

Novel ADAMTS-13 Mutations in an Obstetric Patient with Upshaw Schulman Syndrome

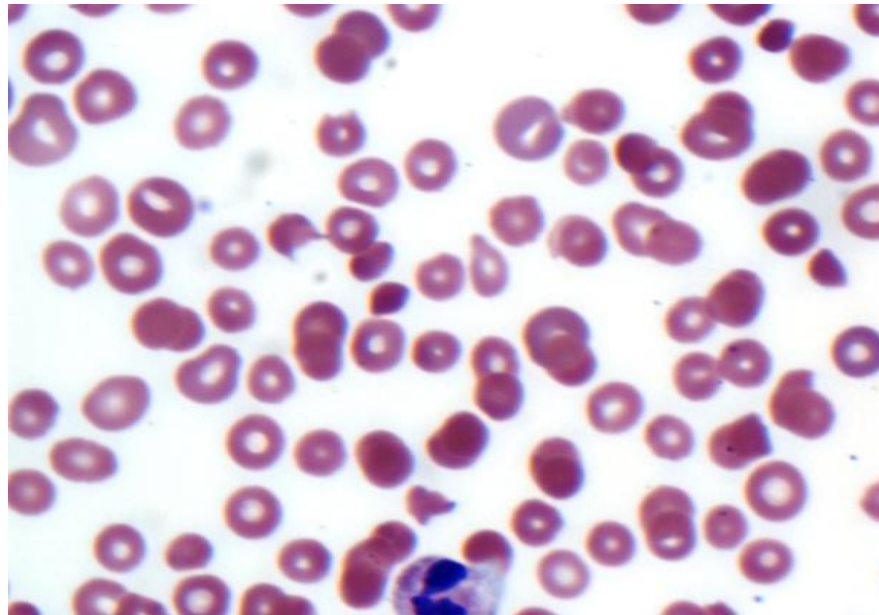
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Case Report

- 21 y/o G1P0 with no past medical history
 - 34 weeks gestation: noticed a “rash” on her neck from the seatbelt.
 - 35 weeks gestation: presented to a local clinic complaining of unilateral vision impairment; an on-call ophthalmologist diagnosed retinal detachment and she was sent home.

Case Report

- Presented the following morning to ER with bilateral blurry vision and cessation of fetal movements
 - Bilateral retinal detachments and fetal demise were confirmed
- CBC showed hemolytic, schistocytic anemia and evolving thrombocytopenia
 - Hematocrit: 16.9
 - Platelet count: 20,000



Case Report

- Patient transferred to UAB where a clinical diagnosis of TTP was made
 - ADAMTS-13 activity → <5% enzyme activity without the presence of an inhibitor/autoantibody; multiple repeat assays showed similar results
 - Plasmapheresis was initiated; the patient recovered after six rounds of TPE and vision returned to normal
- Congenital TTP was suspected
 - Persistent absence of inhibitor despite low activity levels
 - Rapid platelet recovery following TPE (normalization after three procedures)

Thrombotic Thrombocytopenic Purpura

- Incidence of TTP is 4-11 patients per million per year in the United States
- Acquired TTP is caused by an autoantibody to ADAMTS-13, also known as von Willebrand factor (vWF) cleaving protease
- ADAMTS-13 deficiency results in an accumulation of ultra-large multimers of vWF leading to severe thrombocytopenia due to spontaneous platelet aggregates in the systemic circulation

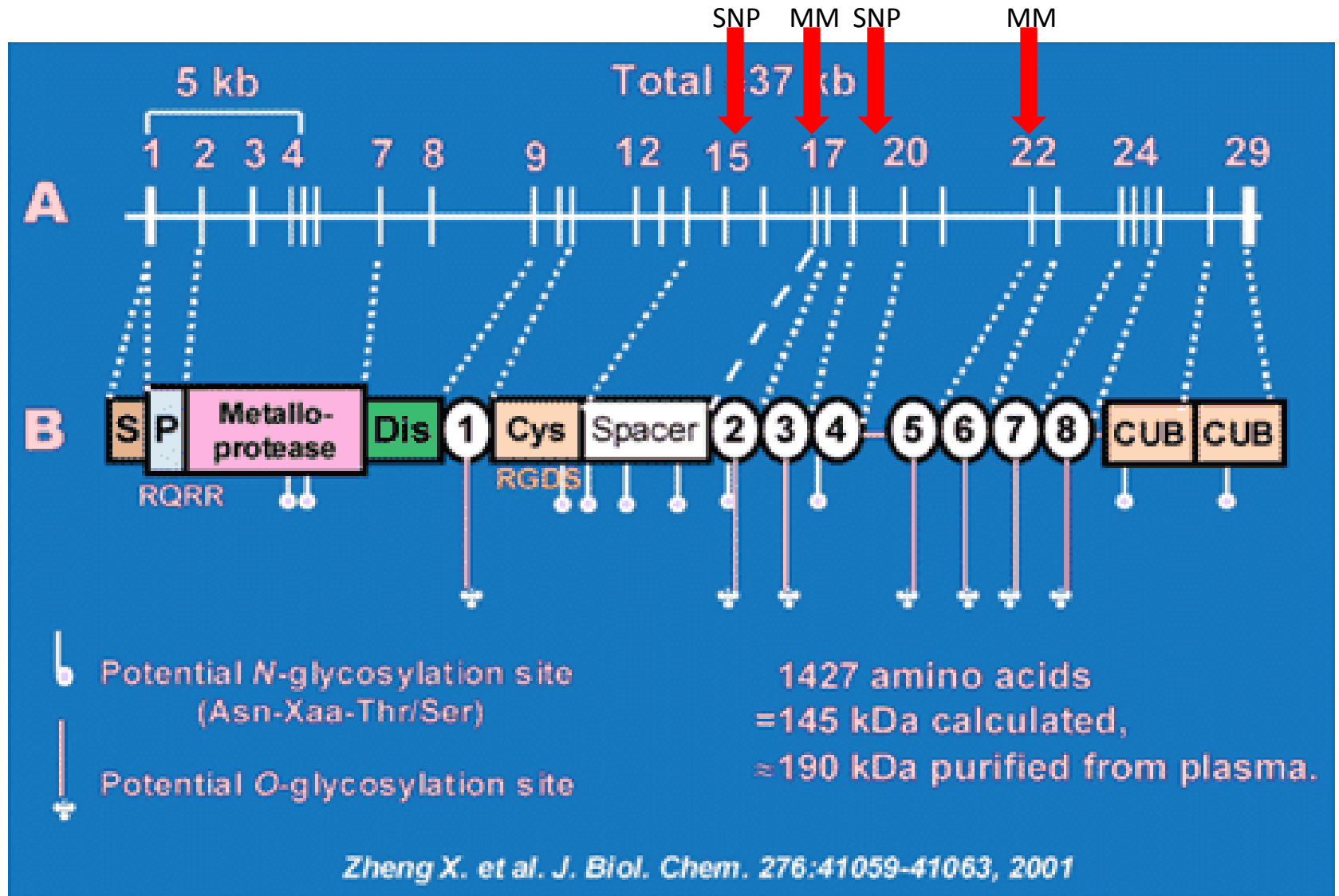
Upshaw-Schulman Syndrome

- Causes
 - Congenital TTP (Upshaw-Schulman Syndrome or USS) is characterized by mutations in the ADAMTS-13 gene resulting in a deficient or defective enzyme.
 - Half of reported cases manifest in infancy or early childhood
 - Other half had first episode during late pregnancy (2nd and 3rd trimester)
 - Pregnancy-related plasma changes include increase in vWF and decrease in ADAMTS-13
- Symptoms
 - Identical to acquired type
- Treatment
 - Plasma exchange in acute TTP
 - Varying degrees of prophylaxis with regular plasma infusions

ADAMTS-13 Sequencing

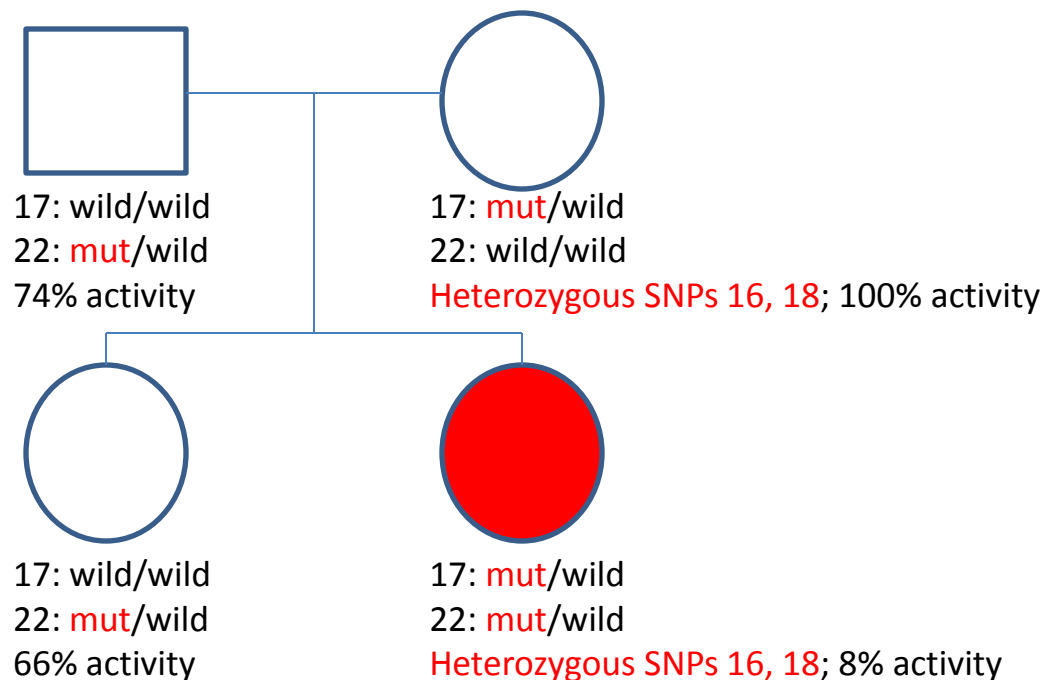
- Specimens from the patient and 1st degree family members were sent to the Hemostasis Research Laboratory at Bern University Hospital, Switzerland for ADAMTS-13 genotyping
- Patient is compound heterozygous for two novel missense mutations
 - maternal exon 17 (Ala 690 Thr due to nucleotide substitution 2068 G→A)
 - paternal exon 22 (Arg 915 Cys due to nucleotide substitution 2746 C→T)
- Two previously described maternally inherited single nucleotide polymorphisms (SNPs) shown to reduce enzyme secretion and activity
 - SNPs P618A (exon 16) and A732V (exon 18)

ADAMTS-13 Gene



Results

- Father, mother, and sister all had normal or near-normal enzyme activity despite heterozygosity for one of the mutations
- USS manifested as a result of multiple genetic lesions



Future Management

- Patient continues to be in remission
- Regular follow-up and laboratory testing with Family Medicine, Hematology, and OBGYN
- Birth control with progesterone-only Implanon (skin implant)
- Future conception questionable
 - Adoption
 - Hysterectomy
 - Possibility of prophylactic plasma infusions starting second trimester

Clinical Impact

- Emergent hematologic evaluation should be considered in pregnant patients presenting with visual deficits
- Importance of ADAMTS-13 activity/inhibitor testing and genetic evaluation for Upshaw Schulman Syndrome in the Obstetric patient
- Enzyme level/genotyping for family members of those with USS

QUESTIONS?