**Supplemental Method file**

**Genetic analysis**

Considering the extent and severity of thrombosis that occurred, an inherited predisposition to hypercoagulability was suspected. In order to determine possible unknown mutations in the coagulation pathway, circulating cell-free DNA was extracted from a cryopreserved serum sample obtained preoperatively. Following the manufacturer’s protocol, a sequencing library was constructed using the KAPA LTP Library Preparation Kit (Kapa Biosystems, Inc., Wilmington, MA) combined with a SureSelect XT V4+UTR Kit (Agilent), and sequenced on the Illumina Hiseq2500 sequencer (Illumina, Inc, San Diego, CA) using paired-end 2x100 base length reads. Generated reads were aligned with the hg19 human reference genome using the Burrows-Wheeler alignment 1. Variant detection and analysis was performed using the GATK (Broad Institute) algorithm run on the Illumina BaseSpace Web platform (*basespace.illumina.com*). The following coagulation pathway genes were analyzed for non-synonymous variants: F2, F2R, F3, F4, F5, F7, F8, F9, F10, F11, F12, F13, FG, TFP1, SERPIN1, SERPINC1, SERPINA5, SERPINA1, SERPINF2, SERPINE1, SERPIND1, CPB2, vWF ,THBD, PROC, PROS1, A2M, PLG, PLAUR, PLAT, and PLAU. Selected polymorphisms were verified with DNA from the patient’s liver samples using selected gene fragment PCR amplification, followed by direct Sanger sequencing using an ABI 3130XL Capillary Sequencer (Applied Biosystems, Foster City, CA). For further verification, reverse-transcription PCR was performed on RNA isolated from formalin-fixed liver samples, followed by selected cDNA fragment PCR amplification and direct Sanger sequencing.

**Results**

Single nucleotide variants (SNVs) identified with exome sequencing included: 96,203 total SNVs, 42,260 exonic SNVs, 22,337 coding sequence SNVs, and10,516 non-synonymous SNVs. All non-synonymous variants detected in coagulation pathway genes are presented in Table 2. One variant in SERPINC1 (Table 2 (in bold)), has not been previously reported. This single nucleotide polymorphism (SNP) causes a missense mutation (A to G base change (T to C on the complementary strand) in chromosome 1: 173873157) in exon 7 of the SERPINC1 gene. This results in an amino acid change of isoleucine to threonine in position 422 of antithrombin III (ATIII) (NP\_000479.1). This genomic mutation was subsequently verified by direct Sanger sequencing of both the patient’s DNA and mRNA transcription of SERC1A from the patient’s liver sample (Figure 2).

The potential for this mutation having functional consequences was estimated using DUET, a web based computational program to study missense mutations in proteins (http://bleoberis.bioc.cam.ac.uk/duet/). DUET uses two complementary approaches to mutation analysis (mCSM and SDM), resulting in a consensus prediction obtained by using Support Vector Machines (SVM). We demonstrated that this method uniformly predicted the destabilizing effects of the new mutation on ATIII (Supplemental Figure 3).

Of note is that sequencing of the mRNA SERPINC1 reverse-transcript indicates allele-specific gene expression (i.e., presence of only the alternate base in the mRNA sequence)2. No other potentially damaging variants were observed in any coagulation pathway genes (Table 2).

1. Li H, Durbin R. Fast and accurate short read alignment with Burrows-Wheeler transform. Bioinformatics 2009;25:1754-60.

2. Buckland PR. Allele-specific gene expression differences in humans. Human molecular genetics 2004;13 Spec No 2:R255-60.