystems, Foster City, CA, USA). A schematic map of the *DMPK* gene and primer locations were shown in Fig. 1.

3) Southern blot analysis

To determine the CTG expansions larger than 500 bp, Southern blot was done. Seven microgram of genomic DNA was digested with the restriction endonucleases *Eco*RI and *Pst*I (New England Biolabs Inc., Ipswich, MA, USA), and was electrophoresed on 0.6% and 0.7% agarose gels, respectively. The gels were depurinated in 0.125 M HCl, denatured in 0.5 M NaOH and 1.5 M NaCl, and transferred to nylon membranes (Hybond XL, Amersham, Buckinghamshire, UK). Hybridizations were performed with ^{32}P-labeled probe pM10M-6 [2] (kindly provided by Dr. E. Newman, University of Nottingham) at 65℃ in Rapid-hyb buffer (Amersham). Blots were washed twice with 2X saline-sodium citrate buffer (SSC)/0.1% sodium-dodecyl sulfate (SDS) for 10 min at 25℃, and twice with 0.1X SSC/0.1% SDS for 15 min at 65℃. Autoradiography was done after 1-5 days exposure at −70℃. The size of CTG expansion was calculated from the migrated distance of each band digested by *Eco*RI or

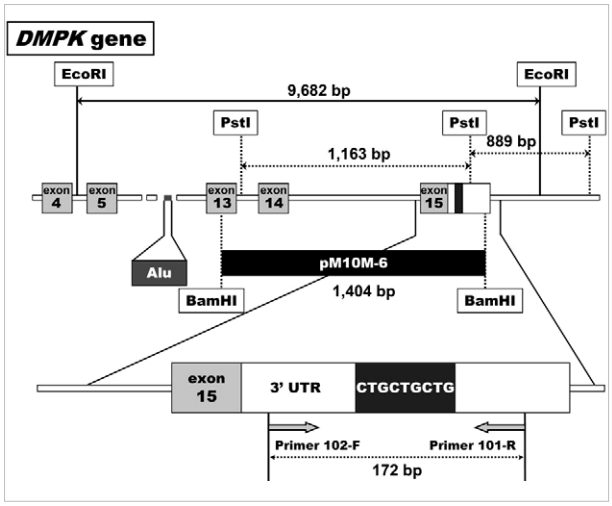

Fig. 1. The schematic map of the *DMPK* gene with relative location of CTG repeats, exons near the repeats, primers, and probe used in this study. The CTG repeats are detected by PCR using primers 102-F and 101-R when the fragment is less than 500 bp. To detect large expansions of more than 500 bp, genomic DNA was digested with the restriction endonucleases *Eco*RI or *Pst*I. The *Eco*RI digestion results in ~9 kb band without *Alu* element, or ~10 kb band with *Alu* insertion. The *Pst*I digestion results in ~1.2 kb and ~0.8 kb bands. Probe pM10M-6 is ~1.4 kb fragment containing the CTG repeats. Each fragment size is from the allele with *Alu* insertion and $(CTG)_{20}$ repeats.

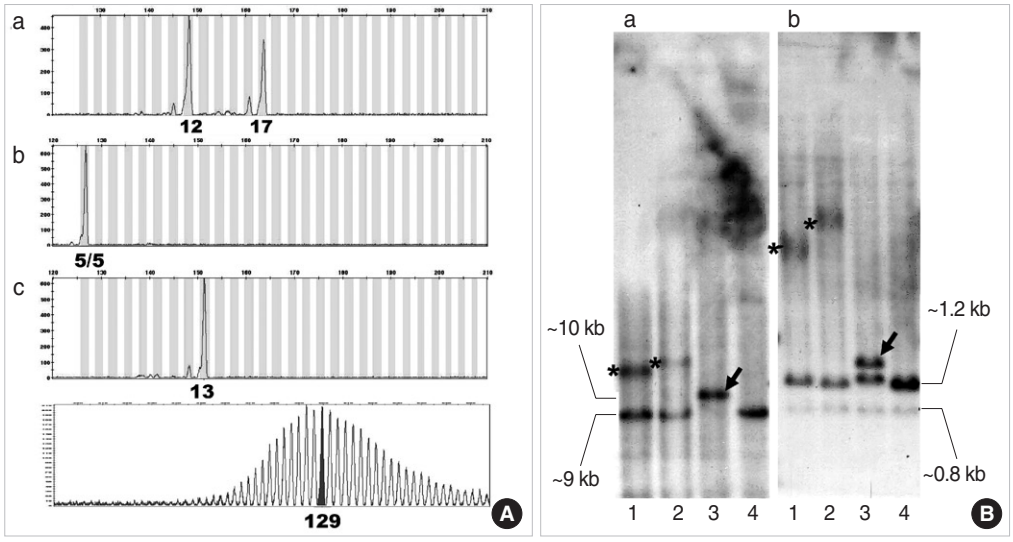

Fig. 2. Representative results from (A) PCR and fragment analysis and (B) Southern blot. (A) Chromatogram obtained (a) from a normal individual with heterozygous 12 and 17 CTG re- peats. (b) from a normal individual with homozygous five CTG repeats. (c) from a DM1 patient with one normal 13 CTG repeat in the upper panel and the expanded 129 repeats in the lower panel. The chromatogram in lower panel was obtained after longer time electrophoresis. (B) (a) an autoradiogram obtained from four individuals by Southern blot after *Eco*RI digestion, and (b) after *Pst*I digestion. In autoradiogram (a), a normal allele of ~9 kb was observed in lanes 1, 2, and 4. Expanded mutant allele larger than ~10 kb was observed in lanes 1 and 2 (marked by asterisk). The expansion of CTG repeats was also suspected in lane 3 (marked by arrow), but not clearly discriminated from a normal band of ~10 kb length. In autoradiogram (b), two normal bands of ~0.8 kb and ~1.2 kb were observed in each lane, and an additional expanded band was observed in lanes 1, 2, and 3. The expanded alleles were estimated as ~690 repeats in lane 1 and ~980 repeats in lane 2. An expanded allele of 75 repeats observed in lane 3 was also determined by PCR and fragment analysis (data not shown). Therefore, these three patients were diagnosed as DM1. Lane 4 was an unaffected individual, heterozygous for 6 and 12 CTG repeats (data from PCR and fragment analysis, not shown).

*Pst*I. The targeted CTG expansion is shown in Fig. 1 with the hybridization probe and the restriction endonuclease sites.

4) Molecular diagnosis

The CTG repeats size in each allele was determined from the fragment lengths from PCR and Southern blot (Fig. 2). The genetic diagnosis was based on the guidelines of the International Myotonic Dystrophy Consortium [6].

3. Genotype-phenotype analysis

The possible relationship of genotype and phenotype was assessed as follows: the associations between CTG expansions and clinical manifestations were assessed by the Mann-Whitney test. The relationships between CTG expansions and the level of serum CK or the age of onset were analyzed by Pearson's correlation coefficient test. The association between the length of CTG expansion and the severity of myotonic discharge in electromyography was analyzed by the Kruskal-Wallis test.

4. Assessment of instability and anticipation

To assess the instability of expanded CTG repeat through transmission, nine DM1 families were selected and the size of repeats was compared between siblings who inherited the same progenitor allele. Anticipation and contraction were assessed in 20 parent-offspring pairs by CTG expansion size and by clinical features. Anticipation according to parent sex was analyzed by the Mann-Whitney test.

5. Statistical analysis

The CTG expansion of each group was expressed as median and range. In each test, a *P* value of less than 0.05 was considered statistically significant. Analyses were performed using SPSS for Windows version 12.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

1. Molecular diagnosis results

A total of 124 patients out of 283 individuals (43.8%) were diagnosed as DM1 by molecular methods (Fig. 2), and one individual harbored a premutation allele of 35 CTG repeats. These 124 DM1 patients included 71 males, 52 females, and a fetus. They consisted of 97 unrelated probands and their 27 family members. Eighteen families had two or more patients confirmed, and are shown in pedigrees (Fig. 3).

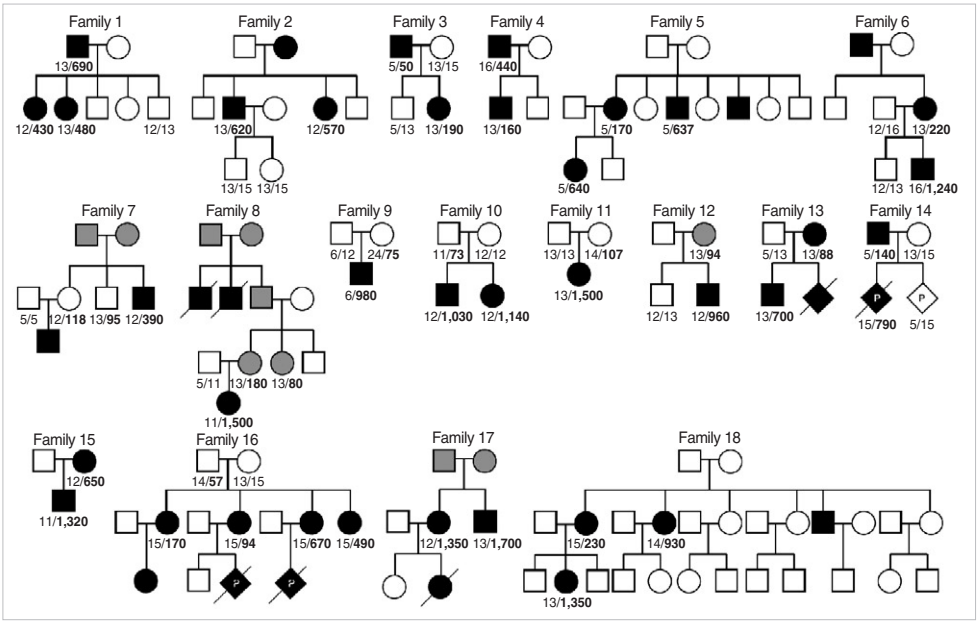

Fig. 3. Pedigrees of 18 Korean DM1 families with two or more patients. Identifier number of each family is indicated above, and the CTG repeats number in the *DMPK* gene is below each symbol of family member.
Circle, female; square, male; diamond, offspring with no information about sex; filled symbol, symptomatic; open symbol, asymptomatic; shaded symbol, affected status not known; P, fetus in pregnant status.

2. Pathologic and normal alleles containing CTG repeats

All 124 patients were heterozygous for the expanded allele. The expanded alleles ranged from 50 to 2,770 CTG repeats (Table 1). The majority of expanded alleles (76.6%) were in the range of classic phenotype, between 100 and 1,000 repeats [6]. Case with the CTG expansions over 2,000 repeats was rare (0.8%). One case was found with 35 CTG repeats in the premutation range. The accurate frequency of premutation alleles could be determined by an additional population study due to their asymptomatic nature.

For all 124 patients, the median size of the CTG repeat expansions was 480 repeats (range 50–2,770), and there was no significant difference between males (median 480 repeats, range 50–2,770) and females (median 480, range 75–1,790). A fetus was 790 repeats. The expansions in 97 unrelated probands (median 550, range 110–2,770) were not significantly different from those of all 124 patients including family members.

The Fig. 4 shows the distribution of non-expanded normal CTG repeat length in 430 alleles, which were from 217 unrelated individuals and 47 normal controls included in this study. Twenty-two different alleles were observed, and the size of CTG repeats ranged from 5 to 31. The most frequently observed allele was 12 CTG repeats (28.8%), followed by 5 (20.7%) and 13 (19.3%) repeats. The frequency of large normal alleles with between 18 and 31 CTG repeats was 4.2% (18/430).

Table 1. The distribution of CTG expansions in 125 Koreans

Molecular diagnosis	Clinical phenotype*	CTG repeat	N
Premutation (mutable normal)		35-49	1
DM1	Mild	50-99	9
		100-149	13
	Classic	150-999	82
		1,000-1,999	19
	Congenital	>2,000	1
		Total DM1 patients	124

*Phenotypes were based on the classification by International Myotonic Dystrophy Consortium (IDMC): mild phenotype, 50 to ~150 repeats; classic phenotype, ~100 to ~1,000; congenital phenotype, >2,000[6].
Abbreviations: CTG, cytosine-thymine-guanine; DM1, myotonic dystrophy type 1.

3. Clinical findings and genotype-phenotype correlation

Clinical records were evaluated in 105 DM1 patients. Table 2 shows the positive rates and CTG expansion levels in patients with or without each clinical parameter. Myotonia was the most frequent manifestation (80.0%). Muscular weakness was also distinctive (77.1%), in which limb weakness was predominant (95.1%). Limb weakness showed a progressive pattern from distal to proximal, and sole proximal weakness was observed in two patients only. Facial weakness was also frequently observed (51.4%). Family history was found in 52.3% of probands. Other clinical manifestations were found less frequently (Table 2). The correlation was assessed between the presence or absence of each symptom and the degree of CTG expansion, and two symptoms showed significant relationships. The CTG expansions

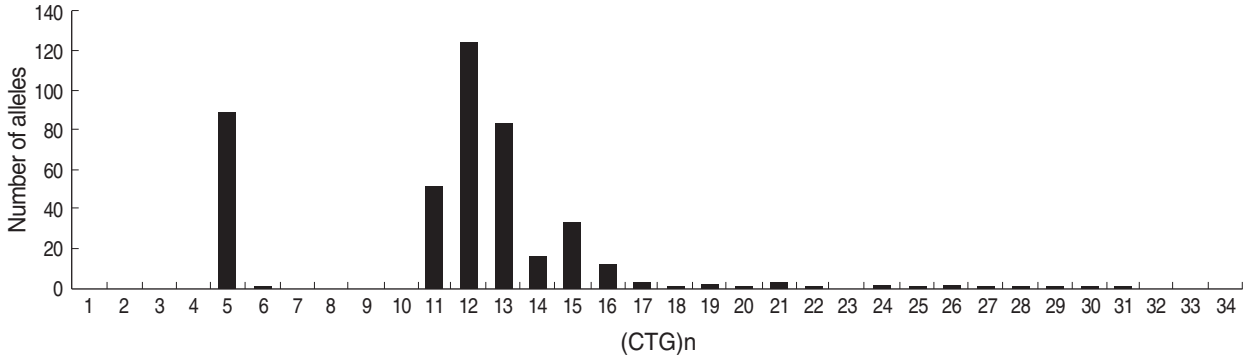

Fig. 4. The distribution of 430 normal alleles with different CTG repeats in the *DMPK* gene. Histogram is derived from the analysis of 94 normal alleles from 47 normal control subjects, 239 normal alleles from 120 unrelated subjects suspicious as DM1 but harbored no expanded alleles of 50 or more CTG repeats, and 97 normal alleles from 97 unrelated DM1 patients diagnosed by molecular analysis.

Table 2. Clinical characteristics in Korean DM1 patients confirmed by molecular tests

Clinical findings	N*	Posivite		Negative		*P*	Comment
		N (%)	CTG expansion median (range)	N	CTG expansion median (range)		
Myotonia	105	84 (80.0)	495 (50-2,770)	21	750 (73-1,500)	>0.05	
Muscular weakness	105	81 (77.1)	560 (50-2,770)	24	280 (73-1,420)	0.019	
Family history	88	46 (52.3)	665 (118-2,770)	42	470 (110-1,420)	>0.05	
Muscular atrophy	105	44 (41.9)	540 (110-1,700)	61	480 (50-2,770)	>0.05	
Frontal baldness	105	35 (33.3)	550 (50-1,700)	70	480 (73-2,770)	>0.05	
CNS dysfunction/ developmental delay	35	17 (48.6)	1,190 (230-2,770)	18	410 (110-1,790)	0.005	
Cataract	56	24 (42.9)	638 (120-2,770)	32	655 (110-1,400)	>0.05	
Endocrine abnormalities	44	17 (38.6)	510 (120-990)	27	450 (50-1,350)	>0.05	
Cardiac abnormalities	76	26 (34.2)	590 (120-1,420)	50	530 (110-2,770)	>0.05	
Electromyography	72	69 (95.8)	510 (110-2,770)	3	550 (230-1,240)	>0.05	
Muscle biopsy	23	19 (82.6)	560 (140-2,770)	4	295 (120-530)	>0.05	
Creatine kinase	50	17 (34.0)	620 (140-1,700)	33	550 (120-1,500)	>0.05	Median 228.0 Range 68.0-1,044.0 (IU/L)

*The number of patients whose clinical information for each symptom was available. For the clinical manifestations that require specific tests, only patients who undergone tests were analyzed.
Abbreviations: CNS, central nervous system; See Table 1.

Table 3. The instability in CTG repeat expansion assessed by comparison between siblings in nine DM1 families

Family identifier	Parent allele (repeats)	Parent sex	Sib1		Sib2		Sib3		Sib4		Maximal difference (repeat)
			Repeats	Onset	Repeats	Onset	Repeats	Onset	Repeats	Onset	
1	690	M	430	A	480	A	–	–	–	–	50
2	Unidentified	F	620	A	570	A	–	–	–	–	50
5	Unidentified	U	170	A	637	A	–	–	–	–	467
7	Unidentified	U	118	N	95	N	390	A	–	–	295
8	Unidentified	M	180	U	80	U	–	–	–	–	100
10	73	M	1,030	J	1,140	J	–	–	–	–	110
16	57	M	170	A	94	A	670	A	490	A	576
17	Unidentified	U	1,350	A	1,700	A	–	–	–	–	350
18	Unidentified	U	230	A	930	A	–	–	–	–	700

Abbreviations: M, male; F, female; A, adult-onset; N, asymptomatic; J, juvenile-onset; U, unknown; See Table 1.

were significantly larger in patients with muscular weakness than in the group without weakness. This difference was also evident between patients with and without a developmental delay or CNS dysfunction (Table 2).

In muscle biopsy, pathologic findings consistent with DM1 were observed in 82.6% of the specimens. Findings in 95.8% of electromyography were consistent with DM1. However, the severity of myotonic discharge subgrouped by three classes, seven mild cases, seven moderate, and one severe case, and the length of CTG expansion showed no significant relationship. The level of serum CK was abnormally high in 34.0% of the patients tested, but no relationship was observed between the CK level and the CTG repeat size (γ=−0.072, P>0.05). In contrast, the age of onset showed a relationship with CTG expansion. Among 83 patients, the age of onset was inversely correlated with the size of CTG repeats (γ=−0.422, P<0.001) (Fig. 5), and the relationship was more obvious in the relatively short CTG expansions below 400 repeats (γ=−0.661, P<0.001).

4. Instability and anticipation

In nine families consisted of two or more affected siblings, the CTG repeat expansion was not identical in size

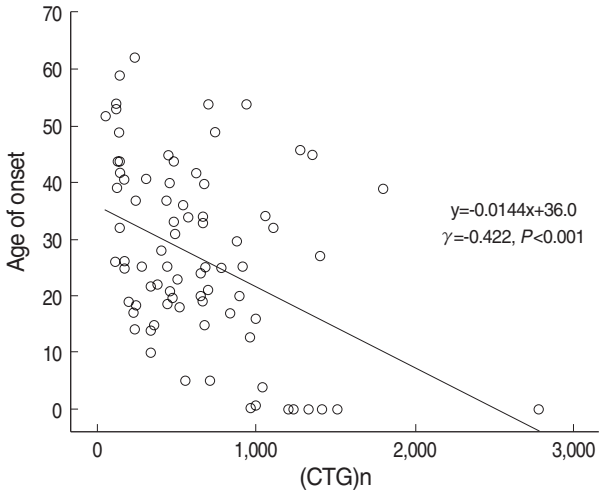

Fig. 5. The CTG repeat expansion and the age of onset in 83 DM1 patients. Two factors show an inverse correlation.

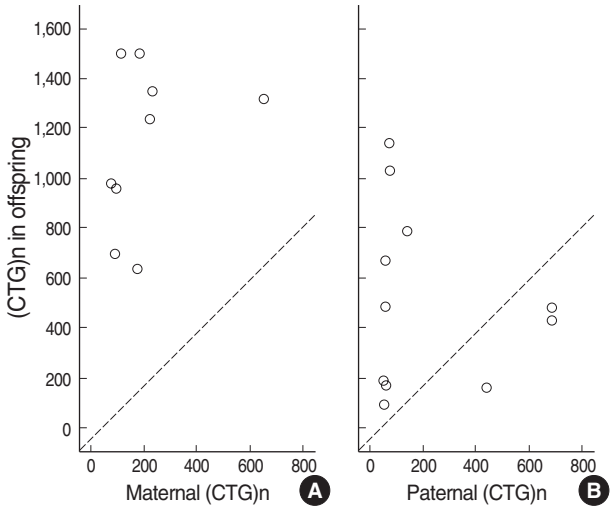

Fig. 6. The size of CTG repeats expansion for (A) mother-offspring, and (B) father-offspring pairs. Anticipation was more evident in maternally-transmitted alleles. Contraction occurred only in paternally-transmitted alleles. Diagonal lines mean that the same allele size was expected between parent and offspring. Open circles located below the diagonal line indicate contraction of CTG repeats in offspring.

between sibships (Table 3, pedigrees in Fig. 3). Instability of CTG expansion as assessed by the maximal difference in sibships was from 50 to 700 repeats. All sibships showing instability had similar clinical phenotypes including the age of onset.

Anticipation was analyzed in 20 pairs of parent and offspring. The CTG expansions increased in 17 pairs, and contracted in 3 pairs (Fig. 6). Anticipation was dependent on the sex of the transmitting parent. Although there was no significant difference in the repeat expansion between nine mothers (median 170, range 75–650) and six fathers (median 106, range 50–690) (P>0.05), CTG expansions in offsprings were greater in the maternally-transmitted cases (median 1,240, range 640–1,500) than those in the paternally-transmitted (median 480, range 94–1,140) (P=0.002). In the eight mother-offspring pairs whose information was available, the median age of onset in the offspring was 0.125 yr (range 0–20 yr), and six of them presented symptoms within one year after birth. On the other hand, the median age of onset in five offspring who inherited paternal alleles was 19.0 yr (range 3–41 yr), and one 26-yr-old offspring was asymptomatic.

Contraction of expanded allele through transmission occurred in paternally-transmitted alleles only. In one family (family 1 in Fig. 3), repeat size decreased from 690 in father to 480 and 430 in two daughters. All three patients showed similar clinical presentations of adult-onset DM1. In the other family (family 4 in Fig. 3), the repeat size decreased from 440 in father to 160 in the son: the father in his mid-forties showed features of myotonic dystrophy, but the 26-yr-old son was asymptomatic.

DISCUSSION

In this study, 430 normal alleles were distributed with the highest peak at 12, and followed by 5 and 13 CTG repeats. The most frequent allele was different between Caucasians and Asians: five repeats is the most common in European, and 12 repeats in Japanese [7, 8]. In Koreans, a previous study reported the range of CTG repeats to be 5 to 34, and $(CTG)_{11-14}$ as the predominant alleles [9]. Another study indicated 12 repeats as predominant [10]. Our result supports the difference between ethnicities in the allelic frequencies of CTG repeats.

Large normal alleles with more than 18 CTG repeats are not a pathologic cause in the individual, but have been considered as a reservoir of further expanded, disease-causing alleles in the successive generation [11]. The frequency of alleles with more than 18 CTG repeats differs according to ethnicity. Alleles of greater than 18 repeats were only

1.4% in Taiwanese with low prevalence of DM1 [12]. In the Japanese population with relatively high prevalence of DM1, 9% harbored alleles with 18 or more repeats [13]. In this study, 4.2% of normal alleles carried between 18 and 31 CTG repeats. The frequency of large normal alleles may help predict the prevalence of DM1 in Koreans before conducting larger diagnostic molecular studies [14].

Among 283 individuals referred for the molecular diagnosis, 124 patients were confirmed as DM1 through this study. One individual carried a premutation allele, and 158 patients harbored no expanded CTG repeats. Other myotonic disorders except DM1 can be the cause of observed phenotype in these patients: proximal myotonic myopathy (PROMM, myotonic dystrophy type 2) might be the most important one, and other myopathy or non-progressive myotonic disorders due to primary ion channel defects should be also considered in the differential diagnosis of DM1 [5]. The molecular tests diagnose patients with 100% accuracy, without overlap between normal alleles and expanded full penetrance alleles. In contrast, the clinical manifestations and their severity broadly correlate with the size of CTG repeat expansion [15-17], but findings vary greatly between patients. In addition, the late-onset character of DM1 sometimes makes it difficult to diagnose patients with early manifestations. In this study, myotonia and muscular weakness were the two most frequent and important symptoms. However, many patients carrying small expansions of 50-99 repeats (44.4%) were asymptomatic and the sole clue suspected as DM1 was the positive family history. Clinical myotonia was obvious in only 33.3% of them. Therefore, the presence of family history was emphasized through this study for the early diagnosis of asymptomatic patients. Careful history taking, physical examination, and subsequent molecular testing will provide earlier and more accurate diagnosis for apparently asymptomatic or relatively young individuals.

Genotype-phenotype relationship in DM1 has been widely studied in many ethnicities, but few researches have been conducted in Korean patients. In the previous studies, CTG expansion was known to be correlated with diverse phenotypic findings such as age at onset, muscle disability, heart involvement, intelligence quotient, phosphate excretion and thyrotropin-releasing hormone, impaired glucose metabolism, and reduced immunoglobulin levels [5]. In this study, 13 phenotypic characteristics of Korean patients were reviewed in relation to genotype, but only the three findings, earlier age of onset, the presence of muscular weakness, and developmental delay or CNS dysfunctions, were related to the larger CTG expansions. These three phenotypic expressions may be used with caution as representative clinical features implying severe molecular defect in Korean patients, until more information becomes available. The possibility of other genotype-phenotype relationships in clinical manifestations should be elucidated through further studies.

Anticipation, contraction, and genotypic differences within sibships are genetic phenomena of DM1 caused by instability of CTG repeat expansion. We assessed the intragenerational instability of expanded CTG repeats within sibships and observed genetic instability with little phenotypic variation, consistent with previous reports [18]. Anticipation, the phenomenon of increased repeat expansion and severe congenital phenotype in the successive generation, was significant in maternal alleles. Contraction occurred in one-third of paternal alleles, which was apparently more frequent than that in a previous report (10%) [19]. Trinucleotide repeat contraction can be a difficult issue in prenatal diagnosis and genetic counseling [20]. The magnitude of contraction differs between reported cases [21], and contraction has even been reported from a pathologic expansion of 1,000 repeats back into the premutation range[8]. In this study, no contraction occurred back into the range of non-disease causing alleles. For prenatal counseling and management of affected offspring, it is important to take into account that these genetic phenomena could be affected by the sex of the transmitting parent and could affect the genotype and phenotype of members of the successive generation.

Overall, the current molecular genetic test detected 124 Korean DM1 patients. Through this study, the molecular spectrum and clinical features were described in Korean patients and the genotype-phenotype correlation was investigated. The degree of anticipation, contraction, and insta-

bility observed in this study are helpful not only for laboratory physicians performing tests and making molecular diagnoses, but also for clinicians diagnosing and counseling patients with variable onset and systemic involvement.

요 약

배경 : 근긴장성 이영양증 제1형(myotonic dystrophy type 1, DM1)은 상염색체 우성 유전의 근육 이영양 질환으로, myotonic dystrophy protein kinase (*DMPK*) 유전자에 위치한 cytosine-thymine-guanine (CTG) 삼염기 반복구조의 증폭에 의해 발생한다. DM1은 여러 장기에서 다양한 임상상을 보이며, CTG 증폭의 불안정성으로 유전형과 표현형의 폭넓은 변화가 일어난다. 본 연구는 한국인 DM1 환자에서 분자유전학적 및 임상적 특성의 분포를 규명하고자 하였다.

방법 : 283명의 한국인 환자에서 CTG 반복수를 PCR 분절분석법과 서던블롯법으로 검사하였다. 임상적 특성은 후향적으로 평가했으며 그 대상은 CTG 증폭의 양상, 임상 양상, 유전형과 표현형 간의 관계, 세대 간 예견과 유전형의 불안정성이었다.

결과 : 분자진단검사에 의해 124명의 DM1 환자가 확진되었으며, CTG 증폭은 50에서 2,770 사이에 분포하였다(중앙값 480 반복수). 가장 빈번한 임상 양상은 근긴장증, 근력 약화, 그리고 가족력이었다. 근력 약화 또는 중추신경계 기능 이상을 보이는 환자군은 각각 그러한 증상이 없는 군에 비해 보다 큰 CTG 반복수를 갖고 있었다($P<0.05$). 발병 연령과 CTG 증폭의 크기는 역의 상관 관계를 보였다($\gamma=-0.422$, $P<0.001$). CTG 증폭의 불안정성은 아홉 가족에서 형제 간 반복수의 차이로 평가되었으며, 그 차이는 50-700이었다. 임상양상의 예견과 CTG 반복수의 증폭은 모계 유전된 대립유전자를 갖는 환자에서 부계 유전의 경우보다 유의하게 높았다($P=0.002$).

결론 : 분자유전학적 검사는 진단에 필수적일 뿐만 아니라, 한국인 DM1 환자들의 유전형과 표현형의 관련성을 파악하는 데에 도움이 되었다.

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