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The Dysprothrombinemias due to Arg596 Mutations: A Conundrum With No Bleeding Tendency and Venous Thrombosis due to Antithrombin Resistance

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The transformation of a bleeding disorder into a prothrombotic one is an extraordinary event in blood coagulation. This is what occurred recently with the description of 3 dysprothrombinemias, prothrombin Yukuhashi, prothrombin Belgrade, and prothrombin Padua 2 which do not cause bleeding but, instead, show antithrombin resistance with consequent thrombosis.[1-4] It is now of paramount importance to verify if the Arg596 mutations are the only ones responsible for the shift from a hemorrhagic condition to a thrombophilic one or if other amino acids of the same area of the prothrombin molecule encoded by exon 14 might also be associated with the change.

Two approaches are available, namely (1) the restudy of cases of prothrombin defect with mutations encoded around the Arg596 residue and (2) chimeric studies in vitro. The 3 prothrombin defects close to the Arg596 residue are prothrombin Scranton (Lys399Thr) downstream and prothrombin Perija (Gly591Ala) and prothrombin Saint Denis (Asp395Glu), upstream.[5-8]

The relation with prothrombin Scranton is interesting. This family had a Lys599Thr mutation, the patients were all heterozygotes and also neither a bleeding tendency nor thrombosis, namely, probably, no antithrombin resistance.[5]

Prothrombin Perija (Gly591Ala) is upstream to Arg596. The patient is homozygote for the defect and shows a mild bleeding tendency despite a prothrombin level of 2% of normal but no thrombosis.[6,7] Prothrombin Saint Denis (Asp595Glu) has no bleeding and no thrombosis and is also upstream (Figure 1).[8]

Mutation involving amino acids: 592, 593, and 594 of the prothrombin molecule, upstream to the Arg596, unfortunately, have not been yet demonstrated in patients. The same is true for the amino acids 597 and 598, downstream of Arg596.[9,10] However, chimeric studies in vitro have shown that the Glu592Gln mutation causes antithrombin resistance.[11]

The mutations seen in the dysprothrombinemias associated with venous thrombosis are Arg596Leu, Arg596Gln, and Arg596Trp. These mutations confer to the prothrombin molecule a resistance to antithrombin. This indicates that the Arg596 is crucial since the antithrombin resistance occurs regardless of the replacing amino acid Leu, Gln, or Trp. It is worth noting that a delayed or defective binding to antithrombin had been suspected to exist also for prothrombin Perija (Arg591Ala) and prothrombin Saint Denis (Asp595Glu). However, since the carriers of these mutation showed no thrombotic event, the finding was not pursued.[7,8]

It would be interesting to know if the patient with prothrombin Saint Denis (Asp595Glu) which is a mutation attached to Arg596 has ever developed thrombosis. Since the patient was reported as a new born and followed for only about 2.5 years (30 months), the occurrence of a thrombotic event could not be excluded.[8] Unfortunately, no further information is available. The mean age for the occurrence of thrombosis, for all the Arg596mutated patients, excluding prothrombin Amrita another case of Arg596Gln mutation seen in India,[12] is about 20 years.

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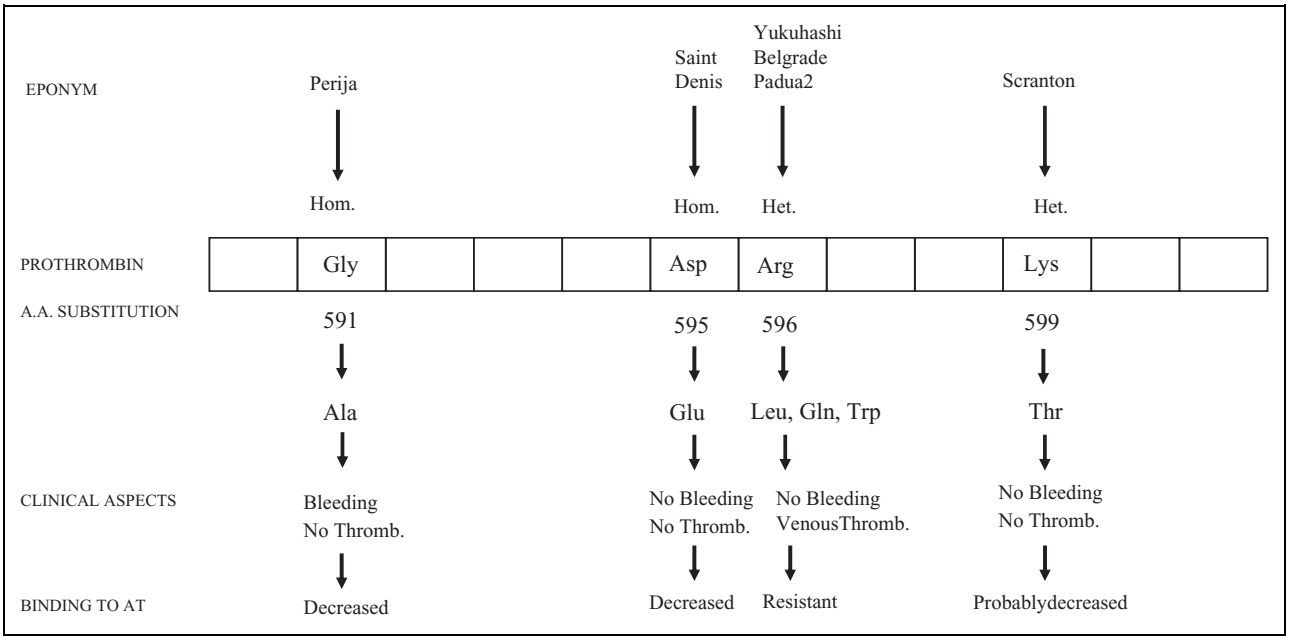

Figure 1. Schematic representation of the main features of the dysprothrombinemias due to Arg596 substitution and of other close dysprothrombinemias, all encoded by exon 14. The probable decreased binding to antithrombin for prothrombin Scranton is inferred from chimeric in vitro studies. A.A. indicates amino acid; AT, antithrombin; tromb, thrombosis.

Chimeric studies in vitro have shown that mutation Lys599Arg and mutation Glu592Gln show antithrombin resistance similar to that seen in prothrombin Yukuhashi (Arg596Leu) and prothrombin Belgrade (Arg596Gln).[9] A mutation similar to Lys599Arg has been found, clinically, in prothrombin Scranton (Lys599Thr), whereas the other mutation (Glu592Gln) so far has no clinical counterpart or confirmation.

Granting the differences that may be present between chimeric in vitro studies and clinical observations, it would seem that the substitution of amino acid Lys599 either with Arg (chimeric studies) or with Thr (Prothrombin Scranton) may cause resistance to antithrombin.[5,9] However, antithrombin resistance has not been searched for in the original paper dealing with in prothrombin Scranton.[5]

These clinical observations and chimeric studies, taken all together, would seem to indicate that the area of prothrombin encoded by exon 14, from Gly591 to Lys599 are associated with impaired or delayed binding to antithrombin and to antithrombin resistance. It is not clear yet whether such features extend to amino acids downstream from Arg596, for example, to prothrombin Scranton (Lys599Thr).

It seems therefore that the area of prothrombin associated with antithrombin resistance spans at least from residue Gly591 (prothrombin Perija) to residue Lys599 (prothrombin Scranton), regardless of the amino acid substitution. Since only patients with the Arg substitutions with Leu, Gln, or Trp are associated with venous thrombosis, it would seem that the lack of Arg, regardless of the substitution, Leu, Gln, or Trp, is responsible for the occurrence of the antithrombin resistance. Alternatively, it could be that these abnormal prothrombins Arg596Leu, Arg596Gln, or Arg596Trp could be the cause of the appearance of antithrombin resistance.

This seem very unlikely because of the great structural differences existing among leucine, glutamine, and tryptophan. Defects in the amino acid 592, 593, 594, and 597, 598 have not been reported yet in patients.[10,11]

The discovery of these patients could be useful in defining the area of the prothrombin molecule encoded by exon 14 associated with antithrombin resistance and the appearance of thrombosis.

Declaration of Conflicting Interests

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