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Blood 142 (2023) 5471–5472

The 65th ASH Annual Meeting Abstracts

ONLINE PUBLICATION ONLY

321.COAGULATION AND FIBRINOLYSIS: BASIC AND TRANSLATIONAL

Evaluation of Innovative Laboratory Tests to Predict a Thrombotic Phenotype in a Family with Dysfibrinogenemia and a Novel *FGG* Mutation

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Background:
Hypodysfibrinogenemia is a rare hereditary fibrinogen disorder characterized by quantitative and qualitative fibrinogen defects. These fibrinogen defects can cause thrombotic and hemorrhagic phenotypes. Unfortunately, predicting the phenotype in a specific patient is often not possible with routine coagulation tests.
Aims:
To characterize the phenotype and the genetic profile of a family with hypodysfibrinogenemia and to investigate the ability of innovative tests to predict bleeding and/or thrombotic phenotypes in asymptomatic family members.
Methods:
The proband, a 60-year-old woman with both bleeding and thrombotic complications who is currently on DOAC treatment, and two daughters were referred to our Hemophilia Treatment Center (HTC) for phenotypical and genotypical analysis of a congenital fibrinogen disorder (CFD). Extensive laboratory testing was done, as well as DNA-sequence analysis and molecular modelling. Thrombin generation and microfluidic testing were also performed to investigate their ability in phenotype prediction.
Results:
Fibrinogen activity and antigen levels led to the diagnosis of dysfibrinogenemia in the proband and hypodysfibrinogenemia in both daughters. In all three cases, the same heterozygous missense mutation in the *FGG* gene was uncovered. This likely pathogenic mutation leads to the p.(Tyr375Cys) amino acid change. Molecular modeling predicted possible conformational changes or covalent dimerization of the fibrinogen molecule. Thrombin generation was elevated in one daughter. Microfluidic testing showed enhanced fibrin formation in both daughters, regardless of the coagulation trigger.
Conclusion:
We described a family with hypodysfibrinogenemia in whom a novel heterozygous missense mutation in the *FGG* gene was found, possibly leading to conformational changes or covalent dimerization of the fibrinogen molecule. Furthermore we

showed that microfluidic testing and thrombin generation can indicate a thrombotic phenotype in these patients, not detected with routine coagulation tests.

Disclosures De Simone: *Diagnostica Stago:* Other: Synapse Research Institute is part of the Diagnostica Stago group.

https://doi.org/10.1182/blood-2023-181894