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Factor V Kuwait alias Factor V R3: A Rare Polymorphism of Uncertain Functional Significance

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We have read with great interest the recent article by Jadaon et al. [1] reporting a novel coagulation factor V (FV) gene polymorphism (FV Kuwait) in the Arab population of Kuwait. While genotyping a group of thrombotic patients for the well-known FV R2 polymorphism (A4070G, H1299R [2]) by Rsa I restriction analysis of exon 13, the authors observed an unexpected restriction pattern suggesting the existence of a different polymorphic Rsa I restriction site in the same amplicon. Direct sequencing of the PCR product revealed an A→G transition at position 3935, which predicts the replacement of His¹²⁵⁴ by an Arg in the B domain of the protein. This polymorphism was detected in 2 out of 188 patients with venous thrombosis, but it was absent in 100 healthy controls, raising the possibility that it might contribute to the risk of venous thrombosis in the Arab population.

Although the FV H1254R polymorphism is not included in any of the major genetic variation databases, it has actually been known since 1998, when it was first described in the Somali population under the name of FV R3 [3]. Since then, its occurrence has been investigated in a few other populations (summarised in table 1), which allows to draw a sketch map of its geographical distribution and prevalence. With the notable exception of Kuwaiti Arabs [1], the FV H1254R allele appears to be confined to populations of African ancestry, i.e. Somali [3] and Costa Rican Blacks from the Limón region [4, 5]. Remarkably, it was not found in the study by Folsom et al. [6], who performed Rsa I restriction analysis of FV exon 13 in 234 African-Americans, suggesting that this allele is very rare or absent in the Black population of the USA. No carriers of the FV H1254R polymorphism were detected in the indigenous populations of Costa Rica (Bribri and Chorotega Indians) [4, 5], in 2 groups of individuals representative of different regions of India [3, 5] and in a large sample of Japanese [7]. In Caucasian populations, for which large cohorts of subjects have been genotyped, the FV H1254R allele was either absent (Italians [3], Germans [4, 5]) or sporadic (Greek Cypriots [3],

Dutch [8], Italians [unpublished observation]), possibly due to admixture. On the basis of this selective geographical distribution, the FV H1254R polymorphism might be one of the numerous alleles that were present in the African population before the out-of-Africa migration but (due to genetic drift) did not make it beyond the Arab peninsula when humans crossed the Red Sea to colonise the other continents some 100,000 years ago.

From a molecular point of view, the FV H1254R polymorphism is in many ways similar to the more frequent and better-known FV H1299R (R2) polymorphism [3]. Both polymorphisms are located in a highly repetitive region of FV exon 13, which is characterised by 31 imperfect tandem repeats of 27 base-pairs (9 amino acids), and they affect homologous nucleotides of 2 different repeats. By changing an A into a G, they both create an Rsa I recognition site and give rise to identical amino acid substitutions (His/Arg) at homologous positions within the respective repeat. Both His residues are conserved among primates (*Pan troglodytes* and *Macaca mulatta*) but not in other mammals (replaced by Gln residues in *Mus musculus* and *Rattus norvegicus*).

FV is a large plasma glycoprotein with pivotal functions both in the procoagulant and in the anticoagulant pathways [9], and several (potentially) prothrombotic mutations and polymorphisms have been described in its gene [10]. At present, no functional data have been reported for the FV H1254R polymorphism. The only piece of information available is that the single carrier identified in the Dutch study had slightly reduced FV levels in plasma (FV:Ag 117 U/dl, as compared to a population mean of 134 U/dl, 95% CI 131–137) and mild activated protein C (APC) resistance (nAPCsr in the undiluted aPTT-based test = 0.78, as compared to a population mean of 1.02, 95% CI = 1.01–1.04) [8]. Interestingly, these same phenotypes have been associated with carriership of the FV R2 allele in large epidemiological studies [2, 8, 11]. Although there is evidence that FV R2-related effects are (partially) mediated by other intragenic polymorphisms (e.g. D2194G) which are genetically linked to the H1299R allele within the FV R2 haplotype, *in vitro* expression and characterisation of the isolated FV H1299R variant has shown that this polymorphism directly interferes with the glycosylation of the B domain, thereby delaying FV secretion [12]. This might also be the case for the FV H1254R polymorphism, which causes an identical amino acid substitution in the same repetitive region of the FV B domain.

In conclusion, the FV H1254R polymorphism is an overall rare FV variant with a restricted geographical distribution (table 1). Whether it is a single-origin allele which originated in Africa and spread to the Middle East and Central America by migration events or whether it has occurred independently in different geographical regions, remains to be elucidated. Comparison of the underlying FV gene haplotype(s) in carriers of the polymorphism from different populations may help clarify this

Table 1. Prevalence of the factor V H1254R polymorphism in different populations

Population	Type of sample	n	Carriers	Allele frequency	Reference
Somali	general population	40	6	0.075	Lunghi et al. [3]
Costa Rican Blacks	general population	95	3	0.016	Herrmann et al. [4, 5]
Costa Rican Indians (Bribri)	general population	77	0	–	Herrmann et al. [4, 5]
Costa Rican Indians (Chorotega)	general population	76	0	–	Herrmann et al. [4, 5]
Kuwaiti Arabs	VTE patients	188	2	0.005	Jadaon et al. [1]
	healthy controls	100	0	–	
Punjab Indians	blood donors	150	0	–	Herrmann et al. [5]
Southern Indians	general population	40	0	–	Lunghi et al. [3]
Japanese	women with pre-eclampsia	133	0	–	Watanabe et al. [7]
	normal pregnant women	224	0	–	
Greek Cypriots	general population	146	1	0.003	Lunghi et al. [3]
Italians	general population	500	0	–	Lunghi et al. [3]
	VTE patients	600	1	0.001	unpublished observation
Germans	blood donors	170	0	–	Herrmann et al. [4, 5]
Dutch	VTE patients	471	0	–	De Visser et al. [8]
	healthy controls	472	1	0.001	

VTE = Venous thromboembolism.

issue. A detailed functional characterisation of the mutant and more solid epidemiological evidence are also needed to firmly establish whether the FV H1254R allele contributes to the risk of venous thrombosis, as suggested by Jadaon et al. [1].

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Reply

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We would like to thank Castoldi et al. [1] for their valuable comments on our previously published article describing a novel mutation in the clotting factor V gene found in 2 Arab patients with venous thrombosis who were living in Kuwait [factor V Kuwait (FVK) mutation or FV H1254R polymorphism] [2]. As stated by Castoldi et al. [1], the FVK mutation is a very rare one. We have to state here that this polymorphism had not been registered in the human gene bank before we found it in our patients, giving us the impression that it had not been described before. We were the first to register it in the human gene bank with the accession number AY881018. In addition, the FVK mutation was not described as a part of the HR2 haplotype, the haplotype we were originally studying when we found the FVK mutation. In fact, both our patients who had the FVK did not have the HR2 haplotype.

As clarified by Castoldi et al. [1], this mutation appeared to be present mainly in populations in Africa or of African origin. Our article was the first to discover the presence of this mutation in cases of Arabic origin, noting the close geographic location between Africa and the Arabian region (the Middle East). We do not know yet what the origin of this mutation is and whether our patients and the African carriers of the mutation had a common ancestor. We agree with Castoldi et al. [1] that comparative genomic studies are needed to determine the origin of this mutation

(African or Arabic) or confirm a multiple occurrence of this mutation in different parts of the world; this mutation is present especially in an area of the factor V gene known to be a highly repetitive region.

Overall, we agree on the rarity of this mutation in the world, being confined to Africa and the Middle East. The mutation was discovered in only 12 cases worldwide. We added 2 cases from the Arab world. We also repeat our previous suggestion on the need for identifying a larger number of cases before confirming any possible risk of developing venous thrombosis in carriers. We suggest an international collaboration and a registry for cases with this mutation. Finally, we believe it is very important that researchers should register all discovered polymorphisms in the gene bank or other similar databases in order to be available to all other investigators worldwide.

References

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