May 2023: Discovering Molecular Mechanisms of Genetic Disorders with NCBI Resources
Exercise 2 Answers

Leslie's Case	NOTES
Phenotype	40-year-old female was referred after a visit to her primary care physician with complaints of constipation, bloody stools and chronic abdominal pain. An ultrasound shows a 2cm diameter mass on her descending colon. She has a personal history of colonic polyps that had been managed by a previous gastroenterologist and the medical records are not available. Upon questioning, she mentioned a family history of several relatives on her maternal side including grandmother, mother and uncle who had been diagnosed with "multiple bouts" of various forms of cancers including breast, endometrium, and colon.
Preliminary Diagnosis	Lynch Syndrome
Genetic Variation(s)	MSH2 p.Glu48|p.Glu48Ter & MSH2 g.4951T|g.4951T>C
Laboratory Assertion(s)	pathogenic, autosomal dominant & benign (respectively)
Variant Information: • Asserted interpretation listed in **ClinVar** • HGVS names from **ClinVar** • Is population data available in **dbSNP**?	pathogenic & benign (respectively)
	(only moved forward with the one designated as pathogenic) NG_007110.2(MSH2):g.5210G>T NP_000242.1(MSH2):p.Glu48Ter
	rs63750615 Yes! A very, very rare variant.
Gene Information in NCBI Gene: • Symbol and Name	MSH2 & mutS homolog 2
• Gene Summary	This locus is frequently mutated in hereditary nonpolyposis colon cancer (HNPCC). When cloned, it was discovered to be a human homolog of the E. coli mismatch repair gene mutS, consistent with the characteristic alterations in microsatellite sequences (RER+ phenotype) found in HNPCC. … [provided by RefSeq, Apr 2012] *Related articles indicate significant role in DNA damage and repair.*
• Tissue Expression information	Almost ubiquitous tissue expression.
• Gene Ontology information	In Nucleus as part of MutSalpha or MutSbeta complex Mismatch sensing, repair activity & recombination regulation
Ultimate Impacted Biomolecule based on: • **GDV** to view the chromosome and gene region	NP_000242.1(MSH2):p.Glu48Ter is located in the coding region within exon 1.
• **RefSeqGene Graphics** view of gene region and transcript(s)	The coding sequence terminates after only 48 residues – producing a non-functional peptide destined for degradation.
• **RefSeq Protein Graphics** view of protein and domains • **CDD or iCn3D** to view a structure, *as needed*	3D structure of the MSH2/MSH6/DNA complex show that the first 48 residues do not make up the protein-protein interaction domain. Thus, it is likely it will never form a functional complex.
Proposed Molecular Mechanism of Variant Impact	As the premature termination of the protein prevents the majority of the protein (including most of its functional portion) to be made, it cannot to join in to form either of the MutSalpha or MutSbeta complexes. Thus, the loss of this one protein will result in the loss of a fully functional DNA damage sensing and repair mechanism.
How does this relate back to the phenotype (symptoms/clinical features & diagnosis)?	Without a fully functional DNA damage and repair mechanism, over the lifespan – somatic mutations (variations) will accumulate and not be repaired. Eventually this is likely to cause dysregulation of cell cycle regulation and the progression of cells to masses, tumors and malignant neoplasia.