Factor VIII Gene Mutation and Hemophilic Arthropathy in Hemophilia A Patients

Tsung-Ying Li [1,2,3], Yung-Tsan Wu [1,2], Liang-Cheng Chen [1,2], Shin-Nan Cheng [3,4], Ru-Yu Pan [3,5] , Yeu-Chin Chen [3,6,]

[1] Department of Physical Medicine and Rehabilitation, Tri-Service General Hospital, [2] Department of Physical Medicine and Rehabilitation, School of Medicine, [3]Hemophilia care and research center, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan [4] Department of Pediatrics, Tung's Taichung Metrohabor Hospital, Taichung, Taiwan.
[5]Department of Orthopedics, [6]Division of Hematology/Oncology, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan.

Introduction

The human F8 gene is 186 kilobases, located on the long arm of the X chromosome (Xq28) with 26 exons. Hemophilia A results from multiple mutations in the F8 gene that include intron 22 inversion, intron 1 inversion, large deletions, small deletions, insertions, missense mutations and nonsense mutations. F8 gene mutation types are categorized as null or non-null mutations, linked to disease phenotypes and an increased risk for inhibitory antibodies . Carcao *et al.* reported that F8 mutation correlate to differences in disease phenotype in very young patients with severe hemophilia A. Patients with F8 null mutations have younger age at first joint bleed when compared with those with F8 non-null mutations . To the best of our knowledge, reports on the correlation between hemophilic arthropathy and F8 gene mutation types in hemophilia A adult patients are not available. The determination of F8 mutation may enable prediction of the hemophilic arthropathy severity in hemophilia A patients, and in doing so may affect clinical decision making.

The aim of the study is to investigate the correlation between hemophilic arthropathy and F8 gene mutation type.

Materials and methods

Hemophilia A patients without primary or secondary prophylaxis at our center were recruited. We collected clinical information including age, height, weight and history of inhibitor. Bilateral shoulders, elbows, hips, knees and ankles joints were evaluated conventional X ray and scored with Pettersson scale. Genetic analysis was done for mutations determination in the FVIII gene, which included null mutation (intron 22 inversion, intron 1 inversion, large deletions and nonsense mutations) and non-null mutation (small deletions, insertions and missense mutations)

Results

128 hemophilia A males were included in the study. Their median age was 38 years old with a range from 20 to 77 years. 81 (63.3%) patients had severe hemophilia, whereas 25 (19.5%) had moderate and 22 (17.2) had mild types of hemophilia. Ten patients had factor VIII inhibitors. The mean BMI was 23.9 kg/m2 (range, 16.4–41.3).

F8 null mutations were present in 53 (41.4%), and F8 non-null mutations were present in 75 (58.6%) of 128 patients. The detailed distribution of F8 null and non-null mutations is reported in Table 1, Figure 1 and Figure 2.

Comparisons of the null mutation group and the non-null mutation group are also shown in Table 1. There were no differences between the two groups in terms of age, BMI, and inhibitor status. The Pettersson score of the ankles ($p<0.001$), knees($p<0.001$), elbows($p<0.001$), shoulders($p<0.025$), and total joints were higher in the null mutation group than in the non-null mutation group. There was no significant difference in Pettersson score of hips between the null and non-null mutation group. As shown in Table 2, Null mutation, Intron 22 inversion, hemophilia severity, age and each hemophilic arthropathy of joins revealed significant correlation.

Conclusion

Our study demonstrates that mutation of FVIII gene did correlate with the hemophilic arthropathy in adult hemophilia A patients. Patients with FVIII non-null mutations had less hemophilic arthropathy as compared with those with FVIII null mutations. FVIII gene mutation type carried a small but significant impact on HA in adult hemophilia A patients.

Table 1. Age, disease severity, Pettersson's score and other clinical characteristics of haemophilia patients with and without F8 null mutation.

	Null mutation group	Non-null mutation group	p value
Patient number	53	75	
Age, y/o,	38.8 ± 12.8	39.2 ± 15.4	0.792
BMI	25.1 ± 5.1	24.0 ± 4.0	0.302
Severity			
A, severe	51 (96.2%)	30 (40%)	
A, moderate	2 (3.8%)	23 (30.7%)	
A, mild	0	22 (29.3%)	
Gene mutation			
Intron 22	32 (60.4%)	0	
Intron 1	5 (9.4%)	0	
Nonsense	10 (18.9%)	0	
Large deletion	6 (11.3)	0	
Missense	0	46 (61.3%)	
Insertion	0	7 (9.3%)	
Small deletion	0	12 (16.0%)	
Other or none	0	10 (13.3%)	
Inhibitor	6 (11.3%)	4 (5.3%)	0.214
Pettersson score of total (IQR)	43 (20-64)	10 (0-41)	<0.001
shoulders (IQR)	0 (0-6)	0 (0-0)	0.025
elbows (IQR)	12 (3-19)	0 (0-13)	<0.001
hips (IQR)	0 (0-0.5)	0 (0-0)	0.07
knees (IQR)	16 (3-23)	0 (0-11)	<0.001
ankles (IQR)	12 (7-18)	3 (0-12)	<0.001

IQR: interquartile ranges; y/o: years old; BMI: body mass index
Pettersson score of joints: sum of Pettersson score of bilateral shoulder, elbow, hip , knee and ankle joints

Tab. 1 Demographic characteristics

Table 2. Correlation between gene mutation type, clinical variables and hemophilic arthropathy in our cohort of 128 hemophiliacs

Pettersson score	Null mutation	Intron 22 inversion	Hemophilia severity	Age	BMI
Total	r=0.384, p<0.01	r=0.307 p<0.01	r=0.683, p<0.01	r=0.375, p<0.01	r=0.216, p=0.01
Knees	r=0.373, p<0.01	r=0.278 p<0.01	r=0.595, p<0.01	r=0.438, p<0.01	r=0.207, p=0.02
Ankles	r=0.346, p<0.01	r=0.242 p=0.06	r=0.598, p<0.01	r=0.268, p<0.01	NS
Elbows	r=0.317, p<0.01	r=0.261 p<0.01	r=0.521, p<0.01	r=0.333, p<0.01	NS
Shoulders	r=0.199, p<0.01	r=0.226, p=0.01	r=0.327, p<0.01	r=0.252, p<0.01	NS
Hips	NS	r=0.251 p<0.01	r=0.307, p<0.01	r=0.240, p<0.01	r=0.209, p=0.02

BMI, body mass index
NS: not significant

Tab. 2 Correlation between gene mutation type, clinical variables and hemophilic arthropathy

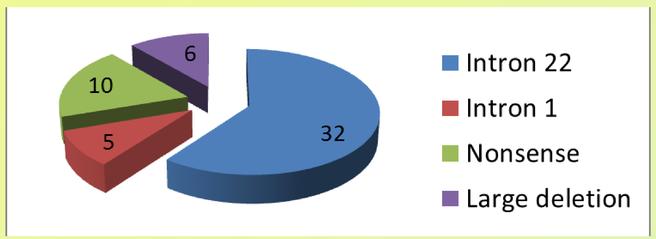

Fig. 1 Gene mutation type in Null mutation group

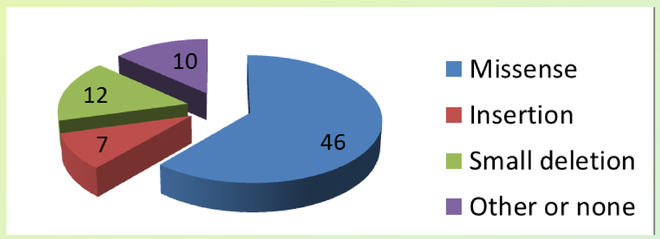

Fig. 2 Gene mutation type in Non-null mutation group