**NCBI Case Study Workflow-based Answer**

**Symptoms/Clinical Features & Preliminary Diagnosis**

James – Serious blood clotting problem

Raven – Some evidence of a minor bleeding problem

**Clinical information**

**Blood & Gene Test Results**

James – His very high INR & APTT (very slow clotting time) and effectively absent of Factor IX (F9) levels is suggestive of severe Hemophilia B. He has one variant copy of the F9 gene, F9:c.223C>T, p.R75X. A termination (stop) codon exists at position 73 of the F9 coding region instead of the “normal” Arginine codon. This is a known pathological variant and causative of Hemophilia B.

Raven – Based on a medical history suggesting “minimal bleeding problems” with high measured INR & APTT (slow clotting time) and decreased Factor IX (F9) levels, it appears that she may be a carrier of one variant F9 gene. She has one “normal” and one of the same variant copy of the F9 gene that her son has inherited. She is heterozygous for Hemophilia B, which has been shown to by symptomatic under stressed conditions.

**Gene information**

F9 is a critical gene product in the blood clotting cascade (it cuts and activates the activator of the common clotting pathway).

It is encoded on the “X” chromosome.

James (a male, ♂) has only one copy of this gene.

Raven (a female, ♀) has two copies of this gene — in some cases, when not under stress, a “normal” gene can produce enough protein to compensate for a pathogenic variant gene.

**Protein information**

This particular variant causes a premature termination (X) very “early” in the production of the protein. The critical region for the function of this protein (Trp, SpC) is never made, thus it can’t perform it’s normal function.

**Molecular Pathway information**

James – Expresses only a truncated protein, so his F9 protein can’t activate the common clotting pathway.

Raven – Expresses one “normal” copy of the F9 protein so, except under stressed conditions, she can clot sufficiently.