Haemophilia (2005), **11,** 438–443 DOI: 10.1111/j.1365-2516.2005.01124.x

Variability in clinical phenotype of severe haemophilia: the role of the first joint bleed

K. VAN DIJK,*† K. FISCHER,*‡ J. G. VAN DER BOM,*§ D. E. GROBBEE† and H. M. VAN DEN BERG*‡

**Van Creveldkliniek, UMC Utrecht; †Julius Center for Health Sciences and Primary Care, UMC Utrecht; ‡Wilhelmina Children's Hospital, UMC Utrecht; and §Department of Clinical Epidemiology, LUMC, Leiden, The Netherlands*

Summary. To quantify variation in clinical phenotype of severe haemophilia we performed a single centre cohort study among 171 severe haemophilia patients. Age at first joint bleed, treatment requirement (i.e. annual clotting factor use), annual bleeding frequency and arthropathy were documented. Because treatment strategies intensified during follow-up, patients were stratified in two age groups: patients born 1968–1985 ($n = 91$), or 1985–2002 ($n = 80$). A total of 2166 patient-years of follow-up were available (median 12.0 years per patient). Age at first joint bleed ranged from 0.2 to 5.8 years. Patients who had their first joint bleed later needed less treatment and developed less arthropathy. In patients born 1968–1985 during both on-demand and prophylactic treatment, the 75th percentile of annual joint bleed frequency was consistently four times as high as the 25th percentile. In both age groups variation in annual clotting factor use between 25th and 75th percentiles was 1.4–1.5 times for prophylaxis and 3.8 times for on-demand treatment. To conclude, the onset of joint bleeding is inversely related with treatment requirement and arthropathy and may serve as an indicator of clinical phenotype. Thus, providing a starting point for aetiological research and individualization of treatment.

Keywords: clinical phenotype, first joint bleed, severe haemophilia, variation

Introduction

Marked variability in clinical phenotype among severe haemophilia patients (<1% factor VIII or FIX) is well known from clinical practice, but formal research describing this phenomenon is limited [1,2]. This variability may be reflected by variability in onset and frequency of bleeding, treatment requirements and haemophilic arthropathy. The distinction of phenotypes may be an important tool for individualization of treatment and aetiological research.

Before the introduction of prophylaxis, bleeding frequency was the main indicator of phenotype [2]. In the case of prophylaxis, however, joint bleed frequency is artificially low. If prophylactic dose is adjusted according to bleeding frequency, as in our clinic [3], variation in treatment requirement (i.e. annual clotting factor use) may reflect the variation in the underlying bleeding tendency. If prophylaxis is started after the first joint bleed, the variability in onset of joint bleeds may still be observed. Over the last three decades continuously fewer joint bleeds were tolerated while on prophylaxis, resulting in gradually more intensified treatment, which is shown by an increased weekly dose, increased frequency and earlier start of prophylaxis [4].

In our cohort we described variation in phenotypes of severe haemophilia, with special emphasize on age at first joint bleed as its earliest available potential indicator.

Design and methods

Study population

A single centre cohort study was performed among all patients with severe haemophilia A and B born between 1968 and 2002 and treated at the Van Creveldkliniek, Utrecht, the Netherlands. Of all

Correspondence: K. van Dijk MD, PhD, Van Creveldkliniek, UMC Utrecht, Room C01.425, PO Box 85500, 3508 GA Utrecht, the Netherlands.
Tel.: 003 130 250 8449; fax: 0031 030-2505438;
e-mail: k_van_dijk@wanadoo.nl

Accepted after revision 15 June 2005

197 patients with severe haemophilia A or B, 26 were excluded for different reasons: insufficient follow-up (<6 years or <50% of total lifetime, $n = 18$), inhibitor activity for more than 1 year ($n = 6$) or significant other pathology ($n = 2$), leaving 171 patients for the current analyses.

All patients visited our treatment centre at least once a year. From 1972 onwards, joint bleed frequency, type of treatment (i.e. prophylactic or on-demand) and clotting factor consumption were recorded at each visit. Patients were followed until their last visit or January 2003.

Treatment

Since the introduction of clotting factor replacement therapy in 1965 [5] and the introduction of prophylaxis in 1968 in our centre, treatment for severe haemophilia has gradually been intensified [4]. Therefore, we studied each treatment-dependent parameter (i.e. annual clotting factor use and annual joint bleed frequency on prophylaxis) according to age groups. The oldest age group comprised patients born between 1968 and 1985 who received on-demand replacement treatment and secondary prophylaxis during their first years. The youngest age group comprised patients born after 1985 who received very early prophylactic treatment [4,6].

Prophylaxis was defined as at least two times weekly administration of FVIII and at least once a week for FIX. After initiation, the prophylactic dose was individually adjusted according to bleeding pattern. Full prophylaxis was defined as prophylaxis for more than 45 weeks per year.

Measurements

Data on the first joint bleed were obtained from the medical files. Joint bleeds were self-reported and were defined as all symptoms in the major joints requiring replacement therapy. Data on bleeding were extracted from the patients' log at each visit to the centre. Haemophilic arthropathy was measured by the Pettersson score [7]. X-rays of knees, elbows and ankles were taken at 5-year intervals. Each joint was attributed a score between 0 (i.e. no arthropathy) and 13-points, resulting in a maximum total score of 78-points. Joints with arthrodesis, ankylosis or arthroplasty were given 13-points. All X-rays were scored by a single radiologist.

Data analysis

For reasons of uniformity, medians were presented for both parameters with a skewed distribution and parameters with a normal distribution.

Median annual number of joint bleeds, median annual clotting factor consumption per kg bodyweight (IU kg^{-1} $year^{-1}$) and their interquartile ranges (IQR) were calculated over all available follow-up years except for the youngest age group. In order to evaluate a similar period for all patients in this youngest age group, the first 5 years since the start of prophylaxis were analysed. This period was chosen because bleeding frequency and clotting factor use tend to stabilize during the first years on prophylaxis [8].

For the description of treatment and outcome in Table 1, the number of patients on on-demand treatment was assessed cross-sectionally for both

Table 1. Characteristics of clinical phenotype of severe haemophilia according to year of birth.

Year of birth	1968–1985 ($n = 91$)	1985–2002 ($n = 80$)
Follow-up per patient (years)	18.0 (14.0–22.0)	6.0 (3.0–10.0)
Age at first joint bleed (years)	1.8 (1.1–2.7)*	
Pettersson score†	14.0 (6.0–22.0)	0 (0.0–2.5)
Prophylaxis		
Age at start prophylaxis (years)	5.3 (3.8–8.2)	2.8 (1.6–4.2)
Annual clotting factor use on full prophylaxis (IU kg^{-1} $year^{-1}$)‡	1945 (1654–2350)	2859 (2282–3321)
Joint bleeds per year on full prophylaxis‡	2.9 (1.3–5.1)	2.1 (1.0–3.7)
On-demand		
On-demand (%)	26	0
Annual clotting factor use on-demand (IU kg^{-1} $year^{-1}$)	268 (163–623)	–
Joint bleeds per year on-demand	3.6 (1.6–8.0)	–

Values are expressed as medians (interquartile range).
*range: 0.6–5.8 years.
†1968–1985 Pettersson scores at 25 ± 2.5 years of age; 1985–2002 at 10 ± 2.5 years.
‡Median of all years on full prophylaxis (i.e. >45 weeks $year^{-1}$).

age groups: at the age of 25 years in the oldest age group, and 10 years in the youngest age group.

Pettersson scores are presented according to limited intervals for each age group, because Pettersson scores are affected by the cumulative number of joint bleeds [9], and therefore highly dependent on age. The following intervals were used: 7.5–12.5 years in the youngest group and 22.5–27.5 years for the oldest group.

To study the consistency of the parameters within patients, associations between the different parameters were assessed. We studied the association of age at first joint bleed with both treatment requirement and arthropathy. Furthermore, the association between treatment requirement and joint bleed frequency on prophylaxis was studied. These associations were studied in the oldest age group, because differences in outcome were more apparent in these patients.

Age at first joint bleed was used to categorize subjects into two groups according to the median value (1.8 years): patients who experienced their first joint bleed before or at the age of 1.8 years were categorized as 'early' and patients who experienced their first joint bleed after the age of 1.8 years as 'late'. Linear regression analysis was used to study the association between age at first joint bleed and annual clotting factor use and the association between treatment requirement and bleeding frequency. The association between age at first joint bleed and Pettersson score was modelled using a log-transformation and linear regression with adjustment for age at Pettersson score.

Results

Of all 171 patients with severe haemophilia A and B, a total of 2166 follow-up years and 415 Pettersson scores were available. The median follow-up was 12.0 years (IQR: 6.0–18.0) and the median number of Pettersson scores per patient was 3.0 (IQR: 2.0–3.8). Characteristics of phenotypes according to age group are given in Table 1. We investigated differences between patients with haemophilia A and B in both age groups and in all parameters. About 19 patients had haemophilia B, of which 10 in the oldest group and nine in the youngest group. No differences in clinical phenotypes were observed between patients with haemophilia A and B, therefore overall findings are presented.

Age at first joint bleed

Age at first joint bleed was available for 68 patients (75%) in the oldest age group and 64 patients (80%) in the youngest age group. Figure 1 shows the distribution of age at first joint bleed among patients in both age groups. Their median age at first joint bleed was 1.8 years (range: 0.2–5.8).

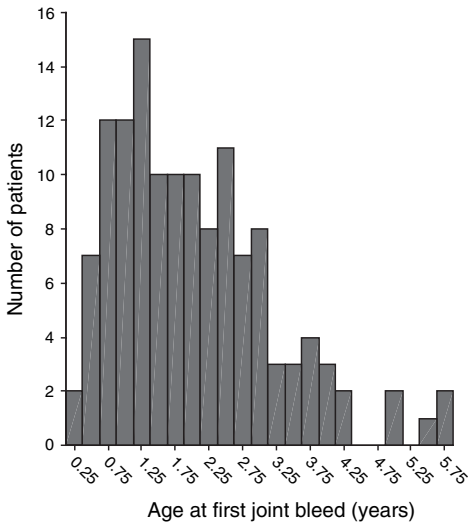

Fig. 1. Age at first joint bleed for patients born 1968–2002. Median age at first joint bleed was 1.8 years [range: 0.2–5.8s, interquartile range (IQR): 1.1–2.7].

Joint bleeds

For patients treated on-demand, the annual joint bleed frequency may provide a direct indicator of phenotype. In adult patients who were never treated with prophylaxis or had switched to on-demand treatment, annual joint bleed frequency varied widely: the 25th and 75th percentile differed fourfold (Table 1). In the oldest age group median annual joint bleed frequency was 3.6 joint bleeds per year for on-demand treatment and 2.9 for prophylaxis.

Under full prophylaxis, the 75th percentile of the annual joint bleed frequency was consistently four times higher than the 25th percentile in both age groups (Table 1).

Annual clotting factor use

For on-demand treatment, median annual clotting factor use was 268 IU kg^{-1} $year^{-1}$ (IQR: 163–623) in the oldest age group and was 7.3 times lower than for prophylactic treatment. Annual clotting factor use differed 3.8-fold between the 25th and 75th percentile in these patients for on-demand treatment.

On prophylaxis, variation in clotting factor use was similar across age groups with the 75th percentile consistently 1.4–1.5 times higher than the 25th percentile. The highest annual clotting factor use on

prophylaxis was observed in the youngest age group. This frequently observed phenomenon may reflect a combination of more intensive treatment and the large increments in vial content of the clotting factor concentrates [4,10,11].

The above calculations were performed using all available years of follow-up. Similar variation was observed when the analysis was restricted to the last 5 years of follow-up for adult patients and the first 5 years of prophylaxis for patients in the youngest age group (data not shown).

Association of treatment requirement and bleeding characteristics

The association between age at first joint bleed and treatment requirement according to age for the oldest age group is presented in Fig. 2. Patients who experienced their first joint bleed at an early age had a consistently higher annual clotting factor consumption than patients who had their first joint bleed later in life [$P < 0.01$; 95% confidence interval (CI): −221 to −134 IU kg^{-1} year^{-1}]. A similar trend was observed for the youngest age group ($P < 0.01$; 95% CI: −439 to −173 IU kg^{-1} year^{-1}).

A positive association was found between annual clotting factor use and joint bleed frequency for patients in the oldest age group, treated with prophylaxis ($P < 0.01$; 95% CI: 206–271 IU kg^{-1} year^{-1}). Annual clotting factor use for on-demand treatment regimens is expected to be directly dependent on the number of joint bleeds. During on-demand treatment there was a similar positive association between annual clotting factor use and joint bleed frequency ($P < 0.01$; 95% CI: 40–85 IU kg^{-1} year^{-1}).

Joint damage, assessed using Pettersson scores

In the oldest age group, Pettersson scores around the age of 25 years were available for 49 patients. Among these patients the scores ranged from 0 to 35. The 75th percentile was 3.6 times higher than the 25th percentile. Four patients (8.2%) had a score of 0.

For the youngest age group, 25 scores around the age of 10 years were available. All scores were very low, ranging from 0 to 6-points: 60% had a score of 0. Thus, little variation was observed among these young patients.

Association of arthropathy with bleeding characteristics and treatment requirement

In order to demonstrate the association of bleeding characteristics and arthropathy, the age at first joint bleed was plotted against the Pettersson score for the oldest age group (Fig. 3). Patients who experienced

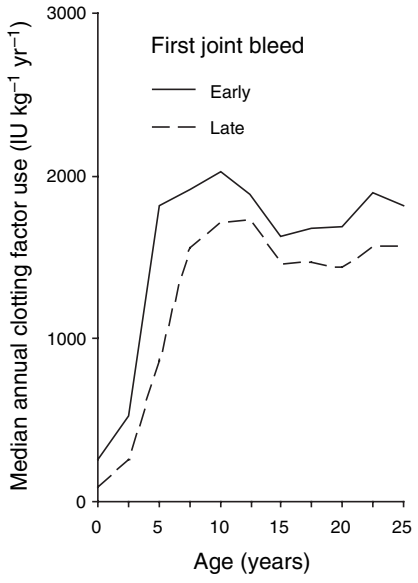

Fig. 2. Annual clotting factor use and age according to the age at first joint bleed. Annual clotting factor use and age were plotted according to the age at first joint bleed for the oldest age group. Patients who experience their first joint bleed 'early' (≤1.8 years) tend to have a higher annual clotting factor use in later years than patients who experience their first joint bleed 'late' (>1.8 years; $P < 0.01$).

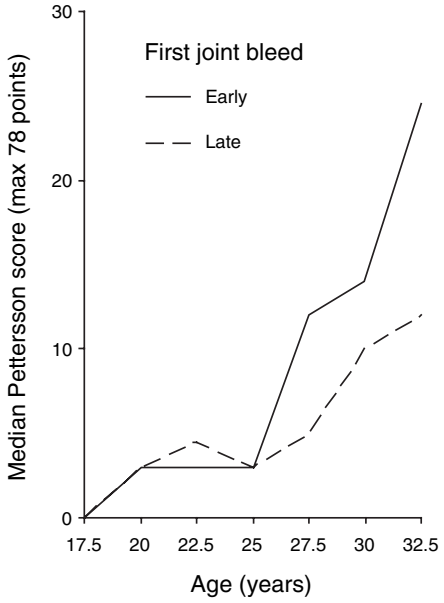

Fig. 3. Pettersson score and age according to the age at first joint bleed. Pettersson score and age were plotted according to the age at first joint bleed for the oldest age group. Patients who experienced their first joint bleed 'early' tend to have more arthropathy than patients who experienced their first joint bleed 'late' ($P = 0.08$).

their first joint bleed at an early age tended to develop more arthropathy than patients who experienced their first joint bleed later in life ($P = 0.08$).

Discussion

The present study describes the variation in phenotypes of severe haemophilia in a well-defined single centre cohort of patients with severe haemophilia. We found considerable variation in onset and frequency of bleeding, treatment requirements and arthropathy. The results for each parameter will be discussed below.

In accordance with earlier findings, age at first joint bleed varied by 5.6 years [6,12,13]. Age at first joint bleed was inversely related to treatment requirement and arthropathy as measured by the Pettersson score, suggesting an association with bleeding pattern and therefore a potential use as indicator of bleeding pattern. Some misclassification may arise, e.g. if the first joint bleed is caused by a trauma. This may cause an underestimation of the effect and therefore the association may be stronger than described in this study if only the first spontaneous joint bleed would have been considered.

Variability in bleeding frequency has been reported by others: Rainsford and Hall distinguished two groups of severe haemophilia patients with a 50% difference in joint bleed frequency [1]. Subgroups of 9–10% of patients with severe haemophilia showing only little radiological joint damage while treated on-demand have been described both by Aledort *et al.* and Molho *et al.* [2,14]. However, the association with other parameters was not presented. When studying bleeding frequency and treatment requirement, misclassification caused by overtreatment or undertreatment on home therapy may occur. A combination of both a low clotting factor use and a low joint bleed frequency may suggest a milder bleeding pattern. This notion is supported by the positive association between these parameters for patients treated on prophylaxis. During on-demand treatment, joint bleed frequency may provide a direct indicator of phenotype.

Variability of treatment requirement has been described in several studies [2,15,16]. The ratios of the 25th and 75th percentiles of treatment requirements on prophylaxis and during demand treatment in the present study were similar to the ratios reported in the literature, 1.7 and 3.3, respectively [16]. In a multicentre study seven of 14 patients treated with 0–500 IU kg^{-1} $year^{-1}$ had no arthropathy after 6 years [2]. Fischer *et al.* reported that about 20% of patients with severe haemophilia permanently switched to an on-demand regimen while maintaining a low joint bleed frequency [15]. Therefore, the ability to remain on on-demand treatment may also suggest a milder bleeding pattern in a cohort intended to be treated with individually tailored prophylaxis.

Until now, arthropathy has been related to bleeding pattern and quality of life [9,17]. Arthropathy showed most variation among the patients born between 1968 and 1985. As higher Pettersson scores may be the result of undertreatment, higher Pettersson scores may not help to identify patients with a more severe phenotype (ceiling effect). However, lower Pettersson scores may help to identify patients with a milder phenotype in this age group. Younger patients predominantly had low scores: 60% had a score of 0 ('floor effect'), because of a low cumulative number of joint bleeds and immaturity of bone.

What is the potential use of indicators of clinical phenotype? Distinction of phenotypes may enhance individualization of treatment. Although primary prophylaxis to prevent bleeds remains the treatment strategy of choice for children with severe haemophilia, patients with a milder phenotype may be able to start prophylaxis later in life or at a lower dose, which will greatly improve cost-effectiveness of treatment and reduce the burden of central venous catheters [6,15,18,19]. Patients with a more severe phenotype however, would require a more intensive treatment with an early onset of prophylaxis to prevent bleeds and subsequent haemophilic arthropathy [8,20].

Moreover, distinction of phenotypes may facilitate research into the causes and mechanisms of clinical variability. Currently, causes of variation in phenotype of severe haemophilia are largely unknown. Several causes have been studied. Pharmacokinetic properties, like FVIII half-life may influence clinical phenotype, but this association could not be established in a study by our group [21]. Factor V Leiden may decrease the severity of disease, but findings on other thrombophilic factors remain inconclusive [22–24]. Furthermore, the type of genetic defect in the gene encoding for FVIII may be of importance for the clinical phenotype. Until now, no association of the genetic defect with clinical phenotype of severe haemophilia has been established [25]. A problem, however, is the rarity of specific genetic defects. An inversion is present in 40–50% of patients with severe haemophilia, making a study of its effect feasible [26,27]. Any study of the effects of other mutations, however, is hampered by small numbers, as these defects are very diverse [28]. Further research is needed in order to study the consistency of our findings in other cohorts.

In conclusion, the onset of joint bleeding (ranging over 5.6 years) is inversely related with treatment requirement and arthropathy and may serve as an indicator of clinical phenotype. Thus, providing a starting point for aetiological research and individualization of treatment.

References

1 Rainsford SG, Hall A. A three-year study of adolescent boys suffering from haemophilia and allied disorders. *Br J Haematol* 1973; **24**(**5**): 539–51.

2 Aledort LM, Haschmeyer RH, Pettersson H. A longitudinal study of orthopaedic outcomes for severe factor-VIII-deficient haemophiliacs. The Orthopaedic Outcome Study Group. *J Intern Med* 1994; **236**: 391–9.

3 van den Berg HM, Fischer K, Mauser-Bunschoten EP *et al.* Long-term outcome of individualized prophylactic treatment of children with severe haemophilia. *Br J Haematol* 2001; **112**: 561–5.

4 Fischer K, van der Bom JG, Mauser-Bunschoten EP *et al.* Changes in treatment strategies for severe haemophilia over the last 3 decades: effects on clotting factor consumption and arthropathy. *Haemophilia* 2001; **7**: 446–52.

5 Pool JG, Shannon AE. Production of high-potency concentrates of antihemophilic globulin in a closed-bag system. *N Engl J Med* 1965; **273**: 1443–7.

6 Fischer K, van der Bom JG, Prejs R *et al.* The effects of postponing prophylactic treatment on long-term outcome in patients with severe haemophilia. *Blood* 2002; **99**: 2337–41.

7 Pettersson H, Ahlberg A, Nilsson IM. A radiologic classification of hemophilic arthropathy. *Clin Orthop* 1980; **149**: 153–9.

8 Liesner RJ, Khair K, Hann IM. The impact of prophylactic treatment on children with severe haemophilia. *Br J Haematol* 1996; **92**: 973–8.

9 Fischer K, van Hout BA, van der Bom JG, Grobbee DE, van den Berg HM. Association between joint bleeds and Pettersson scores in severe haemophilia. *Acta Radiol* 2002; **43**: 528–32.

10 Lofqvist T, Nilsson IM, Berntorp E, Pettersson H. Haemophilia prophylaxis in young patients – a long-term follow-up. *J Intern Med* 1997; **241**: 395–400.

11 Nilsson IM, Berntorp E, Lofqvist T, Pettersson H. Twenty-five years' experience of prophylactic treatment in severe haemophilia A and B. *J Intern Med* 1992; **232**: 25–32.

12 Pollmann H, Richter H, Ringkamp H, Jurgens H. When are children diagnosed as having severe haemophilia and when do they start to bleed? A 10-year single-centre PUP study. *Eur J Pediatr* 1999; **158** (Suppl. 3): S166–70.

13 Onwuzurike N, Warrier I, Lusher JM. Types of bleeding seen during the first 30 months of life in children with severe haemophilia A and B. *Haemophilia* 1996; **2**: 137–40.

14 Molho P, Rolland N, Lebrun T *et al.* Epidemiological survey of the orthopaedic status of severe haemophilia A and B patients in France. The French Study Group. *Haemophilia* 2000; **6**: 23–32.

15 Fischer K, van der Bom JG, Prejs R *et al.* Discontinuation of prophylactic therapy in severe haemophilia: incidence and effects on outcome. *Haemophilia* 2001; **7**: 544–50.

16 Steen CK, Hojgard S, Glomstein A *et al.* On-demand vs. prophylactic treatment for severe haemophilia in Norway and Sweden: differences in treatment characteristics and outcome. *Haemophilia* 2003; **9**: 555–66.

17 Fischer K, van der Bom JG, van den Berg HM. Health-related quality of life as outcome parameter in haemophilia treatment. *Haemophilia* 2003; **9** (Suppl. 1): 75–82.

18 Berntorp E. Prophylactic therapy for haemophilia: early experience. *Haemophilia* 2003; **9** (Suppl. 1): 5–9.

19 Van Dijk K, van der Bom JG, Bax KN, van der Zee DC, van den Berg HM. Use of implantable venous access devices in children with severe hemophilia: benefits and burden. *Haematologica* 2004; **89**: 189–94.

20 Astermark J, Petrini P, Tengborn L *et al.* Primary prophylaxis in severe haemophilia should be started at an early age but can be individualized. *Br J Haematol* 1999; **105**: 1109–13.

21 Van Dijk K, Van der Bom JG, Lenting PJ *et al.* Factor VIII half-life and clinical phenotype of severe hemophilia A. *Haematologica* 2005; **90**: 494–8.

22 Van Dijk K, van der Bom JG, Fischer K, Grobbee DE, van den Berg HM. Do prothrombotic factors influence clinical phenotype of severe haemophilia? A review of the literature. *Thromb Haemost* 2004; **92**: 305–10.

23 Arbini AA, Mannucci PM, Bauer KA. Low prevalence of the factor V Leiden mutation among 'severe' hemophiliacs with a 'milder' bleeding diathesis. *Thromb Haemost* 1995; **74**: 1255–8.

24 Lee DH, Walker IR, Teitel J *et al.* Effect of the factor V Leiden mutation on the clinical expression of severe hemophilia A. *Thromb Haemost* 2000; **83**: 387–91.

25 Van Dijk K, van der Bom JG, Ploos van Amstel JK *et al.* Is clinical phenotype of severe hemophilia dependent on factor VIII genotype? *Blood* 2003; **102**: 801a.

26 Lakich D, Kazazian HH Jr, Antonarakis SE, Gitschier J. Inversions disrupting the factor VIII gene are a common cause of severe haemophilia A. *Nat Genet* 1993; **5**: 236–41.

27 Naylor JA, Green PM, Rizza CR, Giannelli F. Analysis of factor VIII mRNA reveals defects in everyone of 28 haemophilia A patients. *Hum Mol Genet* 1993; **2**: 11–7.

28 Kemball-Cook G, Tuddenham EG, Wacey AI. The factor VIII structure and mutation resource site: HAMSTeRS version 4. *Nucleic Acids Res* 1998; **26**: 216–9.