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ACTIVITY AND ANTIGEN OF COAGULATION FACTORS VII AND X IN FIVE PATIENTS WITH ABNORMAL CHROMOSOME 13

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Summary Coagulation factors VII (F7) and X (F10) were investigated in three patients with terminal deletion of 13q [46,XX,del(13)(q32)], a patient with complete 13 trisomy and a patient with a balanced X;13 translocation [46,X,t(X;13)(p11.21;q12.3)]. Though a patient of terminal 13q− syndrome had normal activities of F7 and F10, the other two patients showed an about 50% deficiency for them. A patient with 13 trisomy and a patient with a X;13 translocation had normal activities of F7 and F10. A 13q− syndrome patient with normal values of coagulation factors VII and X might have an intact terminal portion of chromosome 13, which is not apparent by R-banding.

INTRODUCTION

The structural genes of coagulation factors VII (F7) and X (F10) were assigned to the long arm of chromosome 13 (13q34) (HGM8, 1985). Pfeiffer *et al.* (1982), de Grouchy *et al.* (1984) and Ott and Pfeiffer (1984) reported patients of 13q34 deletion affected with deficiency of F7 and F10 activity. We analyzed activity and antigen of F7 and F10 in 5 patients with abnormal chromosome 13. The purpose of this work was to present data on expression of activities of F7 and F10 in various abnormality of chromosome 13.

CASE REPORTS

Clinical findings of Cases 1 through 3 are summarized in Table 1. They were unrelated but exhibited similar peculiar facies (Fig. 1), multiple anomalies and mental retardation. They are compatible with findings of "categories" 1a and 4 of 13q− syndrome (Niebuhr, 1977). Case 4, $2^{1}/_{12}$ year-old girl, was 13 trisomy

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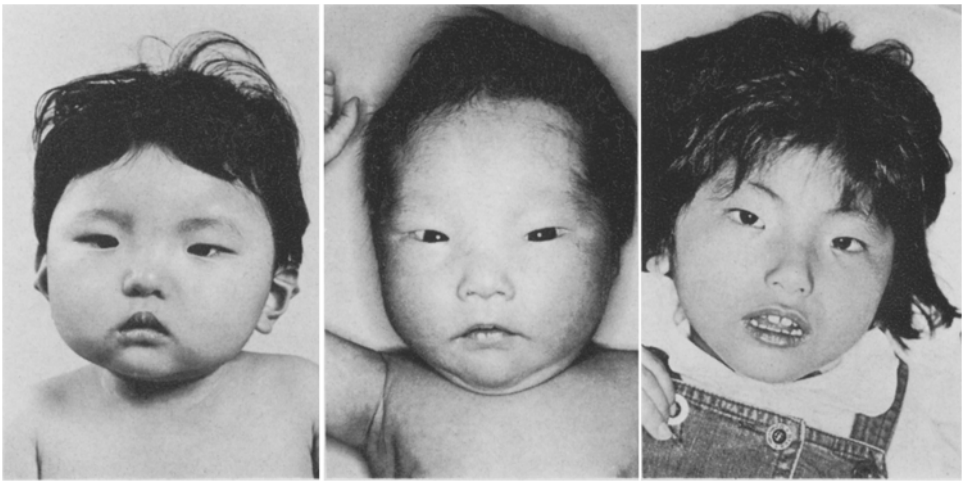
Table 1. Summary of clinical findings in Cases 1 through 3.

	Case 1	Case 2	Case 3
Age	2y8m	2m	4y3m
Sex	female	female	female
Paternal age at birth	33y	28	
Maternal age at birth	27	32	
Consanguinity	−	−	−
Gestational age	41w3d	41w4d	
Birth weight (g)	2,800	3,010	
Growth retardation	+	+	+
Length (cm)	83.5 (−2.1 SD)	52.2 (−1.2 SD)	
Weight (kg)	10.9 (−1.6 SD)	3.8 (−1.8 SD)	
Head circumference (cm)	44.8 (−2.0 SD)	34.0 (−1.8 SD)	
Developmental delay (DQ)	+ (44)	?	+
Peculiar facies	+	+	+
Brachy-trigonocephaly	+	+	+
High nasal root	+	+	+
Hypertelorism	+	+	+
Micro-retrognathia	+	+	+
Large-malformed ears	+	+	+
Short neck	+	+	+
Congenital heart disease	+ (PS)	+ (VSD)	−
Ano-rectal anomaly	+	+	
Gastroesophageal reflux	+	−	−
Karyotypes of parents	normal	normal	normal

syndrome. Case 5, $4^{6}/_{12}$ year-old girl, suffered from bilateral retinoblastoma, severe mental retardation and multiple congenital anomalies. Her clinical features and karyotypical analysis were previously reported by Kajii *et al.* (1985).

CYTOGENETIC INVESTIGATIONS

Chromosome preparations were obtained from 3-day cultures of peripheral lymphocytes. Standard trypsin G-banding analysis was performed in all five cases. The results of karyotype analysis are shown in Table 2. Each deleted chromosome 13 in three patients, Cases 1, 2 and 3 seemed to be a terminal deletion at band q32 (Figs. 2a, 2b, 2c). We failed to confirm that the deleted chromosome 13 in Case 3 was an interstitial deletion, although we used R-banding analysis (Fig. 2d). A karyotype of Case 4 showed standard 13 trisomy (47,XX,+13). Case 5 had a



a b c

Fig. 1. Facial appearance of patients with terminal 13q−. a, Case 1; b, Case 2; and c, Case 3.

Table 2. Karyotypes and coagulation activities in five patients.

Patient	Age	Karyotype	VII-C	VII-Ag	X-C	X-Ag
Case 1	2y8m	46,XX,del(13)(q32)	58%[a]	50%	45%	44%
Case 2	2m	46,XX,del(13)(q32)	55%	59%	39%	36%
Case 3	4y3m	46,XX,del(13)(q32)	100%	100%	100%	100%
Case 4	2y1m	47,XX,+13	100%	100%	66%	66%
Case 5	4y6m	46,X,t(X;13)(p11.21;q12.3)	100%	92%	88%	100%

[a] % average normal.

karyotype of a balanced X;13 translocation [46,X,t(X;13)(p11.21;q12.3)] (Fig. 3). X-chromosome replication studies using 5-bromodeoxyuridine revealed that late replication of the derivative X chromosome was present only in 9% of cultured peripheral lymphocytes and in 1% of skin fibroblasts (Kajii, 1985), suggesting that most of the derivative X is active.

COAGULATION STUDIES

Blood samples were collected in plastic tubes containing sodium citrate (10% of blood volume). After centrifuging, plasma was immediately used for testing or stored at −30°C until assayed. F7 (VII-C) activity and F10 (X-C) activity were assayed with a one stage method based on the prothrombin time using F7 or F10

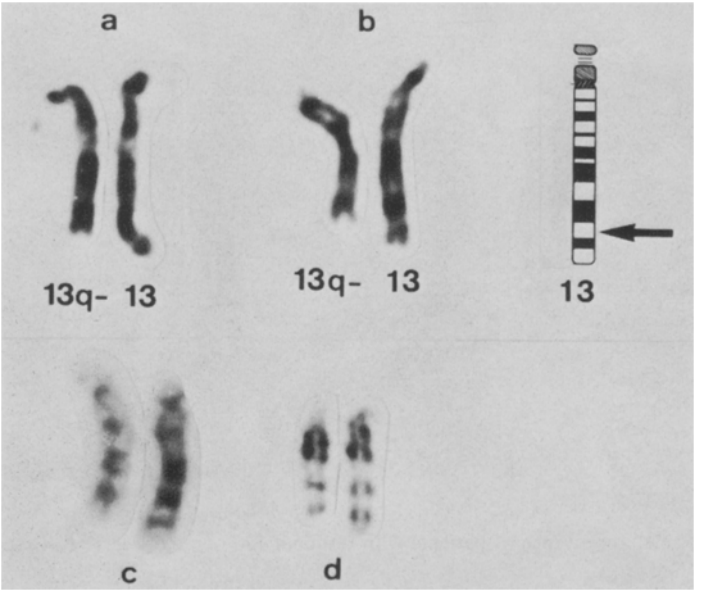


Fig. 2. a, b and c: Chromosome 13 after G-banding from Case 1, Case 2 and Case 3, respectively. d: Chromosome 13 after R-banding from Case 3. An arrow shows a breakpoint 13q32.

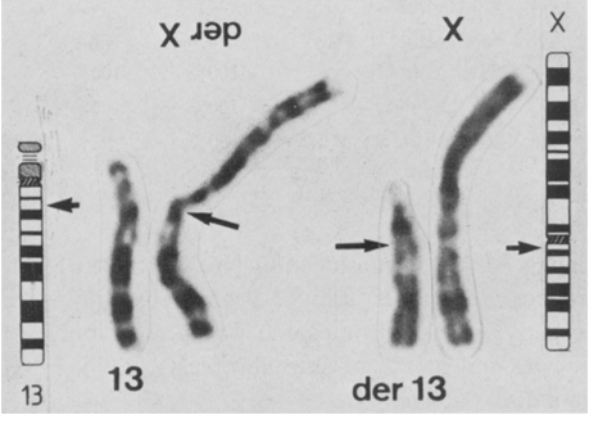


Fig. 3. Chromosome X and chromosome 13 of Case 5. Arrows show breakpoints: Xp11.21 and 13q12.3.

deficient plasma. F7 antigen (VII-Ag) and F10 antigen (X-Ag) were measured by an inhibitor neutralization test and Laurell method, respectively. The activities of F7 and F10 were normal in one of terminal 13q− patients, a patient with complete 13 trisomy and a patient with a balanced X;13 translocation, and about 50% of the normal value in the other two patients with terminal 13q− (Table 2).

DISCUSSION

The present results of an about 50% deficiency of F7 and F10 in Cases 1 and 2 confirms previous observations that the structual genes of F7 and F10 are located on the long arm of chromosome 13 (13q34) (Pfeiffer *et al.*, 1982; de Grouchy *et al.*, 1984; Ott and Pfeiffer, 1984).

On the other hand, Case 3 with the same karyotype as Cases 1 and 2 showed the normal activities of F7 and F10. It is plausible that the karyotype of Case 3 is interstitial deletion of 13q and the subtle terminal portion, where the structural genes of F7 and F10 are located, remains intact, although we failed to confirm the interstitial deletion by R-banding. The fact indicates that locations of the structural genes of F7 and F10 are closely linked to telomere of the long arm of chromosome 13.

Ott and Pfeiffer (1984) proposed that a deficiency of F7 and F10 was a useful marker of terminal deletion of chromosome 13. However, it is noteworthy that exceptional cases like Case 3 could exist. Normal activity of F7 and F10 does not always rule out distal 13q− syndrome.

Case 4 with 13 trisomy showed normal activities of F7 and F10. de Grouchy (1984) reported a patient with distal trisomy 13q and a patient with complete trisomy 13, who had normal values for F7 and F10. Activity and antigen of F7 and F10 seems to have no gene-dose effects in a trisomy state of 13q34.

Case 5 carried a balanced translocation t(13;X). Late replication pattern showed that the derivative X with 13q was mostly activated at least in peripheral lymphocytes and skin fibroblasts examined, though this patient suffered from retinoblastoma which might be related with the inactivated derivative X (Kajii *et al.*, 1985). However, the inactivated derivative X seemed not to affect activities of F7 and F10.

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