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Geographical Distribution of Factor V Laden in Different Regions of India

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Aim: This study was carried out to know the incidence of Factor V mutation in various regions of India.

Methods: The presence of factor V mutation was determined by PCR- RFLP from patients suspected of thromboembolic etiology from medical, surgical, obstetrics and neonatology departments.

Results: Analysis of 94 patients with coagulation disorders, factor V mutation was seen in 20 cases.

Discussion: Although many reports from India indicate the absence of this mutation or the presence of homozygous mutation in a low level we report about 26 percent of the cases having the homozygous mutation which is the first for India.

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Geographical Distribution of Factor V Laden in Different Regions of India

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I. Introduction

Factor Van Leiden mutation has been reported in 3 to 8 percent of the Caucasian population with thrombophilia, and absolutely absent in Hispanics, African and Asian populations in the US.

Factor V Leiden named after the city Leiden (The Netherlands), was first identified in 1994 by Prof R. Bertina et al. In normal individuals Activated protein C (APC) prevents blood clots from growing too large by inactivating factor V. In factor V Leiden mutation, there is single nucleotide substitution of adenine for guanine (single nucleotide polymorphism) changes the protein's 506th amino acid from arginine to glutamine, which is the cleavage site for APC (Bertina et al).

Factor V Leiden can be associated with the following complications such as deep vein thrombosis (DVT), superficial thrombophlebitis, sinus vein thrombosis, mesenteric vein thrombosis, Budd-Chiari syndrome, pulmonary embolism (PE), recurrent unexplained miscarriage, preeclampsia and/or eclampsia.

PCR is a simple genetic test that can be done for diagnosis of factor V mutation. The mutation (1691G→A substitution) removes a cleavage site of the restriction endonuclease MnlI, which can be detected by PCR - RFLP.

In Asian-Indian populations 1% to 8.5% has been reported. In Tamil Nadu, south India, 4 out of 72 were reported to be heterozygous for FVL mutation (5.5%), while none were detected for homozygous mutation. Another study to know the association between portal vein thrombosis and FVL, reported 4.1% heterozygous mutation for factor in healthy Indians. However, contradic¬tory results were found when the presence of this mutation was studied in healthy populations from Turkey, Korea, and even from some Indian populations (**Wan Zaidah Abdullah** et al 2009).

The presence of the mutation markedly increases the risk for renal vein thrombosis, particularly in neonates, and renal transplant vein thrombosis in transplant cases resulting in rejection. Routine screening for factor V Leiden mutation by polymerase chain reaction, and appropriate perioperative and postoperative anticoagulation after renal transplantation might be a valuable strategy to prevent thromboembolic complications in transplant recipients (Craig J Della Valle MD et al).

The factor V Leiden mutation is associated are two to three times more likely to have recurrent miscarriages or a pregnancy loss during the second or third trimester (8).

II. Materials and Methods

A total of 94 samples were received from patients attending medicine, surgery, neonatology and OBG departments from April 2007 to December 2010 from different states like Karnataka (2, 24.5%), Andhra Pradesh (43, 45.7%), Punjab (18, 19%) West Bengal (5, 5.9%) and Nepal (2, 2.1%). Patients with history of spontaneous DVT, postsurgical, venous thrombosis, haemorrhaegic infarct, stroke, unexplained DVT, primary DVT, hypercoagulable state. The EDTA blood samples were shipped at – 20°C, DNA extraction was done using Qiagen DNA columns. The samples were analyzed for mutant gene by Polymerase Chain Reaction - Restriction Fragment Length Polymorphism (PCR - RFLP) followed by analysis of fragments of digestion by gel electrophoresis. Positive and negative controls were included in the assay, normal (wild) sample showed 3 bands at 86, 46 and 37 bp region, and positive control

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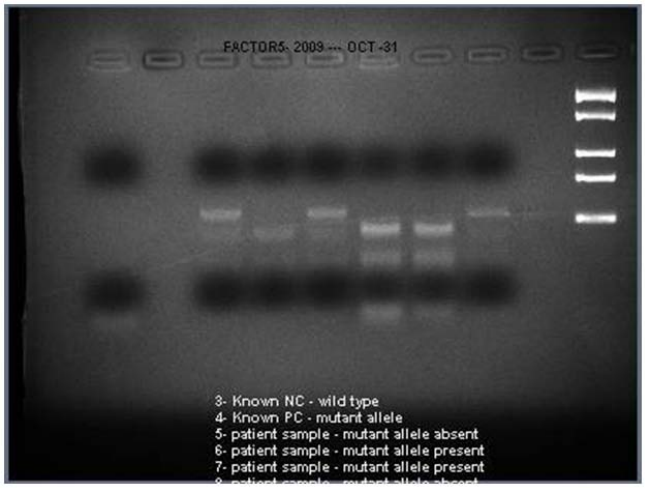
showed 2 bands at 123 and 46 bp region, and negative control did not show any bands. The procedure was followed as per Craig J Della Valle MD et al. 2001.



III. Results

Out of 94 samples screened for the mutation, in the age group ranging from zero to 65 years of age. Of the total 59 were males, age ranging from 1 day to 60 years, with a mean age of 33.5 and a stdev of 16.2. Among the 35 females studied, the age range was 1 day to 60 with a mean of 34.7 and stdev of 12.4. Of these 46 (48.9%) were from Andhra Pradesh, 23(24.5%) from Karnataka from southern region, 19.1% from Punjab in the north, 5.3% from west, and. 2.1% from Nepal.

20 samples were positive for heterozygous mutation, 11 were males in the age group in the range of 1 year to 60 years with a mean of 33 and stdev of 16. In the female cases 9 were positive in the age group in the range of 20 years to 40 years with a mean of 29.8 and stdev of 6.6.

A total of 20 patients were positive for heterozygous mutation, of which 11 were males and 9 were females. 7 cases (7.4%) were from Punjab, of which 5 were females and 2 were males constituting 35% of the positives. These cases were obtained by screening 18 suspected cases from Punjab, giving a positive rate of 35%. Even though 43 cases were screened from Andhra Pradesh, 9 were positive of which 5 were males and 4 were females accounting to 18%, with positive rate of 45%, 3 from Karnataka all 3 were males with a positive rate of 15%, 1male from West Bengal with a positive rate of 5%. All the positive samples showed two bands for heterozygous mutation of Factor V Leiden, while the wild type showed 3 bands.

IV. Discussion

The present study was carried out in patients with various clinical conditions such as, spontaneous DVT, post- surgical venous thrombosis, hemorrhagic infarct, stroke, unexplained DVT, primary DVT, hypercoagulable state and pregnant women with history of miscarriages. 20 out of 94 patients had FVL, our findings were similar to the largest series reported from Singapore.

As per Gupta et al both these polymorphisms were totally absent in Indian population, and cannot be considered as independent risk factors or as a predictor for CAD (Gupta N et al. 2003). Factor V Leiden and G20210 prothrombin gene mutations are infrequent in Indian patients with PVT and are unlikely to be responsible for PVT in the Indian population (Sharma S et al. 2006).

There were no association of FVL mutation and prothrombin gene mutation in genetic predisposition to CADs and MI in north Indian population. The discrepancies in studies relating to FVL mutation and FII G20210A allele to CADs may be due to difficulties in estimating low allelic frequency in general population (Gupta N et al. 2003).

The prevalence have been estimated for Poland (Warsaw) 5.0%, Argentina (Buenos Aires) 5.1%, Venezuela (Valencia) 1.6%, Costa Rica (San José) 2.0%, and India (Punjab) 1.3%. Based on worldwide distribution, it can be hypothesized that the factor V Leiden mutation has originated and accumulated in central European Caucasians and spread over the world by migration (Herrmann FH et al 1997). The allele frequency in 618 Europeans was 4.4%, with the highest prevalence among Greeks (7%) and 0.6% in Asia Minor. Factor V Leiden was not found in any of 1600 chromosomes from Africa, Southeast Asia, Australasia, and the Americas, which explains the rarity of thromboembolic disease in these populations (Rees DC et al 1995).

FVL mutations, usually rare in populations other than Caucasians, exceptions do exist. In Asian-In¬dian populations 1% to 8.5% has been reported. In Tamil Nadu, south India, 4 out of the 72 were reported to be heterozygous for FVL mutation (5.5%). Another study

was aimed at finding a possible association between portal vein thrombosis and FVL, and it reported a slightly lower prevalence in its control group of healthy Indians (4.1% were heterozygous for this mutation). However, contradic¬tory results were found when the presence of this mutation was studied in healthy populations from Turkey, Korea, and even from some Indian populations). Singapore report says 10.74% (6.84, 14.64) of Indian pa¬tients were positive for FVL mutation, while less than 0.5% and 1.83% were detected as positive among Chinese and Malay patients respectively (Wan Zaidah Abdullah et al 2009). The factor V Leiden mutation is associated are two to three times more likely to have recurrent miscarriages or a pregnancy loss during the second or third trimester (genetic home reference).

VTE consists of 2 related conditions: deep vein thrombosis (DVT) and pulmonary embolism (PE). Between 20% and 60% of patients with recurrent VTE display APC resistance on laboratory testing, which is mostly due to mutation in the factor V gene. Among the European white population, the factor V Leiden mutation is the most prevalent hereditary thrombophilia. Approximately 4% to 6% of the general population are heterozygous for this trait (which is autosomal dominant), but it is extremely rare among native populations of Africa, Southeast Asia, and Australia (Frederick A et al).

The presence of the mutation markedly increases the risk for renal vein thrombosis, particularly in neonates, and renal transplant vein thrombosis in transplant cases resulting in rejection. Routine screening for factor V Leiden mutation by polymerase chain reaction, and appropriate perioperative and postoperative anticoagulation after renal transplantation might be a valuable strategy to prevent thromboembolic complications in transplant recipients (R P Wüthrich et al).

The prevalence of FVL in the general population varies from 0% to 7%, which is common in Europe and being almost absent in Africa and the Middle East. In patients with venous thrombosis, the prevalence is higher at 19% in the Netherlands and 39% in northern India but is only 3% in Mumbai. In patients with PVT, the prevalence is 7.6% in the Netherlands and 8% in Mumbai. The highest prevalence of 30% has been reported in a study of Egyptian children with PVT (Abraham Koshy et al).

In our study, 20 patients were positive for heterozygous mutation, of which 11 were males and 9 were females who had clinical history of thromboembolic disorders. Particularly 9 females in the reproductive age group most probably with a history of eclampsia. One male baby one day old was positive from AP.

Patients with recurrent thrombotic events related to factor V Leiden mutation have been reported, e.g. deep venous thrombosis in the lower limb followed by cerebral venous thrombosis resulting in quadriplegia. Awareness of the condition and a high index of suspicion is needed to prevent life-threatening complications. It is important to screen all patients less than 50 years of age presenting with spontaneous lower limb deep venous thrombosis are screened for factor V Leiden mutation (Meenakshi et al).

Molecular and epidemiological studies provide evidences that FVL should have occurred as a single event in the past. The Mediterranean region has the highest prevalence of FVL in the world, suggesting the origin of mutation possibly 10,000 years ago, and later spread to other parts of the world (Herrmann FH et al).

Venous thrombosis is a common problem, predominantly affecting people of European origin. This European predisposition has been explained to some extent by the recent characterization of factor V Leiden, and the G20210A prothrombin variant. Analysis of 22 samples for FVL from different non-European countries showed that prothrombin variant is very rare outside Europe except for one case from India (Rees DC et al).

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