Contact information to the presenting author:
Marie Skogstad Le
Department of medical biochemistry,
Section for hemostasis and thrombosis (SHOT)
Oslo University hospital, Oslo, Norway
E-mail: UXRIOG@ous-hf.no

We have no conflicts of interest

PATIENT WITH FREQUENT NOSEBLEEDS AND DYSPROTHROMBINEMIA CAUSED BY THE HOMOZYGOUS MUTATION ALA563VAL (*F2* GENE) HAD ABSENT THROMBIN GENERATION

Carola Henriksson[4,5], Marie Skogstad Le[4], Marit Sletten[3], Marit Hellum[4,5], Nina Iversen[3], Heidi Glosli[1,2]

[1]Centre for Rare Disorders, Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

[2]Division of Paediatric and Adolescent Medicine, Oslo University Hospital, Oslo, Norway

[3]Department of Medical Genetics, Oslo University Hospital, Oslo, Norway

[4]Department of Medical Biochemistry, Oslo University Hospital, Oslo, Norway

[5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway

Background and aim: Prothrombin (FII) deficiency is a very rare bleeding disorder (1:2 mill.), which may be inherited or acquired. Inherited dysprothrombinemia is an autosomal recessive disorder associated with moderate to severe increased bleeding tendency. We report on a three-year old boy with frequent nosebleeds, and the aim was to identify the causative mutation and to elucidate the thrombin generating capacity in the proband and his closest family.

Methods: Mutation analysis of the *F2* gene was performed by Sanger sequencing of all the 14 exons and the exon/intron boundaries. Clotting time coagulation analyses, FII-antigen/activity and thrombin generation (TG) were performed to characterize the effect of the mutation and to optimize the treatment.

Results: The patient was homozygous for a missense mutation in exon 13 at position c.1688 C>T (Ala563Val), a mutation only previously described in a compound heterozygous patient. The boy had dysprothrombinemia, with evidently prolonged prothrombin time Quick and APTT, strongly reduced FII-activity (~1%), and normal FII-antigen. In the TG assay, the proband did not display any thrombin generation. The proband's parents (first cousins) and one of the two sisters were carriers, the other sister was normozygous, all of them asymptomatic. The heterozygous family members had FII-activity of ~50%, and compared with the normozygous sister, the TG (parameter: peak) was reduced by 50%. Octaplex®-treatment was initiated every fortnight, and TG was measured at peak concentration of the drug, and 1, 2, 7, and 14 days (through concentration) after drug injection. TG was ~50% compared to the normozygous sister

at peak concentration, and decreased rapidly. Treatment with Octaplex® was changed to once a week, and the nosebleeds disappeared.

Conclusion: Measurement of thrombin generation may be a potential tool to monitor treatment in patients with severe dysprothrombinemia, and to estimate the thrombin-generating capacity of heterozygotes with borderline FII-activity levels.