Carrier Detection by DNA Linkage Analysis in Eighty Thai Hemophilia A Families

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Abstract

DNA linkage analysis was performed in Thai hemophilia A families to evaluate its value for carrier detection. Both intragenic and extragenic polymorphic DNA regions of the factor VIII gene, including *Bcl* I-RFLP in intron 18, microsatellites (CA repeats) in introns 13 and 22, and extragenic St14 (DXS 52) VNTR, were amplified by polymerase chain reaction (PCR) before analyses by appropriate electrophoretic procedures. A total of 80 Thai hemophilia A families (48 with a family history and 32 with a sporadic case), containing 349 DNA samples from 90 hemophilia A patients, 143 parents, and 116 relatives, were analyzed. Heterozygosities in the patients' mothers from both families with a family history and with a sporadic case were observed in 71 out of 80 families (88.75%) for all polymorphic DNA markers analyzed. The carrier status could be identified in 36 females and excluded in 44 females. This result indicates that the DNA linkage analysis can be used for carrier detection or exclusion in the majority of Thai hemophilia A families. It should also be useful for prenatal diagnosis in families at risk of hemophilia A, which is part of the prevention and control of this disease.

Key word : Hemophilia A, DNA Linkage Analysis, Carrier Detection, Factor VIII Gene

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Hemophilia A is the most common X-linked recessive bleeding disorder found in all human populations. Its incidence in Thailand is about 1: 20,000[1]. The disease results from the deficiency of factor VIII coagulant activity (F VIII:C) due to the mutations in the factor VIII gene, which is located on the distal region of the long arm of the X chromosome (Xq28). The factor VIII gene, cloned and characterized since 1984[2-4], is a large gene with the length of 186 kb containing 26 exons. The gene encodes factor VIII precursor consisting of 2351 amino-acid residues. The factor VIII protein with 2332 amino-acid residues results from post-translational cleavage of a signal peptide comprising 19 amino acids from the precursor protein[5].

Diagnosis of hemophilia A is generally based on family history, patient's bleeding record, and standard coagulation studies[6]. Among Thai hemophilia A patients, about 60 per cent of the cases were found to be familial and 40 per cent sporadic (unpublished data). The molecular defects of hemophilia A identified consisted of gene inversions, gene deletions, and a large number of different types of point mutations including nucleotide substitutions, deletions, and insertions[7]. Some of these defects such as gross gene deletions and gene inversions are readily identified by DNA hybridization using appropriate DNA probes[7]. However, the majority of defects caused by different types of point mutations cannot be detected by such a method. In the situation that a specific defect of the factor VIII gene has not been characterized in a hemophilia A family, abnormal factor VIII gene tracking in the family is crucial in terms of carrier detection and prenatal diagnosis. This has been possible through DNA linkage study using different kinds of extragenic and intragenic polymorphic DNA markers[6,7].

The restriction fragment length polymorphisms (RFLPs) of enzymes *Bcl* I, *Xba* I, *Bgl* I in the factor VIII gene and of *Bgl* I and *Taq* I at linked loci, DX13 (DXS15) and St14 (DXS52), respectively, detected by DNA hybridizations, in Thai females were previously studied[8]. The *Bgl* I-RFLP was found to be absent in Thais while the frequencies of other polymorphisms were similar in Thais and Caucasians. Availability of the polymerase chain reaction (PCR) technique has made it possible to detect RFLPs in the factor VIII gene and the extragenic variable number of tandem repeat (VNTR) polymorphism linked to the factor VIII gene (St14) without performing DNA hybridization[9]. Highly polymorphic DNA markers, microsatellites or CA repeats, in introns 13 and 22 of the factor VIII gene were described and used for the linkage analysis [10-12]. The frequencies of these two microsatellite markers and their usefulness in DNA linkage analysis in Thai hemophilia A families have not been established. In the present study, the authors report the frequencies of these markers and informativeness of using intragenic *Bcl* I-RFLP, microsatellites in introns 13 and 22, and extragenic St14 (DXS 52) VNTR polymorphism, detected by PCR technique, in the linkage analysis for carrier detection in 80 Thai hemophilia A families.

PATIENTS AND FAMILIES

From October 1993 to July 1997, blood samples from members of 80 Thai hemophilia A families were taken for routine laboratory services and investigations. The families were informed for the factor VIII gene analyses, the results of which would be used as a part of genetic counseling and beneficial to the families. Of these 80 families, 48 families were found to have a family history and 32 families without, described as familial and sporadic, respectively. The total number of individuals examined was 349 and their statuses were indicated in Table 1. Among 90 hemophilia A patients from the 80 families, the disease was found to be severe with F VIII:C <2.5 per cent in 71, moderate with F VIII: C 2.5-5 per cent in 14, and mild with F VIII:C >5 per cent in 5 cases. DNA was prepared from blood samples by the standard proteinase K digestion and phenol/chloroform extraction procedure.

Table 1. Number of hemophilia A patients and family members.

Status	Number
Patient	90
Mother	80
Father	63
Female sibling	72
Male sibling	21
Female relative	16
Patient's spouse	3
Patient's daughter	4
Total	349

METHOD

DNA linkage analyses by using PCR methods

Both intragenic and extragenic polymorphic DNA regions in the factor VIII gene were amplified by the PCR methods as previously described[10-15]. The *Bcl* I-RFLP in intron 18 and the St14 (DXS 52) VNTR were detected by acrylamide gel and agarose gel electrophoresis, respectively. The microsatellites or CA repeats in introns 13 and 22 were analyzed by sequencing gel electrophoresis followed by autoradiography. Nucleotide sequences of primers and references of the methods used are provided in Table 2.

RESULTS

The results of DNA linkage analysis in 80 hemophilia A families using four polymorphic DNA regions including three intragenic and one extragenic marker showed that each marker had variable power (informativeness) to differentiate between the normal and mutant alleles, depending mainly on its degree of polymorphism, which could be demonstrated initially by the state of heterozygosity of the marker alleles in the carrier especially the patient's mother. The result of analysis using *Bcl* I-RFLP showed that the patients' mothers in 23 out of 48 families with a family history (47.9%) and in 9 out of 32 families with sporadic cases (28.1%) were found to be heterozygous. Thus, the overall heterozygosity of the *Bcl* I-RFLP marker in the patients' mothers was 32 out of 80 families (40%) (Table 3). The examples of hemophilia A families heterozygous and homozygous for this marker in the patient's mother are presented in Fig. 1 and 2.

The results of analysis of CA repeats within intron 13 of the factor VIII gene revealed that the patients' mothers in 31 out of 48 families with a family history (64.6%) and in 10 out of 32 families with sporadic cases (31.3%) were heterozygous. The overall heterozygosity of this intron 13 marker was 51.3 per cent (Table 3). The results of analysis of CA repeats within intron 22 demonstrated that the patients' mothers in 28 out of 48 families with a family history (58.3%) and in 10 out of 32 families with sporadic cases (31.3%) were heterozygous. The

Table 2. Polymorphic DNA markers and nucleotide sequences of primers for linkage analyses of the factor VIII gene by PCR methods.

Site	Restriction enzyme		Sequence of primers	Sizes of allele (bp)	References
Intron 18	*Bcl* I	8.1	5′-TAAAAGCTTTAAATGGTCTAGGC-3′	142, 99 + 43	13, 14
		8.2	5′-TTCGAATTCTGAAATTATCTTGTTC-3′		
Intron 13	-	1A	5′-TGCATCACTGTACATATGTATCTT-3′	143 - 155	10, 11, 12
		2A	5′-CCAAATTACATATGAATAAGCC-3′		
Intron 22	-	1B	5′-TTCTAAGAATGTAGTGTGTG-3′	82 - 88	10, 11, 12
		2B	5′-TAATGCCCACATTATAGA-3′		
St14 (DXS 52)	-	St14-R	5′-GGCATGTCATCACTTCTCTCATGTT-3′	660 - >2,000	15
		St14-L	5′-CACCACTGCCCTCACGTCACTT-3′		

Table 3. Per cent heterozygosities of four polymorphic DNA markers in the factor VIII gene region in the patients' mothers in 80 Thai hemophilia A families.

Site	Restriction enzyme	Number of allele	Per cent heterozygosity in the patients' mothers		
			Familial	Sporadic	Overall
Intron 18	*Bcl* I	2	47.9	28.1	40.0
Intron 13	-	7	64.6	31.3	51.3
Intron 22	-	4	58.3	31.3	47.5
St14 (DXS 52) VNTR	-	11	58.3	75.0	65.0 (61.8)*

* with 5% recombination

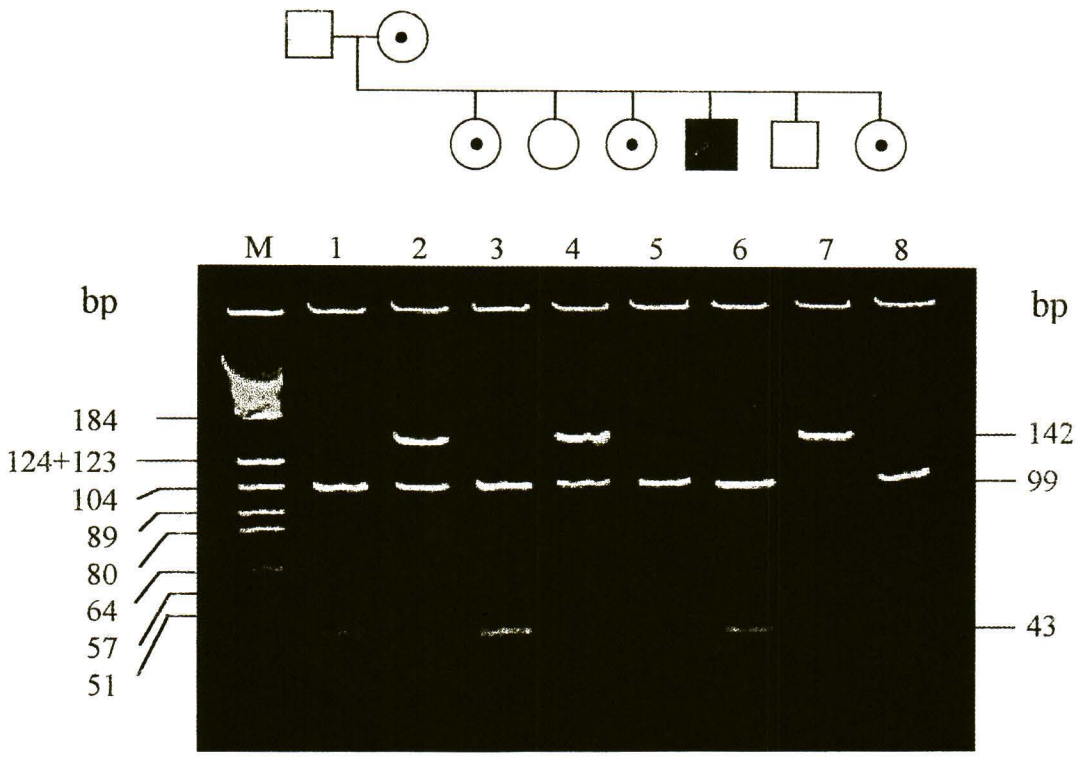

Fig. 1. The DNA linkage analysis by *Bcl* I-RFLP in a hemophilia A family showing the informative result. The mother who was a carrier (lane 2) was heterozygous for the polymorphic alleles with the sizes of 142 bp and 99+43 bp. The patient (lane 6) had the allele with the size of 99+43 bp inherited from the mother. The unaffected son (lane 7) had the allele with the size of 142 bp from the mother. Three daughters (lane 3, 5, 8) were homozygous for the allele with the size of 99+43 bp inherited from the mother and from the father; therefore they were carriers. The other daughter (lane 4) had the alleles with the sizes of 142 bp from the mother and 99+43 bp from the father; therefore, she was a non-carrier.

overall heterozygosity of this intron 22 marker was 47.5% (Table 3). The numbers of the alleles and their frequencies are shown in Table 4.

The result of linkage analysis using extragenic St14 (DXS 52) VNTR marker showed that the patients' mothers in 28 out of 48 families with a family history (58.3%) and in 24 out of 32 families with sporadic cases (75.0%) were heterozygous. The overall heterozygosity of this marker was 65.0 per cent but when calculated by taking the 5 per cent recombination rate into account, it was reduced to 61.8 per cent. At least 8 alleles were detected; their allele sizes and frequencies are shown in Table 5.

From the results of linkage analysis using all DNA markers, 36 female carriers of hemophilia A were identified in families with a family history. Of these, 33 were patients' siblings and 3 were mothers' relatives from two families. In addition, 27 females in the hemophilia A families were identified to be non-carriers.

In the families with sporadic cases of hemophilia A, although the patients' mothers were heterozygous for the polymorphic DNA markers and one of the alleles in the mother was detected in the patient, the carrier status of female siblings and relatives in the families could not be identified with certainty. The results of linkage analysis were, however, useful for exclusion of the carrier status in the female siblings and relatives who did not carry the same allele as the patients. Thus, among females from the sporadic families, 17 were excluded as being hemophilia A carriers.

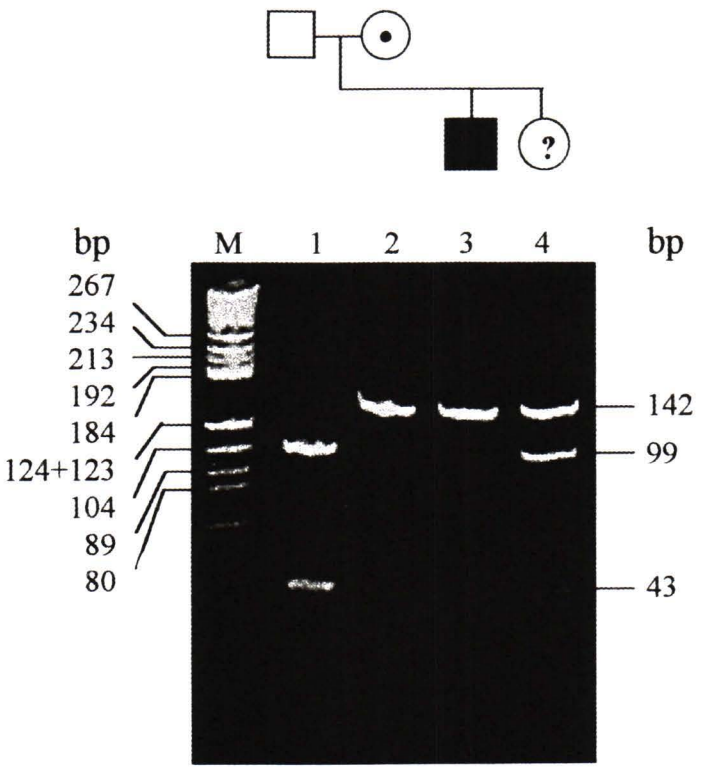

Fig. 2. The DNA linkage analysis by *Bcl* I-RFLP in a hemophilia A family showing the non-informative result. The mother (lane 2) was homozygous for the allele with the size of 142 bp and her hemophilic son also carried one allele with the size of 142 bp. Therefore, it was unable to predict which of the two alleles with the size of 142 bp from the mother was inherited to the daughter (lane 4) who carried an allele with the size of 142 bp from the mother and that of 99+43 bp from the father.

There were 8 females in whom the carrier or non-carrier status could not be identified although they were heterozygous for the polymorphic DNA markers. One was a female sibling of two hemophilia A patients from a family with a family history whose father was not available for the investigation and there were no other male or female siblings in the family (Fig. 3). The other 7 females (2 siblings and 5 relatives of the hemophilia A patients) were found in 5 unrelated families with sporadic cases. Thus, female carriers and non-carriers identified by DNA linkage analysis in 80 Thai hemophilia A families are summarized in Table 6.

DISCUSSION

Several intragenic and extragenic polymorphic DNA regions in the factor VIII gene have been described. RFLPs within the gene including *Bcl* I-RFLP in intron 18[13], *Xba* I RFLP in intron 22[16], *Hind* III RFLP in intron 19[17] were commonly used for carrier detection and prenatal diagnosis. The rates of the female heterozygosity, especially in the patient's mother, of these markers were found to be between 42-48 per cent in various ethic groups and the marker with the highest rate was *Xba* I-RFLP [16]. This polymorphic marker was successfully detected by the Southern blotting method but was difficult to detect using the PCR-RFLP method due to interference of specific amplified product. In the present study, the detection of *Bcl* I-RFLP was carried out because the method has been well established; it is simple and non-radioisotopic with informativeness between 31 per cent and 47 per cent [6]. There was no reason to analyze other RFLP

Table 4. Allele frequencies of polymorphic CA repeats markers in introns 13 and 22 of the factor VIII gene observed in Thai hemophilia A families.

Intron 13		Intron 22	
CA repeats	Allele frequency	CA repeats	Allele frequency
(CA)21	0.017	(CA)18	0.013
(CA)22	0.050	(CA)19	0.353
(CA)23	0.245	(CA)20	0.546
(CA)24	0.399	(CA)21	0.088
(CA)25	0.206		
(CA)26	0.050		
(CA)27	0.017		

Table 5. The allele sizes and frequencies of polymorphic St14 (DXS 52) VNTR marker observed in Thai hemophilia A families.

Allele sizes (bp)	Allele frequencies
660	0.417
1,210	0.243
1,280	0.026
1,315	0.009
1,350	0.115
1,500	0.030
1,550	0.030
1,650	0.047
1,800	0.021
2,000	0.011
> 2,000	0.051

markers since they are normally in linkage disequilibrium with the marker that had been examined and the results would not add more information, as previously reported by Goodeve et al[8]. Using this *Bcl* I-RFLP marker alone, approximately 48 per cent of Thai hemophilia A families with a family history were informative. As it is an intragenic marker and its detection method is simple, it should be the first marker of choice for carrier detection or prenatal diagnosis. However, about half of the families were not informative, and other markers are required for the detection and diagnosis.

The extragenic St14 (DXS 52) VNTR close to the factor VIII gene is a highly polymorphic marker, which should be another marker of choice for the detection. It was previously reported that nearly 90 per cent of females would be heterozygous[18] for this marker. However, the result in the present study showed that heterozygosity in the patients' mothers in the hemophilia A families with a family history was about 58 per cent, much less than was previously reported. The heterozygosity in the patients' mother in the families with sporadic cases was 75 per cent, raising the overall heterozygosity to be the highest of all the markers analyzed. The reason for the difference between the two groups of hemophilia A families is unknown, possibly due to a bias from a smaller number of families with sporadic cases. The crossing over in the region between the factor VIII gene and the marker can occur between 3 per cent and 5 per cent[5] which will partly limit its utility in the carrier and prenatal detection.

Table 6. Female carriers and non-carriers identified by DNA linkage analysis in 80 Thai hemophilia A families.

Status	Number in the families with family history	Number in the families with sporadic case
Carrier	36	-
Non-carrier	27	17
Unknown	1*	7

* No result of DNA analysis from other family members for verification.

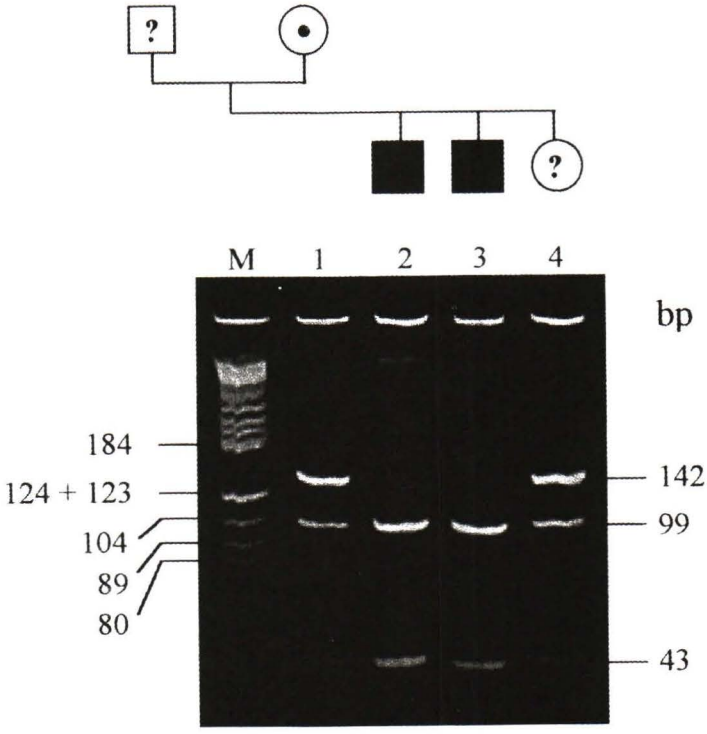

Fig. 3. **The DNA linkage analysis by *Bcl* I-RFLP in a hemophilia A family showing the non-informative result, since the father was not available for testing although the patients' mother (lane 1) was heterozygous for the polymorphic alleles with the sizes of 142 bp and 99+43 bp. The allele with the size of 99+43 bp was observed in her two hemophilic sons (lanes 2 and 3). The daughter (lane 4) could have either the allele with the size of 142 bp or 99+43 bp from her mother; therefore, her carrier status could not be identified.**

The polymorphic microsatellite (CA repeats) markers within introns 13 and 22 of the factor VIII gene were more difficult to analyze since they required detection of radioactive PCR products using sequencing polyacrylamide gel and autoradiography. Previous studies in various racial groups revealed different numbers of CA repeats and allele frequencies[12,19]. The allele numbers of CA repeats in introns 13 and 22 were found to be 7-11 alleles and 5-11 alleles, respectively. The rate of informativeness were between 58-80 per cent, of which the highest was seen among black Africans[20] and lowest in the Chinese[21]. The present result of the CA repeats study in both introns revealed fewer allele numbers (7 and 4 alleles, respectively) than that previously reported. The informativeness of the analysis using the CA repeats in introns 13 and 22 in the hemophilia A families with a family history were about 65 per cent and 58 per cent, which were higher than that of the *Bcl* I-RFLP marker. The families that were not informative by the *Bcl* I-RFLP marker were informative by these two CA repeat markers. Therefore, the CA repeats analysis in introns 13 and 22 would contribute additional information to the detection.

The DNA linkage analysis is very useful for hemophilia A carrier detection in families with a family history of this disease. However, its informativeness is dependent on the availability of at least one affected male and most importantly heterozygosity of the detected marker in the obligate carrier mother. The examples of DNA linkage analysis for

informative and non-informative families are shown in Fig. 1 and 2. In the circumstance that *Bcl* I-RFLP, which is a bi-allelic marker, is used especially in the family that has only one daughter and one hemophilic son, the father is also required for testing. The authors saw one family in whom the carrier status could not be identified in the daughter because the father was not available for testing (Fig. 3). In the families with sporadic hemophilia A cases, although the result of DNA linkage analysis could not be used for the carrier detection, it was helpful for exclusion of the carrier status. In these families as well as those non-informative families with a family history, analysis of mutation and development of direct methods for mutation detection will be necessary.

In conclusion, the DNA linkage analysis can be used for carrier detection or exclusion in the majority of Thai hemophilia A families. It should also be useful for prenatal diagnosis in families at risk of hemophilia A, which is a part of the prevention and control of this disease.

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การตรวจหาพาหะโรคฮีโมฟีเลีย เอ ในครอบครัวผู้ป่วยไทย 80 ครอบครัว ด้วยวิธีวิเคราะห์ดีเอ็นเอลิงค์เกจ

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คณะผู้วิจัยได้ทำการวิเคราะห์ดีเอ็นเอลิงค์เกจในครอบครัวผู้ป่วยไทยโรคฮีโมฟีเลีย เอ เพื่อประเมินคุณค่าของวิธีนี้ในการตรวจผู้ที่เป็นพาหะ ดีเอ็นเอที่หลากหลายในขนาด ทั้งที่อยู่ภายในและภายนอกยีนแฟคเตอร์แปด ได้แก่ *Bcl* I-RFLP ในอินตรอน 18, microsatellites (CA repeats) ในอินตรอน 13 และ 22, และ St14 (DXS 52) VNTR ซึ่งอยู่ภายนอกยีน ถูกเพิ่มปริมาณด้วยวิธีพีซีอาร์ก่อนการตรวจด้วยวิธีอิเล็คโตรโฟรีซีสตามประเภทของดีเอ็นเอที่ถูกตรวจ จำนวนครอบครัวผู้ป่วยที่นำมาศึกษาทั้งหมดมี 80 ครอบครัว (48 ครอบครัวมีประวัติของโรคภายในครอบครัว และ 32 ครอบครัวไม่มีประวัติ) ซึ่งมีจำนวนดีเอ็นเอทั้งหมด 349 ตัวอย่าง (90 ตัวอย่าง จากผู้ป่วย, 143 ตัวอย่าง จากบิดาและมารดา, และ 166 ตัวอย่างจากญาติพี่น้อง) ผลการศึกษาพบว่าครอบครัวผู้ป่วยฮีโมฟีเลีย เอ จำนวน 71 จาก 80 ครอบครัว (คิดเป็น 88.75%) สามารถตรวจได้ด้วยดีเอ็นเอที่หลากหลายในขนาดหนึ่งชนิดหรือมากกว่า นอกจากนี้ ภาวะที่เป็นพาหะพบในผู้หญิงจำนวน 36 ราย และภาวะที่ไม่ใช่พาหะพบในผู้หญิง 44 ราย ผลของการศึกษานี้แสดงว่าการวิเคราะห์ดีเอ็นเอลิงค์เกจสามารถจะนำไปใช้เพื่อตรวจผู้ที่เป็นพาหะและไม่ใช่พาหะในครอบครัวผู้ป่วยโรคฮีโมฟีเลีย เอ ส่วนใหญ่ได้ วิธีนี้น่าจะเป็นประโยชน์สำหรับใช้ในการวินิจฉัยโรคก่อนกำเหนิด ในครอบครัวที่เสี่ยงต่อการให้กำเหนิดทารกที่เป็นโรคฮีโมฟีเลีย เอ ซึ่งเป็นส่วนหนึ่งของการควบคุมและป้องกันโรคนี้

คำสำคัญ : โรคฮีโมฟีเลีย เอ, การวิเคราะห์ดีเอ็นเอลิงค์เกจ, การตรวจพาหะ, ยีนแฟคเตอร์แปด

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