Revised Ghent Criteria is Comparable to Original Diagnostic Criteria for Marfan Syndrome with Increased Ability to Clinically Diagnose Related Disorders

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Background: *Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with major features in cardiovascular, ocular, and skeletal systems. Due to its genetic heterogeneity and variable expressivity, Ghent nosology was established for clinical diagnosis of MFS. In 2010, Ghent diagnostic criteria were revised to better diagnose MFS and categorize its related disorders. There is no previous clinical comparison between the original and revised Ghent criteria for diagnosis of MFS in Thai patients.*

Objective: *To compare application and efficacy of Ghent and revised Ghent criteria in adult Thai patients with clinical suspicion of MFS.*

Material and Method: *This study was a retrospective analysis of patients with clinical suspicion of MFS who attended the Medical Genetics Clinic, Siriraj Hospital between January 2003 and December 2013. Patients were clinically examined for diagnosis of MFS using both the Ghent and revised Ghent criteria. Multidisciplinary data, including physical examination, echocardiography, slit-lamp examination, and genetic testing, were analyzed.*

Results: *Clinical and genetic data of 138 (77 males and 61 females) individuals with clinical suspicion of MFS were reviewed. The most common presentation was cardiovascular manifestation. Of 92 patients diagnosed as MFS by original Ghent nosology, 70 of those patients (76.1%) were also diagnosed as MFS by revised Ghent criteria. Forty-eight of 138 patients (34.8%) had undergone genetic testing, with FBN1 mutations detected in 23 patients. Twenty-two patients with detectable FBN1 mutations fulfilled both the Ghent and revised Ghent criteria. Of 22 patients whose diagnoses were not fulfilled by revised Ghent nosology, most were due to inadequate systemic score (SS). The use of revised Ghent nosology also facilitated improved diagnosis of MFS-related disorders.*

Conclusion: *Revised Ghent nosology has further differentiated MFS from other MFS-related disorders and has further expanded the classification of MFS-related disorders. Genetic testing of FBN1 helps physicians to more accurately diagnose patients with MFS and related disorders.*

Keywords: *Criteria, FBN1, Fibrillin, Ghent criteria, Marfan syndrome, Nosology, Revised Ghent criteria*

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Marfan syndrome (MFS) is an autosomal dominant connective tissue disorder with major features in cardiovascular, ocular, and skeletal systems with a prevalence of 1 in 5,000 individuals[1,2]. Due to the genetic heterogeneity and variable expressivity of MFS, the Ghent nosology was established for the clinical diagnosis of MFS[3]. The condition is often found to be caused by loss-of-function mutations in *FBN1*, which encodes fibrillin-1 protein[4]. Accurate clinical diagnosis of MFS is essential for patients on medical and surgical management, because *FBN1* mutation detection rate is approximately 70 to 90% in MFS patients and not all *FBN1* mutations are associated with MFS[5,6]. There is currently no single diagnostic method for the definite diagnosis of MFS.

In 2010, diagnostic criteria were revised to better categorize MFS and its related disorders[7]. The revised Ghent criteria has given more weight to aortic root dilatation, ectopia lentis, and *FBN1* mutation to emphasize the importance of manifestation in cardiovascular, ocular, and skeletal systems, differentiate MFS from other fibrillinopathies, and remove some of the less specific manifestations of MFS. The new criteria have been simplified to facilitate

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faster and more accurate identification of MFS patients and to decrease the use of expensive and sometimes unnecessary investigation. Clinical comparison between the original and revised Ghent criteria for diagnosis of MFS has been undertaken in various MFS cohort studies and the data has shown that the revised Ghent nosology delivers different rates of concordance for MFS diagnosis between Caucasian and Asian individuals. There is no such data available on other Asian individuals diagnosed with MFS. Accordingly, the objective of this study was to investigate the clinical diagnosis of MFS by comparing the Ghent and revised Ghent nosologies in Thai adult MFS patients.

Material and Method

The research protocol for this study was approved by the Siriraj Institutional Review Board (SIRB). The Siriraj Hospital Marfan clinical database was reviewed. This retrospective study reviewed 138 consecutive patients aged 18 years or more with clinical suspicion of MFS and/or family history of MFS who attended the Medical Genetics Clinic, Siriraj Hospital between January 2003 and December 2013. All 138 patients were evaluated for diagnosis of MFS by both original Ghent and revised Ghent criteria. All relevant clinical data, including family history, physical examination, transthoracic echocardiography, slit-lamp eye examination, radiographic imaging, and genetic test results, were analyzed. For evaluation of aortic root aneurysm, aortic diameter at the sinuses of Valsalva was measured by transthoracic echocardiography. Aortic diameter measurement was corrected for age and body surface area and interpreted as a Z-score[7]. Diagnosis of ectopia lentis by ophthalmologist was based on slit-lamp examination after maximal pupil dilatation. Scoliosis was evaluated by radiologic examination of plain radiographic, computed tomography (CT), and/or magnetic resonance imaging (MRI) images. Plain radiography, CT scan, or MRI can be used to detect protrusion acetabuli. Dural ectasia was evaluated by CT scan or MRI, when clinically indicated[9]. The *FBN1* mutation testing method was previously published and described[5,6].

Statistical analysis

All patients were classified regarding fulfillment of criteria based on the published standards of the original Ghent and revised Ghent criteria[3,7]. Concordance between Ghent and revised Ghent criteria was analyzed using Cohen's kappa statistic and Chi-square test. Descriptive data were calculated by Mann-Whitney U test and reported as mean ± SD or n (%). All statistical analyses were performed with SPSS for Windows version18 (SPSS, Inc., Chicago, IL, USA).

Results

Study population

Patient characteristics

There were 138 patients (77 males and 61 females) with ages ranging from 18 to 73 years. Median age at time of MFS diagnosis was 24.3 years. Frequencies of main organ system manifestations associated with MFS that initiated referral of 138 patients for initial evaluation at the Division of Medical Genetics, Siriraj Hospital are shown in Fig. 1. The most common presentation was cardiovascular manifestation (51/138 patients; 37.2%), with five of 51 patients (9.8%) presenting with aortic dissection at first visit. Ectopia lentis was found in 51.2% of patients. Only 48 of 138 patients (34.8%) had undergone genetic testing. Patient characteristics of 138 patients with clinical suspicion of MFS diagnosis are presented in Table 1.

Comparison of Ghent and revised Ghent criteria in study cohort

Ninety-two of 138 patients (66.7%) fulfilled the original Ghent nosology for diagnosis of MFS. Of those 92 patients, 70 (76.1%) fulfilled the revised Ghent criteria for diagnosis of MFS. Of the 22 patients (23.9%) whose diagnoses were not fulfilled, most were due to inadequate systemic score (SS). Over half of patients (58.7%) had MFS diagnosis made by Ghent nosology based on history, physical examination, echocardiographic and radiologic studies, and slit-lamp eye examination, but without *FBN1* mutation analysis.

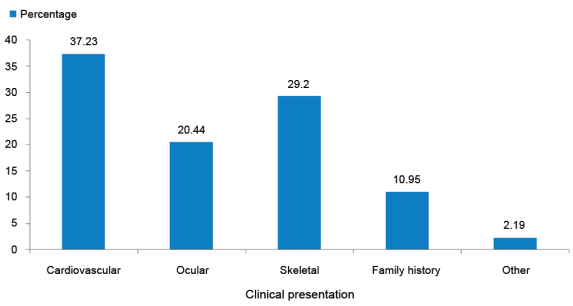

Fig. 1 Frequency of phenotypic manifestations associated with Marfan syndrome (MFS) that initiated referral of 138 patients for initial evaluation at the Division of Medical Genetics, Siriraj Hospital.

Table 1. Characteristics of 138 patients with clinical suspicion of MFS

Characteristics	Patients with clinical suspicion of MFS (n = 138)
Age at first visit (year)	23.3±12.9
Age at diagnosis of MFS (year)	24.3±12.3
Height (cm)	171.1±15.5
Weight (kg)	53.7±15.3
Male	77 (55.8)
Major cardiovascular manifestation	51 (37.2)
Aortic dissection at first presentation	5 (9.8)
Aortic diameter at sinus of Valsalva (cm)	3.8±1.49
Aortic dissection	24 (17.7)
Aortic graft or valve surgery	44 (32.1)
Mitral valve prolapse	59 (42.8)
Ectopia lentis	64 (51.2)
Myopia	68 (53.1)
Skeletal manifestation	95 (78.5)
Pulmonary manifestation	8 (7.8)
Skin manifestation	41 (45.6)
Family history of MFS	41 (29.7)
Genetic analysis of *FBN1*	48 (34.8)
Presence of *FBN1* gene mutation	23 (47.9)
Treatment with beta blocking agents	107 (78.7)
Treatment with angiotensin receptor blocking agents	47 (35.1)

MFS = Marfan syndrome; FBN1 = fibrillin-1 gene
Major cardiovascular manifestation defined by aortic root dilatation or aortic dissection
Data presented as mean ± SD or n (%)

Only 41.3% (38 of 92 patients) had undergone genetic testing. *FBN1* mutations were detected in 22 patients, with all 22 patients fulfilling both the original Ghent and revised Ghent criteria. Of the 46 patients who failed to fulfill the Ghent criteria for MFS diagnosis, two patients were subsequently diagnosed with MFS according to the revised Ghent criteria that included aortic size and systemic score.

The revised Ghent nosology resulted in the diagnosis of 36 cases of MFS-related disorders. Sixteen patients were diagnosed with MASS (myopia, mitral valve prolapse, borderline non-progressive aortic root dilatation, skeletal, and skin findings), seven patients with mitral valve prolapse syndrome (MVPS), and 13 patients with ectopia lentis syndrome (ELS). However, only 10 patients (27.8%) in this group initially fulfilled the original criteria. Most failed to meet both criteria due to inadequate systemic score and/or lack of genetic testing result. Among those who did not fulfill both criteria, 5 patients had aortic root dilatation and two of them had aortic dissection without additional organ manifestation. Criteria fulfillment of the study population is described in flowchart format in Fig. 2.

Concordance of revised Ghent and original Ghent criteria for MFS diagnosis

In this study, original Ghent nosology showed high concordance with revised Ghent nosology in MFS patients (97.2%) (Table 2).

Our study categorized patients clinically suspected of having MFS into 4 groups, including: 1) patients that fulfilled both the Ghent and revised

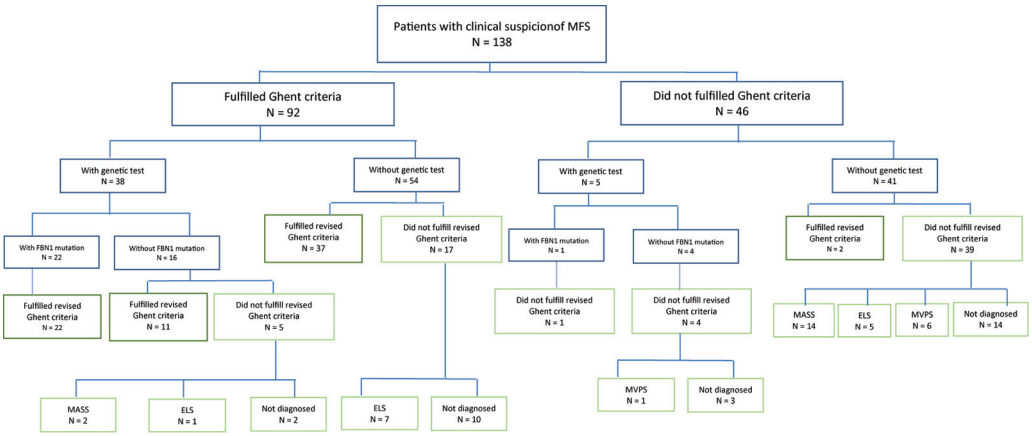

Fig. 2 Outcome of clinical evaluation based on original and revised Ghent nosologies among 138 patients. MFS = Marfan syndrome; *FBN1* = fibrillin-1 gene; MASS = mitral valve prolapse, myopia, borderline and non-progressive aortic enlargement, and non-specific skin and skeletal findings; ELS = ectopia lentis syndrome.

Table 2. Comparison of original and revised Ghent criteria for diagnosing MFS

Tools	Fulfilled original Ghent nosology	
	Concordance rate (%)	Discordance rate (%)
Fulfilled revised Ghent	97.2	2.8
Did not fulfill revised Ghent	65.7	34.3

MFS = Marfan syndrome

Ghent nosologies; 2) patients that fulfilled the original, but not the revised Ghent nosology; 3) patients that did not fulfill the original, but fulfilled the revised Ghent nosology; and 4) patients that did not fulfill either the original or revised Ghent nosologies. Clinical criteria were analyzed on whether the patients in each group had a clinical phenotype in each criterion. We found the frequencies for aortic Z-score greater than 2, presence of ectopia lentis, systemic score (SS) higher than 7, and presence of *FBN1* mutations to be statistically significantly higher in groups 1, 2, and 3.

Discussion

MFS is an autosomal dominant connective tissue disorder with major features in the cardiovascular, ocular, and skeletal systems. Accurate diagnosis is dependent on clinical and investigational information, with some clinical features difficult to characterize due to patient age and severity of presentation[10].

The revised Ghent nosology can be used to establish diagnosis in most MFS patients and the simplicity of the criteria does not decrease its diagnostic power[1,7,8]. However, the revised Ghent nosology was developed based on critical review of clinical characteristics from large published patient cohorts, most of which had Caucasian subjects[6,11]. As such, race-related bias may exist that limits interpretation in non-Caucasian racial groups[12]. Radonic et al demonstrated that, out of 180 MFS patients who fulfilled the Ghent criteria, only 91% of those patients fulfilled the revised Ghent criteria[1]. Yang et al[8] enrolled 106 patients aged older than 20 years that were suspected of having MFS. Eighty-one percent of those patients fulfilled the Ghent criteria, with 79% fulfilling the revised Ghent criteria. *FBN1* mutations were detected in 69% of the 106 patients and all of them fulfilled both Ghent and revised Ghent nosologies[8].

Similar to prior studies, the results from our study suggest that MFS patients who fulfilled the original Ghent nosology generally tend to also fulfill the revised criteria[1,8,13]. However, approximately 24% of the patients that fulfilled the original criteria in our study were not diagnosed with MFS according to the revised Ghent criteria. Half of those were instead diagnosed with MFS-related disorders (8 patients with ELS and 2 patients with MASS). In addition, 56% of the patients in our study that failed to fulfill both the original Ghent and revised Ghent nosologies were also diagnosed with MFS-related disorder. We also found that the revised Ghent nosology led to an increase in the diagnosis of MVPS. We, therefore, postulate that the revised criteria increased the diagnosis of other MFS-related disorders, mainly due to the lowering of the diagnostic threshold for MASS and MVPS.

Our study had several limitations. First, the revised Ghent criteria place more emphasis on *FBN1* mutation test in confirming diagnosis of MFS. Because of the high cost of *FBN1* testing, only one-third of patients in our study underwent genetic testing for *FBN1*. Second, several previous studies reported that dural ectasia is a feature that is highly associated with MFS, with a prevalence of 40 to 91%[14-16]. However, dural ectasia was not routinely screened among our cohort. Finally, approximately 20% of our patients were not formally diagnosed with MFS or MFS-related disorders. This outcome is mainly due to inadequate systemic score (SS), which could be the result of incomplete clinical investigation.

To our knowledge and based on our review of the literature, this is the first study that compares the original and revised versions of the Ghent criteria for diagnosis of MFS and related disorders in Thai adults.

Conclusion

Revised Ghent criteria provided a simplified tool for diagnosis of MFS and helped physicians to differentiate and further classify other MFS-related disorders. The revised criteria were comparable to the original Ghent nosology for diagnosis of MFS in adult Thai individuals. Genetic testing of *FBN1* may provide more accurate diagnosis in patients with MFS and related disorders.

What is already known on this topic?

The original Ghent criteria for MFS had been adopted since 1996. In 2010, diagnostic criteria were revised and gave more weight to aortic root dilatation, ectopia lentis, and *FBN1* mutation to differentiate the emphasis of each organ manifestation between cardiovascular, ocular, and skeletal systems, and remove some less specific features of MFS. Clinical comparison between the original and revised Ghent

criteria for diagnosis of MFS has been undertaken in various MFS cohort studies and the data has shown that the revised Ghent nosology delivers different rates of concordance for MFS diagnosis between Caucasian and Asian individuals. Besides Korean population, there is no such data available on other Asian individuals diagnosed with MFS.

What this study adds?

This study investigated the relationship between the original and revised Ghent diagnostic criteria and how definite and suspected Thai MFS patients were categorized after revised criteria was implemented. The study found high concordance rate between original and revised criteria on Thai patients. The result also showed that the revised criteria resulted in increased diagnosis of other MFS related disorders.

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Potential conflicts of interest

None.

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Revised Ghent criteria มีผลเทียบเท่าเกณฑ์วินิจฉัยต้นแบบในการวินิจฉัยผู้ป่วย Marfan syndrome และเพิ่มการวินิจฉัยภาวะที่เกี่ยวข้อง

วรวรรณ เพ็ญภัทรกุล, มานพ พิทักษ์ภากร

ภูมิหลัง: *Marfan syndrome (MFS) เป็นกลุ่มโรคพันธุกรรมที่มีความผิดปกติในหลายระบบ ทั้งระบบหัวใจและหลอดเลือด สายตา โครงสร้างกระดูก และกล้ามเนื้อ ผู้ป่วยอาจมีการแสดงออกทางคลินิกที่หลากหลายและแตกต่างกันในแต่ละบุคคล MFS เกิดจากความผิดปกติของจีน FBN1 ซึ่งมีหน้าที่ความคุมการสร้างโปรตีน fibrillin-1 ในอดีตการวินิจฉัย MFS ใช้เกณฑ์ทางคลินิก คือ Ghent nosology ซึ่งมีความซับซ้อนและยุ่งยาก ปัจจุบันมีการปรับปรุงเกณฑ์การวินิจฉัยใหม่คือ revised Ghent nosology โดยเน้นประวัติครอบครัว อาการแสดงทางระบบหัวใจและหลอดเลือด และอาการแสดงทางตาของผู้ป่วยเพิ่มมากขึ้นในการวินิจฉัยโรค เพื่อช่วยให้แพทย์สามารถให้การวินิจฉัยแยกโรคได้อย่างสะดวกและรวดเร็วมากยิ่งขึ้น มีการศึกษาย้อนหลังเปรียบเทียบระหว่าง Ghent และ revised Ghent nosology ในผู้ป่วย MFS ในหลายชนชาติ แต่ไม่เคยมีการศึกษาเปรียบเทียบในผู้ป่วยชาวไทยมาก่อน*

วัตถุประสงค์: *เพื่อศึกษาเปรียบเทียบระหว่างเกณฑ์ทางคลินิก Ghent และ revised Ghent nosology ในการวินิจฉัย MFS ในผู้ป่วยชาวไทย*

วัสดุและวิธีการ: *ทำการศึกษาย้อนหลังจากเวชระเบียนผู้ป่วยที่มีอาการทางคลินิกสงสัย MFS ที่รับการตรวจที่คลินิกพันธุศาสตร์ โรงพยาบาลศิริราช ตั้งแต่เดือนมกราคม พ.ศ. 2546 ถึง ธันวาคม พ.ศ. 2556 โดยใช้ข้อมูลประวัติ ผลการตรวจร่างกาย ผลการตรวจสายตา slit-lamp ผลตรวจ echocardiography และผลตรวจทางพันธุกรรม เพื่อประเมินการวินิจฉัย MFS ตาม Ghent และ revised Ghent nosology*

ผลการศึกษา: *การศึกษารวบรวมผู้ป่วยทั้งสิ้น 138 ราย เป็นชาย 77 ราย หญิง 61 ราย ผู้ป่วย 92 ราย เข้าเกณฑ์การวินิจฉัย MFS โดย Ghent nosology ในจำนวนนี้ผู้ป่วย 70 ราย ยังคงเข้าเกณฑ์การวินิจฉัยเมื่อใช้ revised Ghent nosology คิดเป็น 76.1% ผู้ป่วย 48 ราย ได้รับการตรวจทางพันธุกรรม และตรวจพบการกลายพันธุ์ของจีน FBN1 23 ราย ในกลุ่มผู้ป่วยที่ไม่เข้าเกณฑ์การวินิจฉัย MFS โดย Ghent nosology สามารถให้การวินิจฉัย MFS ได้ 2 ราย โดย revised Ghent nosology นอกจากนี้พบว่า revised Ghent nosology สามารถให้การวินิจฉัยผู้ป่วยในกลุ่ม MFS-related disorder เพิ่มขึ้นจากเดิม 35 ราย*

สรุป: *ทั้ง Ghent และ revised Ghent nosology สามารถให้การวินิจฉัย MFS ในผู้ป่วยชาวไทยได้ทัดเทียมกัน การตรวจหาการกลายพันธ์ของจีน FBN1 จะช่วยเพิ่มความแม่นยำในการวินิจฉัยโรคได้*