PROGENE LAB
For Medical And Genetic Tests
معمل بروجين للتحاليل الطبية

Target Variant Confirmation Report

Patient Name: **********	**اسم المريض:** **********
Sample type: Blood sample	**DOB:** **********
Patient phone No.: **********	**Sex:** Male
Referring Doctor: **********	**City, Country:** **********
Report type: Target variant Confirmation	**Report date:** **********
Reason of referral: Confirmation of carrier state of target variant	

Clinical Information: A 40-year-old male subject for confirmation of carrier state of *CRIPT* gene variant: **NM_014171.6:c.1A>G, NP_054890.1:p.(Met1?)** for which his daughter was diagnosed to have autosomal recessive Microcephaly and Distinctive Facies (SSMCF; OMIM#615789) with the referred variant in homozygous state.

Summary of The Results

Positive result

A heterozygous variant in *CRIPT* gene causing Microcephaly and Distinctive Facies; SSMCF, with autosomal recessive mode of inheritance

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Interpretation of the test results:

Primary findings:

Gene	Variant Coordinates	Zygosity/Protein effect	Heredity	MAF	Classification
CRIPT	NC_000002.11:g.46844422A>G NM_014171.6:c.1A>G NP_054890.1:p.(Met1?)	Heterozygous/ Start loss	AR	0.00	**Likely Pathogenic**

Cysteine-Rich PDZ Domain-Binding Protein gene (*CRIPT*; OMIM*604594) is mapped to chromosome 2p21[1]. CRIPT, the cysteine-rich PDZ-binding protein, binds to the third PDZ domain of PSD-95 (post synaptic density protein 95) family proteins and directly binds microtubules, linking PSD-95 family proteins to the neuronal cytoskeleton[2]. Biallelic variants of *CRIPT* gene are reported to cause Short Stature with Microcephaly and Distinctive Facies (SSMCF; OMIM# 615789).

Short Stature with Microcephaly and Distinctive Facies is characterized by pre- or postnatal growth retardation, frontal bossing, high forehead, sparse hair and eyebrows, and telecanthus. Patients also show skin dyspigmentation, with hyper- and/or hypopigmented areas. Additional clinical features include high myopia, admixed hyper- and hypopigmented macules primarily on the face, arms, and legs, and syndactyly of toes[3]. Averdunk et al., 2023 described 5 children with biallelic variants in *CRIPT* gene causing Rothmund-Thomson-syndrome-like features. All children presented with developmental delay, frontal bossing, alopecia, scoliosis, foot anomalies, as syndactyly of toes, skewfoot and pes planus[4].

The homozygous start-loss variant in exon-1 of the *CRIPT* gene in our proband, **NM_014171.6:c.1A>G, NP_054890.1:p.(Met1?)** is evaluated as **Likely Pathogenic**, according to the American College of Medical Genetics (ACMG) criteria for the classification of pathogenic variants[5]. Loss-of-function is a known disease-causing mechanism of the syndrome (*CRIPT* has 9 reported pathogenic LOF variants). Furthermore, the variant is predicted as deleterious by the absolute majority of predictor tools and is completely absent in population databases (MAF 0.00 in gnomAD).

Information for Table Interpretation:

Human Genome Variation Society (HGVS) recommendations were used to describe sequence variants (http://www.hgvs.org).

Classification: Refers to the possible pathogenicity of a variant, but does not necessarily provide clear evidence of clinical significance. Variants are evaluated based upon current data and specific criteria according to ACMG guidelines[3], variants were assigned to one of five interpretation categories (Pathogenic, Likely Pathogenic, Variant of Uncertain Significance, Likely Benign and Benign) and using

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computational pathogenicity calculators. All variants for which clinical relevance cannot be conclusively confirmed or excluded are referred as variants of unknown clinical significance (VUS).

Recommendation:

- Genetic counseling has to be offered to the family.
- Further genetic analysis to the family member and prenatal testing of future pregnancies.

Methods:

The DNA extracted from the sample was tested for single nucleotide variation using Sanger Sequencing. This technique amplified by PCR a genomic DNA fragment that contains these nucleotide positions by means of specific primers. The amplified fragments were detected by fluorescent capillary electrophoresis (3500XL, Applied Biosystems) that separate fragments with one nucleotide of difference. The detection limit was determined by sequence analysis software, which optimum range of peak height is 1,000-31,000, the minimal is 100 and the maximal is ≥40,000. Sensitivity: the estimated sensitivity per allele is 100%. Specificity: the estimated specificity per allele is 100%. Overall accuracy: the estimated overall accuracy per allele is 100%.

Test restrictions and limitations:

This assay is targeted to the specific genetic variant investigated and cannot detect other variants that could be present in this gene or other genes of the patient. Therefore, absence of a detectable variant does not rule out the possibility that the patient has an altered variant that cannot be detected with this method. Furthermore, when 2 or more variants are identified, the cis/trans. status (whether the variants are on the same or opposite chromosomes) is not always known, and assumptions about phase and content are made to assign alleles. This method cannot rule out totally that the presence or absence of the variant to detect was or not located in a pseudogene which can interfere with the appropriate interpretation.

Disclaimer:

DNA studies don’t constitute a definitive test for the selected condition(s) in all individuals. It should be realized that there are possible sources of error. Errors can result from trace contamination, rare technical errors, rare genetic variants that interfere with analysis, recent scientific developments, and alternative classification systems. This test should be one of many aspects used by the healthcare provider to help with a diagnosis and treatment plan, but it shouldn't be a sole diagnostic criterion. This test is used for

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clinical purposes. It should not be regarded as investigational or for research. Any preparation and processing of a sample from patient material provided by a physician, clinical institute or a laboratory (by a "Partner") and the requested genetic testing itself is based on the highest and most current scientific and analytical standards.

References:

1- Niethammer, M., Valtschanoff, J. G., Kapoor, T. M., Allison, D. W., Weinberg, T. M., Craig, A. M., Sheng, M. CRIPT, a novel postsynaptic protein that binds to the third PDZ domain of PSD-95/SAP90. Neuron 20: 693-707.

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3- Leduc, M. S., Niu, Z., Bi, W., Zhu, W., Miloslavskaya, I., Chiang, T., Streff, H., Seavitt, J. R., Murray, S. A., Eng, C., Chan, A., Yang, Y., Lalani, S. R. CRIPT exonic deletion and a novel missense mutation in a female with short stature, dysmorphic features, microcephaly, and pigmentary abnormalities. Am. J. Med. Genet. 170A: 2206-2211, 2016.

4- Averdunk L, Huetzen MA, Moreno-Andrés D, Kalb R, McKee S, Hsieh TC, Seibt A, Schouwink M, Lalani S, Faqeih EA, Brunet T, Boor P, Neveling K, Hoischen A, Hildebrandt B, Graf E, Lu L, Jin W, Schaper J, Omer JA, Demaret T, Mayatepek E, Wieczorek D, Wang LL, Antonin W, Jachimowicz RD, von Felbert V, Distelmaier F. Biallelic variants in CRIPT cause a Rothmund-Thomson-like syndrome with increased cellular senescence. Genet Med. 2023 Jul;25(7):100836.

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With kind regards

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