Ambry Genetics
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FINAL REPORT - 11/24/2025

Ordered By	Contact ID:7046493	Org ID:22797	Patient Legal Name: **Kiani, Ayesha**
Medical Professional:	Hou, June, MD		Accession #: **25-743747** Specimen #:
Client:	Columbia Gyn Onc (25663)		AP2 Order #: 3392141 Specimen: Blood EDTA (Purple top)
			Birthdate: 06/25/1985 Sex assigned at birth: F
			MRN #: 1011021118 Collected: 11/04/2025
			Indication: Family history Received: 11/05/2025
			Test Started: 11/05/2025

CancerNext-Expanded® +RNAinsight®: Analyses of Genes Associated with Hereditary Cancer (77 genes)

RESULTS

MBD4	**Pathogenic Mutation:**	**c.1293delA/c.1293delA**
PDGFRA	Variant, Unknown Significance:	p.S755P

SUMMARY

POSITIVE: Pathogenic Mutations Detected

INTERPRETATION

- This individual is homozygous for the **c.1293delA (p.K431Nfs*54)** pathogenic mutation in the *MBD4* gene.
- This result is consistent with a diagnosis of *MBD4*-associated neoplasia syndrome (MANS).
- **Risk estimate**: increased risk for acute myelogenous leukemia and colorectal cancer.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

This individual is also heterozygous for the p.S755P (c.2263T>C) variant of unknown significance in the *PDGFRA* gene, which may or may not contribute to this individual's clinical history. Refer to the supplementary pages for additional information on this variant. No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (77 total): ***AIP, ALK, APC, ATM, BAP1, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CEBPA, CHEK2, DICER1, ETV6, FH, FLCN, GATA2, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH6, MUTYH, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RET, RPS20, RUNX1, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** **and** ***WT1*** **(sequencing and deletion/duplication);** ***AXIN2, CTNNA1, DDX41, EGFR, HOXB13, KIT, MBD4, MITF, MSH3, PDGFRA, POLD1*** **and** ***POLE*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only).** RNA data is routinely analyzed for use in variant interpretation for all genes.

MBD4 **Additional Information**

The **c.1293delA** pathogenic mutation, located in coding exon 5 of the *MBD4* gene, results from a deletion of one nucleotide at nucleotide position 1293, causing a translational frameshift with a predicted alternate stop codon (p.K431Nfs*54). This variant was reported in individual(s) with features consistent with MBD4-associated neoplasia syndrome (MANS) (Ambry internal data). This alteration is expected to result in loss of function by premature protein truncation or nonsense-mediated mRNA decay. As such, this alteration is interpreted as a disease-causing mutation.

The *MBD4* gene (NM_001276270) is located on chromosome 3q21.3, encodes the methyl-CpG-binding domain protein 4, and contains 8 coding exons. Pathogenic variants in this gene are known to cause *MBD4*-associated neoplasia syndrome (MANS), which is inherited in an autosomal recessive fashion. Biallelic pathogenic variants in *MBD4* confer a significantly increased risk for gastrointestinal adenomatous polyposis, colorectal cancer (CRC), and acute myelogenous leukemia (AML) or myelodysplastic syndrome (MDS). Additional tumors have been reported in

the literature (including uveal melanoma, schwannoma, and meningioma); however, current evidence for these tumor risks is limited. Average age of onset is in the third decade of life, and *MBD4*-deficient tumors exhibit a distinct mutational signature known as SBS96, characterized by an accumulation of somatic CpG>TpG mutations. Penetrance in MANS is incomplete, and variable expressivity is observed; therefore, cancer risks will differ based on individual and family history (Palles C, et al. (2022) *Am J Hum Genet* 109(5):953-960; Terradas M, et al. (2023) *Eur J Hum Genet* 31(10):1185-1189). Heterozygous pathogenic variants in *MBD4* have been reported in individuals with uveal melanoma and other cancers; however, current evidence is insufficient to support a clear increase in risk of cancer over that of the general population (Villy, 2024;Derrien, 2021). Biallelic loss of function has been reported as the mechanism of disease for MANS.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- CancerNext-Expanded® +RNAinsight® (Product Code 8875-R)

ELECTRONICALLY SIGNED BY

Martin P. Powers, M.D., FCAP, on 11/24/2025 at 08:41:40 am