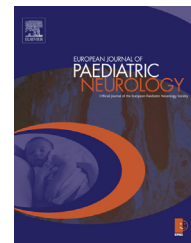




Official Journal of the European Paediatric Neurology Society



## Original article

# Fibrinogen alpha and beta gene polymorphisms in pediatric stroke – Case–control and family based study



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## ARTICLE INFO

## Article history:

Received 4 October 2014

Received in revised form

27 November 2014

Accepted 28 November 2014

## Keywords:

Stroke

Children

FGA gene

FGB gene

Gene polymorphism

## ABSTRACT

**Background/purpose:** Data on the role of the –455G > A polymorphism of the gene encoding  $\beta$  fibrinogen subunit (FGB) and the Thr312Ala polymorphism of the gene for the  $\alpha$  fibrinogen subunit (FGA) in childhood ischemic stroke are insufficient. Therefore the aim of the study was to evaluate a possible association between these two polymorphisms and arterial ischemic stroke.

**Methods:** The study group consisted of 85 children after ischemic stroke, 146 of their parents and 159 controls. Both polymorphisms were genotyped using the restriction fragment length polymorphism method. Two study designs were used: a case–control model and a family-based transmission-disequilibrium test. Statistica 7.1 and EpiInfo 6 softwares were used in all analyses.

**Results:** In the TDT test, a tendency to a higher transmission of the 312Ala allele of the FGA gene and the –455A allele of the FGB gene was observed, however, it was statistically non-significant. The frequencies of alleles and genotypes of both FGA and FGB genes polymorphisms did not differentiate children from both groups also in the case–control model. Additive or synergistic effects between FGA and FGB genes polymorphisms were not observed.

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<http://dx.doi.org/10.1016/j.ejpn.2014.11.011>

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**Conclusion:** An analysis of the results obtained in this study and a critical review of previously published data indicate that examined gene polymorphisms are not related to ischemic stroke in children.

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## 1. Introduction

Arterial ischemic stroke (AIS) in children is a disorder of the estimate frequency of 3 per 100,000 children per year; it seems to be a rather rare condition but it is one of the ten most common causes of death in this group of patients. A history of acute brain ischemia is related to various neurological consequences such as motor impairment (most commonly – hemiparesis) and seizures (up to 70% of all AIS children), speech impairment, psychomotor developmental delay, stroke recurrence (about 20%) and death (10% of pediatric AIS patients).<sup>1,2</sup> The most frequently reported risk factors of pediatric AIS are cerebral arteriopathies, cardiac disorders, head traumas, infections and metabolic diseases, like mitochondrial encephalopathies and prothrombotic disorders. As the childhood AIS has a multifactorial etiology it probably also has a multigenic inheritance pattern.

The frequency of the prothrombotic state leading to hypercoagulability in children is estimated to be 20% to 50% in most studies.<sup>3</sup> This is why genes encoding elements involved in homeostasis regulation are the most important targets in searching for genetic determinants of childhood onset AIS.

Fibrinogen is a 340-kDa dimeric glycoprotein; each dimer consists of 3 different subunits known as  $\alpha$ ,  $\beta$  and  $\gamma$  chains linked by disulfide bonds. Each polypeptide subunit is encoded by a different gene and all 3 genes are clustered on chromosome 4 in region q28. The 3 genes are arranged in the following order as FGA (for the  $\alpha$  chain), FGB (for the  $\beta$  chain) and FGG (for the  $\gamma$  chain) span a distance of about 50 kb with the direction of transcription of the FGB gene opposite to the FGA and FGG genes.<sup>4</sup> The experimental data suggest that the synthesis of the  $\beta$  fibrinogen subunit is a crucial step in the assembly of mature fibrinogen and this seems to be the most important factor affecting the level of plasma serum fibrinogen.<sup>5,6</sup>

The data on adult patients suggest that  $-148C > T$ ,  $-448G > A$  and  $-455G > A$  polymorphisms of the FGB gene are associated with ischemic stroke of large vessels in adults.<sup>7–9</sup>

According to some authors, the Thr312Ala (c.154586438A > G) variant of the FGA gene lowers plasma fibrinogen levels to a modest extent. Additionally, in adults, GG homozygotes had decreased fibrinogen levels and a decreased risk of ischemic stroke when compared with AA homozygotes.<sup>10</sup> Contrary to previous results, the study of Titov et al. showed that the A allele carrier state of the FGA gene Thr312Ala polymorphism revealed a protective effect on ischemic stroke when occurred in combination with the CC genotype of the *IL6* (interleukin-6) gene  $-174G > C$  polymorphism,<sup>11</sup> whereas another study showed that haplotypes

of FGA and FGG genes, were associated with ischemic stroke.<sup>12</sup> This association was independent of fibrinogen levels, thus suggesting that the association between ischemic stroke and variation in the FGA/FGG genes was mediated by qualitative rather than quantitative effects on fibrinogen.<sup>12</sup>

The data on the role of the FGB  $-455G > A$  polymorphism and especially of the FGA Thr312Ala polymorphism in childhood ischemic stroke are insufficient. The aim of the study was to evaluate a potential association between both the polymorphisms and AIS using case–control and family-based models. Moreover, we have evaluated the additive/synergistic effects of FGA and FGG genes polymorphisms.

## 2. Materials and methods

The study group consisted of 375 individuals, including 85 children after ischemic stroke, 146 of their biological parents and 144 controls. All studied subjects were white Polish Caucasians. Patients were recruited from the Department of Neuropediatrics at the Medical University of Silesia in Katowice (44 patients + 140 controls), the Department of Neurology at the Polish Mother's Memorial Hospital-Research Institute in Lodz (10 patients), the Department of Developmental Neurology at the Medical University of Gdansk (18 patients + 4 controls) and the Department of Pediatric Neurology at the Polish-American Children's Hospital Collegium Medicum at the Jagiellonian University of Krakow (13 patients). The age of patients at the acute phase of stroke was 6 months up to 18 years (mean age  $8.8 \pm 5.6$ ). There were 37 girls (43.2%) and 48 boys (56.8%). The diagnosis of AIS was based on clinical symptoms and brain imaging techniques. Neurological and neuroimaging examinations were performed at least twice (at the acute phase and in the follow-up). The control group consisted of age and sex matched children without any symptoms of stroke or other vascular diseases. The study protocol was approved by the Ethics Committee of Medical University of Silesia in Katowice and written consents were submitted by parents of the patients.

### 2.1. Genetic analysis

Genomic DNA was extracted from peripheral blood leukocytes using the MasterPure genomic DNA purification kit (Epicentre Technologies). All polymorphisms were genotyped using the restriction fragments length polymorphism (RFLP) method. We used the methods described previously by Nishiuma S et al. (FGB  $-455G > A$  polymorphism, rs1800790) and by Carter A et al. (FGA Thr312Ala polymorphism, rs6050) with some own

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