Homozygous and double heterozygous Factor V Leiden and Factor II G20210A genotypes predispose infants to thromboembolism but are not associated with an increase of foetal loss

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Summary
Prospective and controlled data about the individual risk profile in asymptomatic children with homozygous or double heterozygous risk genotypes for Factor V Leiden (FVL) and factor II (FII) G20210A are currently unavailable. The systematic and prospective observational study presented here was designed to determine the impact of the homozygous and double heterozygous FVL and FII G20210A genotypes on the prenatal and postnatal risk profiles of affected children. Risk infants and heterozygous controls were identified by screening of 85,304 neonates. Follow-up included the comparison of prenatal and postnatal development, ultrasonography of brain and kidneys, and a panel of independent determinants of thrombophilia. The numbers of identified or expected FVL homozygotes and double heterozygotes did not differ significantly (FVL: 116 versus 91, p=0.08; FVL/FII: 94 versus 76, p=0.17), indicating the absence of a prenatal disadvantage. A prenatal advantage was suggested in FII homozygotes, whose identified number far exceeded the expected (19 versus 4, p=0.002). Clinical and/or imaging abnormalities indicated spontaneous thromboembolic events in 4 of 129 risk infants (3%) but in none of the 178 controls (p=0.02). Physical and neurological development was normal in both groups during the first 2 years of life. The risk genotypes appear to confer a significant predisposition for spontaneous thromboembolic events in infancy without impeding development within the first two years of life. Foetal risk genotypes do not cause an increased foetal loss rate. Moreover, homozygous FII G20210A appears to be associated with a prenatal advantage.

Keywords
Factor V Leiden, neonatal screening, prothrombin G20210A, thrombophilia in childhood

Thromb Haemost 2003; 90: 628–35
**Introduction**

Thromboembolic- (TE-) events during childhood are rare and are estimated to occur with a frequency of between 0.07 and 0.14 in 10,000 children from 1 month to 18 years (1, 2) and 0.51 per 10,000 infants in the neonatal period (3). Most of these events occur during the neonatal period and the first year of life (2, 4, 5). FVL and FII G20210A mutations in children are associated with a risk of both venous and arterial TE-events involving a variety of organs (6-16), although the overall risk in asymptomatic heterozygous children appears to be low (17). Furthermore, a possible role of these risk genotypes in prenatal TE-events and in prenatal loss was suggested by various anecdotal reports, case studies and reports of an elevated prevalence in preterm infants with very low birth weight (18-22).

In most children with heterozygous risk genotypes and TE-events, additional genetic or acquired risk factors can be identified (5, 10, 23), whereas numerous reports of spontaneous TE-events suggested a particular risk in homozygous (6, 8, 24-28) or double heterozygous children (15, 29). Currently, prospective data about the individual risk profile of unselected homozygous or double heterozygous children are not available. These children may be expected to be at particular risk for either foetal loss or for prenatal and postnatal events that may previously not have been attributed to thrombophilia. The study presented here was designed to prospectively determine the impact of the homozygous and double heterozygous FVL and FII G20210A genotypes on the risk of thrombosis in affected children.

**Materials and methods**

**Study design**

As part of this study, material from the filter cards obtained from >98% of all newborns in Berlin for routine neonatal screening was used for FVL and FII G20210A genotyping. Parents of newborns with the homozygous or the double heterozygous genotypes born in the same week were asked in an initial contact letter to participate in this study. Following written informed consent, the children were enrolled in the study. We contacted the parents of two heterozygous children per homozygous or double heterozygous proband to account for a potential higher dropout rate in the control group. We enrolled heterozygous infants as controls, because the heterozygous genotype is unlikely to confer a significantly higher risk than the normal genotype. If the thromboembolic risk were higher in unselected heterozygous individuals compared to children with a normal genotype at the FV and FII loci, this would have introduced a bias that would at most lead to underestimating a potential difference between the groups with or without risk genotypes. Moreover, at the outset of the study it was felt that heterozygous parents may potentially benefit from counselling and from the avoidance of acquired risk factors. The occurrence of a severe TE event and loss to follow-up defined end points of the study. Early detection of an increased incidence of severe TE-events in probands that might necessitate the development of prophylactic strategies represented a termination criterion of the study.

During the primary visit the personal and family histories were documented. The social status of the families was estimated by a previously-validated questionnaire that enquires about the number of siblings, the parents’ school education, the presence of either both or only a single parent in the family, and the available housing space (30). The children were physically examined with particular attention to their physical and neurological development and to their vascular status. In all probands and controls, repeated ultrasonography of the brain and the kidneys including the adrenal glands was performed by a paediatric radiologist. Follow-up visits were performed at 3-month intervals during the first year of life and at 6-month intervals during the second year of life. The developmental status of the children was determined by Revised Prescreening Developmental Questionnaires (R-PDQ) (31) at 12 months of age and by the Griffith test (32) at 20 months of age by a specially qualified developmental psychologist. The psychologist and the radiologist were unaware of the children’s genotypes. In the second year of life laboratory analyses of independent genetic or acquired risk factors for TE-events were performed.

**Laboratory analyses**

The allele specific multiplex PCR for the identification of the FVL and FII G20210A mutations was performed as previously described (27). This method has been validated by PCR with individual primer pairs in both orientations and restriction analysis of PCR products in a subset of 2000 samples. Additionally, the genotypes of the probands and controls were confirmed using a new blood sample in the second year of life. The analysis of the MTHFR C677T and the PAI-1 4G/5G polymorphisms was performed as previously described (33, 34). The activities of protein C and protein S were determined by clotting assays (STA clotting test, Roche Diagnostics). The activities of anti-thrombin, plasminogen and α2-antiplasmin were determined by chromogenic assays (STA Chromogen, Roche Diagnostics), and the activities of factor II and factor VIII by clotting assays using factor II/VIII deficient plasma (Immuno, Dade Behring). The serum levels of D-dimers, von Willebrand factor antigen and lipoprotein(a) were determined by latex enhanced immunoassays (Roche Diagnostics) and the serum levels of phospholipid antibodies by enzyme linked immuno-sorbent assays (Orgentec). The serum levels of homocysteine were measured by HPLC of a freshly deproteinized blood sample (35). When a concentration of >17µmol/l was measured, the assay was repeated with a blood sample that was obtained after a fasting period of at least 4 hours.
Data protection and ethical considerations
The generation of genetic information for research purposes by neonatal screening has so far been unique in Germany. The parents of children with risk genotypes and those with heterozygous genotypes who were born in the same week were contacted by mail and were asked to participate in the study. We are aware that the linkage of personal data to the FVL and FII genotypes represented a critical issue in the design of the study even though this affected only a small minority of all screened infants. This issue was addressed by not specifying the genotype of the children in the initial contact letter. The data of children whose parents did not respond to this initial contact letter or who did not wish to participate in the study were irreversibly deleted. Personal information was thus matched to genotype only for those infants whose parents gave written consent to participate in the study. This design was in accordance with the then-current guidelines of the German Medical Council (Bundesärztekammer) and was approved by the ethics committee of the Medical Faculty of the Humboldt University and by a panel of independent referees of the Deutsche Forschungsgemeinschaft (DFG), who agreed that the likely medical benefit of this study outweighs any remaining concerns about data protection.

In March 2001, new general guidelines for the routine endocrine and metabolic neonatal screening programme were implemented in the Berlin screening programme. This included asking for written informed consent even for the long-established phenylketonuria, galactosaemia and hypothyroidism screening. This new policy enabled us to change the study design and ask for parents’ informed consent to participate in this study prior to genotyping of the infants.

Statistics
The comparison of quantitative and qualitative data are performed by the Mann-Whitney-U test and by χ²-analysis, respectively.

Results
From January 1999 through September 2001 we screened a total of 85,304 samples representing ≈98% of all infants born in Berlin. We identified 116 homozygotes and 5,338 heterozygotes for FVL, 19 homozygotes and 1,132 heterozygotes for FII G20210A, and 94 double heterozygotes. The gene frequencies of FVL and FII G20210A in this population can thus be calculated at 0.0326 and 0.0069, respectively. Based on the respective gene frequencies and the Hardy-Weinberg equation, we would have expected to identify 91 FVL homozygotes, 4 FII G20210A homozygotes and 76 double heterozygotes. Considering that maternal but also foetal FVL and FII G20210A were reported to be associated with prematurity and low birth weight (22, 36-38), one might have expected to find fewer than the calculated number of homozygotes and double heterozygotes. The numbers of identified FVL homozygotes and double heterozygotes did not differ significantly from the calculated numbers (FVL: 116 vs. 91, p=0.08; double heterozygote: 94 vs. 76, p=0.17), indicating that there is no major prenatal loss of foetal carriers. There was a higher than calculated number of FII G20210A homozygotes (19 vs. 4; p=0.002), suggesting that this genotype confers a prenatal advantage, the mechanism of which must remain speculative at this point.

A large proportion of the parents responded and agreed to participate in the study that now, to our knowledge, represents the largest cohort of children with heterozygous and double heterozygous FII and FVL risk genotypes. Until September 2001, 129 of the 229 infants with risk genotypes were enrolled in the proband group (73 FVL homozygotes, 8 FII G20210A homozygotes, and 48 double heterozygotes). Forty-three of the 100 families, who did not participate in the study, did not respond to the initial contact letter, whereas 57 of 100 opted not to participate after being informed about the study in detail. A subset of 178 out of the total of 6,470 heterozygotes born in the same week as the probands were enrolled in the control group (125 FVL, 53 FII G20210A). Fourteen of 129 probands (11%) and 25 of 178 (14%) controls were lost to follow-up.

The proband and control groups were similar with respect to their base-line characteristics (Table 1) except for a significantly increased proportion of Turkish families in the proband group than in the control group (32% vs. 17%, p=0.002). This ethnic difference was observed in the homzygous FVL and in the double heterozygous FVL/FII groups only, which likely reflects the different FVL gene frequencies and marital traditions between the indigenous German population and the population of Turkish origin (39). In contrast, the gene frequency of the FII G20210A mutation is similar in Germans and in Turks and only 2 out of 10 FII homozygotes were of Turkish origin, which approximately reflects the proportion of ethnically Turkish infants born in Berlin and the proportion of Turkish infants in the control group. There were no differences in the distribution of the activities of protein C, antithrombin, plasminogen, α2-antiplasmin, factor II, or factor VII. The protein S activity was significantly lower in the proband group, which is most probably due to an interference of activated protein C (APC) resistance with the protein S assay. Serum levels of D-dimers were significantly higher in the proband group, indicating a more active fibrinolytic system in the proband group. Serum levels of von Willebrand factor antigen, homocysteine, or lipoprotein(a), as well as the PAI-1 4G and the MTHFR 677T allele frequencies were similar for both groups. One of the probands showed elevated levels of antiphospholipid IgM antibodies. Neither antiphospholipid IgG antibodies, nor lupus anticoagulant were detected in any of the probands or controls.

The physical development profile during the first 2 years of life corresponded to the normal range, and did not differ
between the proband and the control groups (Fig. 1). At the age of 12 months, the parents were asked to answer the questions of the R-PDQ. Responses were received for 89 of 115 probands and 121 of 153 controls. A normal score was recorded in 82 of 89 probands and in 113 of 121 controls (92.1% vs. 93.4%; p=0.73). The paediatric examination performed on all study participants at each follow-up visit revealed no evidence for a developmental delay in probands and controls whose parents did not answer the R-PDQ. The Griffith test was performed in 73 probands and 109 controls at 20 months of age. The mean developmental quotients (DQ) did differ significantly between the proband (mean DQ 100, standard deviation (SD) 9, range 54-114) and the control groups (mean DQ 103, SD 6, range 83-117) (p=0.011), but were within the normal range for both groups.

In 6 of the 7 probands with a pathologic result of the R-PDQ, Griffith testing was performed at the age of 20 months. One of these 6 children showed a distinct impairment of mental and motor development (DQ 54) and suffered from cerebral palsy. Cranial ultrasonography revealed no cerebral abnormalities at 6 weeks up to 9 months of age. The parents did not consent to a more detailed diagnostic follow-up. In the other 5 probands, the Griffith test revealed normal results.

The Griffith test was performed in 7 of 8 controls with a pathologic result of the R-PDQ. One of these children is microcephalic and shows a delay of mental and motor development

| Table 1: Base-line characteristics of the proband and the control groups |

<table>
<thead>
<tr>
<th></th>
<th>Probands (n=129)</th>
<th>Controls (n=178)</th>
<th>P</th>
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<tr>
<td>Male-to-female ratio</td>
<td>1.0</td>
<td>1.1</td>
<td>0.60</td>
</tr>
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<td><strong>Data at birth</strong></td>
<td></td>
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<tr>
<td>Gestational age, weeks:days</td>
<td>39:3 ± 2:1</td>
<td>39:4 ± 1:3</td>
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<tr>
<td>Weight, g</td>
<td>3278 ± 541</td>
<td>3397 ± 528</td>
<td>0.13</td>
</tr>
<tr>
<td>Length, cm</td>
<td>51 ± 3</td>
<td>51 ± 3</td>
<td>-</td>
</tr>
<tr>
<td>Head circumference, cm</td>
<td>35 ± 2</td>
<td>35 ± 2</td>
<td>-</td>
</tr>
<tr>
<td><strong>Social status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Turkish families, %</td>
<td>32</td>
<td>17</td>
<td>0.002</td>
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<tr>
<td>Consanguineous parents, %</td>
<td>9</td>
<td>6</td>
<td>0.27</td>
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<tr>
<td>Single parent families, %</td>
<td>3.5</td>
<td>7.6</td>
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<tr>
<td>Number of siblings</td>
<td>0.8 ± 1.0</td>
<td>0.6 ± 0.8</td>
<td>0.47</td>
</tr>
<tr>
<td>Maternal school years</td>
<td>10.3 ± 2.5</td>
<td>10.9 ± 2.2</td>
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<tr>
<td>Paternal school years</td>
<td>10.4 ± 2.7</td>
<td>11.0 ± 2.3</td>
<td>0.05</td>
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<tr>
<td>Housing space, number of rooms</td>
<td>2.9 ± 0.7</td>
<td>3.0 ± 0.8</td>
<td>0.78</td>
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<tr>
<td><strong>Laboratory data</strong></td>
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<tr>
<td>PAI-1 4G allele frequency</td>
<td>0.48</td>
<td>0.52</td>
<td>0.56</td>
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<tr>
<td>MTHFR 677T allele frequency</td>
<td>0.34</td>
<td>0.31</td>
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<td>Fibrinogen, mg/dl</td>
<td>260 ± 62</td>
<td>273 ± 63</td>
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</tr>
<tr>
<td>Antithrombin activity, %</td>
<td>121 ± 10</td>
<td>120 ± 9</td>
<td>0.33</td>
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<tr>
<td>Plasminogen activity, %</td>
<td>97 ± 13</td>
<td>98 ± 12</td>
<td>0.72</td>
</tr>
<tr>
<td>a2-antiplasmin activity, %</td>
<td>106 ± 12</td>
<td>107 ± 20</td>
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<td>Protein C activity, %</td>
<td>84 ± 15</td>
<td>83 ± 15</td>
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<tr>
<td>Protein S activity, %</td>
<td>66 ± 18</td>
<td>77 ± 16</td>
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<tr>
<td>Factor II activity, %</td>
<td>100 ± 15</td>
<td>96 ± 11</td>
<td>0.13</td>
</tr>
<tr>
<td>Factor VIII activity, %</td>
<td>95 ± 32</td>
<td>100 ± 34</td>
<td>0.34</td>
</tr>
<tr>
<td>Von Willebrand factor antigen, %</td>
<td>87 ± 25</td>
<td>89 ± 25</td>
<td>0.63</td>
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<td>D-dimer, mg/l</td>
<td>0.29 ± 1.1</td>
<td>0.07 ± 0.11</td>
<td>0.015</td>
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<td>Homocysteine, μmol/l</td>
<td>9.8 ± 4.0</td>
<td>9.3 ± 3.0</td>
<td>0.49</td>
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<tr>
<td>Lipoprotein (a), mg/dl</td>
<td>29 ± 27</td>
<td>27 ± 22</td>
<td>0.85</td>
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<td>0</td>
<td>0.32</td>
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<tr>
<td>APLA positive (IgG)</td>
<td>0</td>
<td>0</td>
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</tr>
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</table>

Data are listed as mean ± standard deviation. LA indicates lupus anticoagulant; APLA, antiphospholipid antibodies.
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(DQ 83). The prenatal, perinatal and neonatal periods were uneventful. Cranial magnetic resonance tomography (MRT) examinations at 1 and 2 years of age revealed enlarged ventricles and periventricular alterations of uncertain aetiology. In a second child of the control group the Griffith test at 20 months of age revealed an isolated delay of speech development. In the other 5 controls the Griffith test revealed normal results.

In 4 children of the proband group (3 homozygous for FVL, 1 double heterozygous), clinical and/or ultrasonographic changes indicated the occurrence of a TE-event (Table 2). No similar changes were noted in any of the children in the control group (p=0.02). In 3 of these 4 infants the independent prothrombotic risk factors targeted by the laboratory analyses of this study were excluded. In one infant (case 1) the parents did not consent to venipuncture.

**Case 1:** This boy with homozygous FVL was delivered spontaneously at term after an uneventful pregnancy. At the age of 3 months ultrasonography and subsequent cranial MRT and MR-angiography revealed a lack of flow in the right sided anterior and a reduced flow in the medial cerebral artery resulting in hypoplasia of the right frontal and temporal lobe. At 6 months of age, relevant developmental delay and hemiparesis of his left arm were noted. Seven café au lait spots of >5mm in diameter on the child, and a large number of café au lait spots on the mother suggested the diagnosis of neurofibromatosis type I.

**Case 2:** This girl of Turkish origin with homozygous FVL was delivered at 25 3/7 weeks following premature rupture of the membranes at 25 weeks. No major complications occurred during the neonatal period, a central venous line was inserted into a correct position from the right arm between days 6 and 16. A patent ductus arteriosus was ligated on day 21 after unsuccessful indomethacin treatment. In her 5th week of life, a sudden and clinically painful enlargement of the left kidney was noted. This was associated with an increase of echogenicity detected by ultrasonography. The Doppler examination of the renal vessels performed at this time could not be evaluated because of superimposed intraabdominal air. Several analyses of the urine as well as repeated blood and urine cultures remained normal except for a very brief period of erythrocyturia. When ultrasonography of the kidneys showed a hypoplastic left kidney at three months of age, renal vein thrombosis was diagnosed. At 6 months of age, renal scintigraphy revealed an almost complete loss of function of the left kidney. The subsequent course was uneventful without development of hypertension or global loss of renal function.

**Case 3:** This boy with homozygous FVL was spontaneously delivered at 38 weeks. The pregnancy was complicated by mild gestosis. Ultrasonography revealed adrenal haemorrhage at 2.5 months of age. The boy remained asymptomatic and the haemorrhage had regressed almost completely at six months of age. The aetiology of the adrenal haemorrhage must, of course, remain speculative, although adrenal vein thrombosis is known to be the cause in most cases (40, 41).

**Case 4:** This boy with double heterozygous FVL/FII G20210A was delivered at 41 weeks following an uneventful pregnancy. The neonatal period was uneventful, but ultrasonography at 1 month of age revealed an intrarenal calcification that was interpreted to represent the remnant of previous segmental renal vein thrombosis.

The physical and neurological development during the first two years of life remained normal in cases 2-4.
**Discussion**

This population based controlled prospective study represents the first systematic analysis of an unselected large group of asymptomatic infants with homozygous or double heterozygous risk genotypes. This study thus represents an important first step to estimate the predictive value of genotype analysis for thrombophilia in children.

In the first two years of life, TE-events occurred in 4 of 129 children with a risk genotype but in none of the 178 controls (p=0.02). Because of the small number of children with TE-events, this statistically significant difference must be considered a preliminary result until a larger number of children is analysed. However, considering the previously estimated rarity of TE-events in children (1-3), the incidence of relevant TE-events of approximately 3% in the proband group is high and is demonstrated to be independent of known additional hereditary or acquired risk factors. Therefore, we propose that homozygous FVL and double heterozygous FVL/FII G20210A represent the major risk factors contributing to the occurrence of thrombosis in the children of our study group. All 4 TE-events observed here occurred during the first 3 months of life and 3 events probably occurred during the pre- or perinatal period. It seems, therefore, that the risk genotypes are particularly relevant during this time of life, when most TE-events in childhood are known to occur (1-3).

This study does not address the issue of potential benefits of a prophylactic strategy. However, it should be noted that anticoagulation carries the risk of severe side effects and at least 3 of the 4 TE-events observed here are unlikely to have been preventable. Furthermore, the development was normal for the proband and the control groups, which suggests that potential subclinical TE-events of the CNS do not cause noticeable developmental delay in children with thrombophilia at least in the first 2 years of life. Follow-up and extension of this cohort will likely enable us to identify potential risk situations that may require prophylactic action.

A further important aspect of thrombophilia in children relates to its contribution to the risk of preterm events that potentially result in miscarriage or in prematurity. Conflicting data were reported for the role of the foetal FVL and FII G20210A genotypes. In some but not other studies the foetal FVL or FII G20210A genotype was associated with a higher risk for preterm birth and foetal growth restriction (36, 37, 42). Similarly, there are conflicting data about the effect of the foetal FVL genotype on fertility, (43, 44). The analysis of gestational age and birth weight of the unselected population studied here revealed data within the normal ranges for both parameters and no significant differences between the proband and the control groups. Furthermore, the almost complete population-wide genotype analysis achieved in this study enabled us to directly address the hypothesis of an increased rate of miscarriage or prematurity associated with foetal risk genotypes. If the homozygous and the double heterozygous FVL and FII G20210A genotypes were causing foetal loss, one would have expected infants with these genotypes to be underrepresented among the live-born children, who participate in the neonatal screening program. In this study, there was no evidence for a major rate of miscarriage of foetal carriers of the homozygous or the double heterozygous genotypes. However, it is possible that a potential implantation advantage in foetal FVL carriers might be counterbalanced by an increased foetal loss rate. We found more infants with the homozygous genotype for FII G20210A than was calculated on the basis of the Hardy-Weinberg equation. In principle, this may be explained by a higher rate of consanguineous marriages and a higher number of children per family in Turkish families (10% of the overall Berlin population (45)). However, this does not seem to be the case, because the proportion of Turkish children homozygous for FII G20210A is not increased and even assuming a frequency of 24% consanguineous marriages for the entire Turkish population living in Berlin (as seen within the study group), the expected number would still significantly differ from the identified number of FII G20210A homozygotes (6 vs. 19, p=0.009).

Hypothetically, this observation could also be explained by a prenatal disadvantage of the heterozygous controls that is not present in the homozygous probands. However, this explanation is unlikely, because the base line characteristics of the heterozy-
gous control group including the gestational age and the physical data at birth correspond to the normal distribution of the general population (Table 1). This study thus suggests a previously unknown protective prenatal effect of FII G20210A. The mechanism of this effect must remain speculative at this time. As suggested previously for FVL (43), the foetal FII G20210A genotype may be associated with an improvement of implantation efficiency. FII G20210A is thought to result in an increased prothrombin plasma concentration (46) by an upregulation of 3'-end processing efficiency (47) or by an increase of translation efficiency (48). The protective effect may therefore be explained by a reduced prenatal bleeding tendency. However, this does not seem likely, because the biological activity of vitamin K dependent clotting factors such as prothrombin is physiologically low during gestation and because a similar effect would have been expected for FVL. An alternative explanation is suggested by the role of thrombin receptor signalling in endothelial cells during embryonic development (49). The protective effect of FII G20210A may thus be independent of the function of thrombin as a regulator of blood coagulation.

Acknowledgements

We thank B. Hermann for excellent technical assistance and R. Hartmann for statistical analysis.

References


