

MOLECULAR GENETIC ANALYSIS REPORT

Patient Name-Surname	: *****	Protocol Number	: *****
Identification Number	: *****	Date of birth/Gender	: *****
Sample Type	:Edta'lı Periferik Kan	Type of Test	:CES (Klinik Ekzom Dizileme)
Reference Doctor	: *****	Reference Institution	:Medical Corner
Sample Arrival Date	: 12.06.2026 18:38	Sample Acceptance Date	: 15.06.2026 08:50
Report Date	:18.08.2026 12:00	Sample Collection Date	: 15.06.2026 09:00
Indication	: Colorectal cancer		

Result

The individual's data were evaluated as part of the **NGS FOCUS Hereditary 113** test, prioritizing the phenotype "**Neoplasm of the colon (HP:0100273)**" together with the available clinical information. No pathogenic or likely pathogenic variants were detected within the scope of this test. However, **variants of uncertain significance (VUS)** considered clinically relevant for further evaluation were detected in the **RUNX1, CTRC, FLCN, RET, and ERCC6** genes. The variants reported in the **CTRC** and **RUNX1** genes have been classified as pathogenic/likely pathogenic in ClinVar.

MLPA analysis was performed on DNA isolated from the patient's peripheral blood sample to evaluate the presence of deletions and/or duplications in the **BRCA1** and **BRCA2** genes. No deletions or duplications were detected in the **BRCA1** or **BRCA2** genes.

REPORT EXPLANATIONS:

The **RUNX1** gene encodes a protein involved in the differentiation of hematopoietic cells and the regulation of blood cell development. In OMIM, monoallelic pathogenic variants in the **RUNX1** gene have been associated with "**Leukemia, acute myeloid**" and "**Platelet disorder, familial, with associated myeloid malignancy.**" A heterozygous variant was identified in the **RUNX1** gene. This variant was classified as a **VUS** according to ACMG criteria and has been reported in ClinVar with classifications including **likely pathogenic, VUS, likely benign, and benign. Genetic counseling is recommended.**

The **CTRC** gene encodes a protein involved in the regulation of digestive enzyme activation in the pancreas. In OMIM, monoallelic pathogenic variants in the **CTRC** gene have been associated with "**Pancreatitis, chronic, susceptibility to.**" A heterozygous variant was identified in the **CTRC** gene. This variant was classified as a **VUS** according to ACMG criteria and has been reported in ClinVar with classifications including **pathogenic, VUS, and benign. Genetic counseling is recommended.**

The **FLCN** gene encodes a protein involved in the regulation of cell growth, energy metabolism, and the mTOR signaling pathway. In OMIM, monoallelic pathogenic variants in the **FLCN** gene have been associated with "**Birt-Hogg-Dubé syndrome**" and "**Pneumothorax, primary spontaneous.**" A heterozygous variant was identified in the **FLCN** gene. This variant was classified as a **VUS** according to ACMG criteria and has been reported in ClinVar with classifications including **VUS, benign, and likely benign. Genetic counseling is recommended.**

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The **RET** gene encodes a protein involved in cell growth, differentiation, and signal transduction. In OMIM, monoallelic pathogenic variants in the **RET** gene have been associated with “**Medullary thyroid carcinoma,**” “**Multiple endocrine neoplasia type IIA,**” “**Multiple endocrine neoplasia type IIB,**” “**Hirschsprung disease, protection against,**” “**Hirschsprung disease, susceptibility to, 1,**” and “**Pheochromocytoma.**” A heterozygous variant was identified in the **RET** gene. This variant was classified as a **VUS** according to both ACMG criteria and ClinVar. **Genetic counseling is recommended.**

The **ERCC6** gene encodes a protein involved in the repair of DNA damage through transcription-coupled nucleotide excision repair. In OMIM, monoallelic pathogenic variants in the **ERCC6** gene have been associated with “**Lung cancer, susceptibility to,**” “**Macular degeneration, age-related, susceptibility to, 5,**” and “**Premature ovarian failure 11,**” whereas biallelic pathogenic variants have been associated with “**De Sanctis-Cacchione syndrome,**” “**Cerebrooculofacioskeletal syndrome,**” “**Cockayne syndrome, type B,**” and “**UV-sensitive syndrome 1.**” A heterozygous variant was identified in the **ERCC6** gene. This variant was classified as a **VUS** according to both ACMG criteria and ClinVar. **Genetic counseling is recommended.**

BRCA1/BRCA2 MLPA CLINICAL DESCRIPTION

BRCA1 and **BRCA2** are tumor suppressor genes involved in the production of proteins that play an essential role in the repair of damaged DNA. Pathogenic variants or other alterations affecting these genes may result in absent or impaired protein function. Failure to adequately repair damaged DNA is an important mechanism contributing to carcinogenesis.

Inherited pathogenic variants in the **BRCA1** and **BRCA2** genes are known to increase the risk of breast and ovarian cancer in women. Approximately 5–10% of all breast cancers are attributable to hereditary factors, and **BRCA1** and **BRCA2** pathogenic variants account for approximately 20–25% of hereditary breast cancer cases.

METHOD

DNA isolated from the patient sample using routine procedures was amplified by multiplex PCR using the SALSA MLPA P002 BRCA1 and P090 BRCA2 Probemixes. Fragment analysis was subsequently performed by capillary electrophoresis using the MLPA method.

This assay is designed to detect copy-number changes within the targeted regions. Alterations outside the target regions, copy-number-neutral inversions and translocations, and point mutations cannot be detected by this method. Sequence variations within the probe-binding regions, including SNPs, point mutations, and short insertions/deletions, may interfere with probe hybridization and may lead to false-positive results.

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Tıbbi Genetik Uzmanı

Uz. Tes. No: 68410



TÜRKİYE CUMHURİYETİ
SAĞLIK BAKANLIĞI

ÖZEL NESİLLER
GENETİK HASTALIKLAR DEĞERLENDİRME MERKEZİ
Laboratuvar Ruhsat No: GHDM.SM/34.09/01



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Variant Details

Gene	Position	HGVSc	Consequence	Genotype	Pathogenicity (ACMG/ClinVar)	Related Diseases
FLCN	chr17: 17222565 Exon 7	ENST00000 285071.9 c.715C>T	Missense Variant	het	VUS/VUS, LB, B	SMu Colorectal cancer SMu Renal carcinoma, chromophobe AD Birt-hogg-dube syndrome AD Pneumothorax, primary spontaneous AD Colorectal cancer Nonpapillary renal cell carcinoma AD Renal carcinoma AD Birt-hogg-dube syndrome AD Birt-hogg-dube syndrome 1 AD Birt-hogg-dubé syndrome AD Familial spontaneous pneumothorax AD Obsolete birt-hogg-dube syndrome Potocki-lupski syndrome
RET	chr10: 43111293 Exon 7	ENST00000 355710.8 c.1350C>G	Missense Variant	het	VUS/VUS	AD Medullary thyroid carcinoma AD Multiple endocrine neoplasia iia AD Multiple endocrine neoplasia iib AD Hirschsprung disease, protection against AD Hirschsprung disease, susceptibility to, 1 AD Pheochromocytoma Differentiated thyroid carcinoma AD Familial medullary thyroid carcinoma AD Isolated familial medullary thyroid carcinoma



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						AD Multiple endocrine neoplasia type 2a AD Multiple endocrine neoplasia type 2b AR Bilateral renal agenesis AD,Mu Haddad syndrome AD,AR,Mu Hirschsprung disease AD Hirschsprung disease, susceptibility to, 1 AD Pheochromocytoma AR Renal agenesis AR Renal agenesis, bilateral AD Renal agenesis, unilateral Sporadic pheochromocytoma/secretory paraganglioma
ERCC6	chr10: 49500564 Exon 7	ENST00000355832.10 c.1659G>T	Missense Variant	het	VUS/VUS	AD,SMu Lung cancer, susceptibility to AR Cerebroculofacioskeletal syndrome 1 AR Cockayne syndrome, type b AR De sanctis-cacchione syndrome Macular degeneration, age-related, susceptibility to, 5 AD Premature ovarian failure 11 AR Uv-sensitive syndrome 1 Cerebroculofacioskeletal syndrome 1 AR Cockayne spectrum with or without cerebroculofacioskeletal syndrome AR Cockayne syndrome type 1 AR Cockayne syndrome type 2 AR Cockayne syndrome type 3 AR Cofs syndrome



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						De sanctis-cacchione syndrome Premature ovarian failure 11 AR Uv-sensitive syndrome AR Uv-sensitive syndrome 1
RUNX1	chr21: 34887027 Exon 4	ENST00000 675419.1 c.167T>C	Missense Variant	het	VUS/LP,VUS,LB,B--	AD,SMu Leukemia, acute myeloid AD Acute myeloid leukemia Acute myeloid leukemia with t(8;21)(q22;q22) translocation Chronic myeloid leukemia AD Platelet disorder, familial, with associated myeloid malignancy ----- Aggressive systemic mastocytosis AD Familial platelet disorder with associated myeloid malignancy AD Hereditary thrombocytopenia and hematologic cancer predisposition syndrome AD Hereditary thrombocytopenia and hematological cancer predisposition syndrome associated with runx1
CTRC	chr1: 15445660 Exon 7	ENST00000 375949.5 c.703G>A	Missense Variant	het	VUS/P,VUS,B	AD Pancreatitis, chronic, susceptibility to AD Hereditary chronic pancreatitis Tropical pancreatitis

Gene Details

FLCN

FLCN "folliculin" (MIM: 607273) gene is associated with Colorectal cancer, Familial spontaneous pneumothorax, Renal carcinoma, Pneumothorax, primary spontaneous, Birt-hogg-dube syndrome, Potocki-lupski syndrome, Renal carcinoma, chromophobe, Nonpapillary renal cell carcinoma, Obsolete birt-hogg-dube syndrome, Birt-hogg-dubé syndrome, Birt-hogg-dube syndrome 1 in OMIM database. The c.715C>T (rs78683075) variant detected as heterozygous in the gene. The variant has been reported at low frequency (0.00046) in ESP6500, ExAC and GnomAD studies. It has been reported as Benign, Likely Benign, Unknown Significance in Clinvar database.

RET

RET "ret proto-oncogene" (MIM: 164761) gene is associated with Hirschsprung disease, protection against, Hirschsprung disease, susceptibility to, 1, Familial medullary thyroid carcinoma, Pheochromocytoma, Differentiated thyroid carcinoma, Isolated familial medullary thyroid carcinoma, Multiple endocrine neoplasia iib, Bilateral renal agenesis, Multiple endocrine neoplasia type 2a, Hirschsprung disease, Renal agenesis, Renal agenesis, unilateral, Multiple endocrine neoplasia type 2b, Sporadic pheochromocytoma/secretory paraganglioma, Renal agenesis, bilateral, Medullary thyroid carcinoma, Haddad syndrome, Multiple endocrine neoplasia iia in OMIM database. The c.1350C>G variant detected as heterozygous in RET gene. The variant has been reported at low frequency (0) in ESP6500, ExAC and GnomAD studies. It has been reported as Unknown Significance in Clinvar database.

ERCC6

ERCC6 "ERCC excision repair 6, chromatin remodeling factor" (MIM: 609413) gene is associated with Lung cancer, susceptibility to, Uv-sensitive syndrome, Cockayne syndrome, type b, Macular degeneration, age-related, susceptibility to, 5, Cockayne spectrum with or without cerebrooculofacioskeletal syndrome, Cockayne syndrome type 3, Cockayne syndrome type 1, Cockayne syndrome type 2, Cofs syndrome, Premature ovarian failure 11, Uv-sensitive syndrome 1, De sanctis-cacchione syndrome, Cerebrooculofacioskeletal syndrome 1 in OMIM database. The c.1659G>T (rs116373975) variant detected as heterozygous in the gene. The variant has been reported at low frequency (0.00018) in ESP6500, ExAC and GnomAD studies. It has been reported as Unknown Significance in Clinvar database.

RUNX1

RUNX1 "RUNX family transcription factor 1" (MIM: 151385) gene is associated with Aggressive systemic mastocytosis, Chronic myeloid leukemia, Platelet disorder, familial, with associated myeloid malignancy, Leukemia, acute myeloid, Hereditary thrombocytopenia and hematologic cancer predisposition syndrome, Acute myeloid leukemia with t(8;21)(q22;q22) translocation, Familial platelet disorder with associated myeloid malignancy, Acute myeloid leukemia, Hereditary thrombocytopenia and hematological cancer predisposition syndrome associated with runx1 in OMIM database. The c.167T>C (rs111527738) variant detected as heterozygous in the gene. The variant has been

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reported at high frequency (0.01876) in ESP6500, ExAC and GnomAD studies. It has been reported as Benign in Clinvar database.

CTRC

CTRC "chymotrypsin C" (MIM: 601405) gene is associated with Pancreatitis, chronic, susceptibility to, Hereditary chronic pancreatitis, Tropical pancreatitis in OMIM database. The c.703G>A (rs140993290) variant detected as heterozygous in the gene. The variant has been reported at low frequency (0.00068) in ESP6500, ExAC and GnomAD studies. It has been reported as Benign, Pathogenic, Unknown Significance in Clinvar database.

Sequence Coverage

Target Coverage 1x	Target Coverage 5x	Target Coverage 20x	Target Coverage 50x	Average Depth
 99.85%	 99.81%	 99.1%	 84.29%	106

Test Method & Limitations

- Bioinformatics analysis of the data was carried out on Genomize SEQ Platform.
- 99.81% of the regions targeted by the kit were covered with a depth of at least 5X. The isolated DNA of the patient was sequenced using the SG CES v3 + mtDNA kit to cover the targeted regions of 6369 genes in a new generation sequencing device.
- Each variant was evaluated on the platform in the light of databases such as ClinVar, OMIM, HPO, GnomAD, dbSNP, scientific publications, clinical correlation and inheritance pattern. Variants selected as a result of this assessment are reported. Mutation terminology was made as suggested by HGVS (Human Genome Variation Society).
- This test has a certain sensitivity in detecting nucleotide changes, small deletions and insertions, and cannot detect stable translocations, complex inversions, large deletions, low-level mosaicism.
- Results are interpreted in the context of the proband's clinical findings, family history, and other laboratory data. Only variants selected as a result of evaluations are reported in this report. The variants reported can not necessarily explain all of the symptoms. Obtaining more clinical details helps in making the final decision about the patient. If the test results and clinical findings do not match, additional tests are recommended. As the information in the literature is updating, pathogenic variants may rarely pass into the benign or unknown class.

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- The preparation, processing and analysis of the requested genetic and/or biochemistry tests are carried out based on the most up-to-date scientific and analytical standards. However, in some cases, genetic and/or biochemical tests may not yield accurate results, such as the quality of the submitted material or unforeseen or unknown reasons. The laboratories that analyze the test and the service provider are not responsible for misleading or false results. This document contains information from the Online Mendelian Inheritance in Man® (OMIM®) database obtained under a license from Johns Hopkins University. This document does not represent the entire and unmodified OMIM® database available at <http://omim.org/downloads>. Regarding OMIM® information: Copyright © 1996- 2020, John Hopkins University, all rights reserved.
- This document has been signed with a secure electronic signature in accordance with the electronic signature law numbered 5070.
- This report cannot be partially copied or reproduced without the written permission of the laboratory.
- Analysis results are valid for the example given above.
- This test result only includes pathogenic/likely pathogenic/VUS variants in the screened genes regarding to the patient clinic and does not involve benign/likely benign variants. Variants with >0.01 allele frequency are not included. This report does not exclude predictions that would not be technically detectable by extensive domain assumptions and sequencing.

SUGGESTIONS:

- It is recommended to reassess the current data in one year, considering new gene and variant information that may be added to the literature.
- It is recommended that information regarding variants not clinically relevant be evaluated in consultation with a genetic expert, and that genetic counseling be provided, taking into account the presence of genetic mutations that cannot be detected by exome sequencing and the risks they may pose.

Gene List

- ACD, DIS3L2, GREM1, PIK3CA, SDHD, AIP, EPCAM, HOXB13, PMS2, SLX4, AKT1, ERCC1, KIF1B, POLD1, SMAD4, APC, ERCC2, KIT, POLE, SMARCA4, ATM, ERCC3, LZTR1, POT1, SMARCB1, BAP1, ERCC4, MAX, PRKAR1A, SMARCE1, BARD1, ERCC5, MEN1, PTCH1, SPINK1, BLM, FAM175A, MET, PTEN, SPRED1, BMPR1A, FANCA, MITF, RAD50, STK11, BRCA1, FANCB, MLH1, RAD51, SUFU, BRCA2, FANCC, MRE11A, RAD51B, TERF2IP, BRIP1, FANCD2, MSH2, RAD51C, TERT, CASR, FANCE, MSH3, RAD51D, TMEM127, CDC73, FANCF, MSH6, RB1, TP53, CDH1, FANCG, MUTYH, RECQL4, TSC1, CDK4, FANCI, NBN, RET, TSC2, CDKN1B, FANCL, NF1, RHBDF2, VHL, CDKN2A, FANCM, NF2, RINT1, WT1, CEBPA, FH, NSD1, RUNX1, XPA, CHEK2, FLCN, NTHL1, SDHA, XPC, CTRC, GALNT12, PALB2, SDHAF2, XRCC2, DDB2, GATA2, PDGFRA, SDHB, DICER1, GPC3, PHOX2B, SDHC
- Not all regions of some genes may be sequenced at 100%

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