



Cerebrum DX *Mito*

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

SAMPLE INFORMATION

Name :	-	Date Received :	-
Medical ID :	-	Date of Report :	-
Date of Birth :	-	Req. Physician :	-
Location :	-	Barcode :	-
Material :	WHOLE PERIPHERAL BLOOD/BUCCAL SWAB/URINE SAMPLE	Reason of referral:	Mitochondrial disorder

CerebrumDX mito analysis by Next Generation Sequencing

Results associated with the reason of referral

NEGATIVE

NO PATHOGENIC OR LIKELY PATHOGENIC VARIANTS WERE IDENTIFIED IN MITOCHONDRIAL DNA (mtDNA)

Methodology

Genomic DNA was extracted from the submitted sample (buccal swab). Target regions of the mitochondrial genome (mtDNA) were enriched by hybridization-based target capture using the Twist Human Core Exome EF Multiplex Complete Kit (Twist Bioscience). Sequencing of the enriched targets was performed on the MGI DNBSEQ-T7 platform. Bioinformatic analysis and interpretation of sequencing data were performed using the Breakthrough Genomics VG PLUS v3.0.8 platform. The predicted impact of mitochondrial missense variants on protein structure and function was assessed using the APOGEE consensus prediction algorithm ([PMID: 28640805](#)). Mitochondrial variants were classified according to ACMG/AMP specifications for the interpretation of mitochondrial DNA variants ([PMID: 32906214](#)). Specialized mitochondrial databases, including MITOMAP and HmtVar, were also used for variant interpretation. The mean sequencing depth was >1,000x, with 100% of the targeted regions covered at a depth of ≥1,000x.

Note:

- This method enables the detection of mitochondrial DNA (mtDNA) variants with a heteroplasmy level >10%. Variants present at lower heteroplasmy levels may not be detected.
- Heteroplasmy levels may vary considerably among different tissues. Therefore, a pathogenic mtDNA variant may be present at a low or undetectable heteroplasmy level in the tested sample while being present at a higher level in other tissues. Consequently, a negative result does not exclude the possibility of a mitochondrial disorder. In cases of strong clinical suspicion, analysis of an alternative tissue may be warranted.



Υπογεγραμμένο ηλεκτρονικά από - Γεωργία Πεπέ, MSc Μοριακός Βιολόγος, ΑΜΚΑ:09038403029

- Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255

Genekor Ιατρική Α.Ε. | Μια εταιρεία πιστοποιημένη με EN ISO 9001:2015 (Αρ.πιστοποιητικού: 041150049) και διαπιστευμένη για αριθμό εξετάσεων με ELOT EN ISO 15189:2012 (Αρ. Πιστοποιητικού: 822)



Cerebrum DX *Mito*

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: -

Barcode : -

- This method has not been validated for the reliable detection of large-scale mtDNA rearrangements (deletions/duplications). If a clinical disorder associated with large-scale mtDNA rearrangements is suspected, testing using an appropriate complementary method is recommended.



Υπογεγραμμένο ηλεκτρονικά από - Γεωργία Πεπέ, MSc Μοριακός Βιολόγος, ΑΜΚΑ:09038403029

- Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255

Genekor Ιατρική Α.Ε. | Μια εταιρεία πιστοποιημένη με EN ISO 9001:2015 (Αρ.πιστοποιητικού: 041150049) και διαπιστευμένη για αριθμό εξετάσεων με ELOT EN ISO 15189:2012 (Αρ. Πιστοποιητικού: 822)



Cerebrum DX *Mito*

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
 email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
 Scientific Director: George Nasioulas PhD

Name: -

Barcode : -

Information on Non-Pathogenic Variants

Non-pathogenic polymorphisms (variants without clinical significance) are not reported, as available evidence indicates that they are not associated with an increased risk of disease and therefore do not alter clinical management beyond that recommended on the basis of the individual's personal and family history.

Genes Analyzed (Table 1)

<i>MT-ATP6</i>	<i>MT-ATP8</i>	<i>MT-CO1</i>	<i>MT-CO2</i>	<i>MT-CO3</i>	<i>MT-CYB</i>	<i>MT-ND1</i>	<i>MT-ND2</i>	<i>MT-ND3</i>
<i>MT-ND4</i>	<i>MT-ND4L</i>	<i>MT-ND5</i>	<i>MT-ND6</i>	<i>MT-RNR1</i>	<i>MT-RNR2</i>	<i>MT-TA</i>	<i>MT-TC</i>	<i>MT-TD</i>
<i>MT-TE</i>	<i>MT-TF</i>	<i>MT-TG</i>	<i>MT-TH</i>	<i>MT-TI</i>	<i>MT-TK</i>	<i>MT-TL1</i>	<i>MT-TL2</i>	<i>MT-TM</i>
<i>MT-TN</i>	<i>MT-TP</i>	<i>MT-TQ</i>	<i>MT-TR</i>	<i>MT-TS1</i>	<i>MT-TS2</i>	<i>MT-TT</i>	<i>MT-TV</i>	<i>MT-TW</i>
<i>MT-TY</i>								



Υπογεγραμμένο ηλεκτρονικά από - Γεωργία Πεπέ, MSc Μοριακός Βιολόγος, ΑΜΚΑ:09038403029

- Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255

Genekor Ιατρική Α.Ε. | Μια εταιρεία πιστοποιημένη με EN ISO 9001:2015 (Αρ.πιστοποιητικού: 041150049) και διαπιστευμένη για αριθμό εξετάσεων με ELOT EN ISO 15189:2012 (Αρ. Πιστοποιητικού: 822)



Cerebrum DX *Mito*

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: -

Barcode : -

Βιβλιογραφία

- Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, Grody WW, Hegde M, Lyon E, Spector E, Voelkerding K, Rehm HL; ACMG Laboratory Quality Assurance Committee. **Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.** Genet Med. 2015 May;17(5):405-24. doi: 10.1038/gim.2015.30. Epub 2015 Mar 5. (PMID: [25741868](#)) PMCID: PMC4544753.
- Harrison SM, Biesecker LG, Rehm HL. **Overview of Specifications to the ACMG/AMP Variant Interpretation Guidelines.** Curr Protoc Hum Genet. 2019 Sep;103(1):e93. doi: 10.1002/cphg.93. (PMID: [31479589](#)) PMCID: PMC6885382.
- Kalia SS, Adelman K, Bale SJ, Chung WK, Eng C, Evans JP, Herman GE, Hufnagel SB, Klein TE, Korf BR, McKelvey KD, Ormond KE, Richards CS, Vlangos CN, Watson M, Martin CL, Miller DT. **Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2016 update (ACMG SF v2.0): a policy statement of the American College of Medical Genetics and Genomics.** Genet Med. 2017 Feb;19(2):249-255. doi: 10.1038/gim.2016.190. Epub 2016 Nov 17. Erratum in: Genet Med. 2017 Apr;19(4):484. PMID: 27854360.
- Landrum MJ, Chitipiralla S, Brown GR, Chen C, Gu B, Hart J, Hoffman D, Jang W, Kaur K, Liu C, Lyoshin V, Maddipatla Z, Maiti R, Mitchell J, O Leary N, Riley GR, Shi W, Zhou G, Schneider V, Maglott D, Holmes JB, Kattman BL. **ClinVar: improvements to accessing data.** Nucleic Acids Res. 2020 Jan 8;48(D1):D835-D844. doi: 10.1093/nar/gkz972. (PMID: [31777943](#)) PMCID: PMC6943040.
- Köhler S, Gargano M, Matentzoglou N, Carmody LC, Lewis-Smith D, Vasilevsky NA, Danis D, Balagura G, Baynam G, Brower AM, Callahan TJ, Chute CG, Est JL, Galer PD, Ganesan S, Griese M, Haimel M, Pazmandi J, Hanauer M, Harris NL, Hartnett MJ, Hastreiter M, Hauck F, He Y, Jeske T, Kearney H, Kindle G, Klein C, Knoflach K, Krause R, Lagorce D, McMurry JA, Miller JA, Munoz-Torres MC, Peters RL, Rapp CK, Rath AM, Rind SA, Rosenberg AZ, Segal MM, Seidel MG, Smedley D, Talmy T, Thomas Y, Wiafe SA, Xian J, Yüksel Z, Helbig I, Mungall CJ, Haendel MA, Robinson PN. **The Human Phenotype Ontology in 2021.** Nucleic Acids Res. 2021 Jan 8;49(D1):D1207-D1217. doi: 10.1093/nar/gkaa1043. (PMID: [33264411](#)) PMCID: PMC7778952.
- Rivera-Muñoz EA, Milko LV, Harrison SM, Azzariti DR, Kurtz CL, Lee K, Mester JL, Weaver MA, Currey E, Craigen W, Eng C, Funke B, Hegde M, Hershberger RE, Mao R, Steiner RD, Vincent LM, Martin CL, Plon SE, Ramos E, Rehm HL, Watson M, Berg JS. **ClinGen Variant Curation Expert Panel experiences and standardized processes for disease and gene-level specification of the ACMG/AMP guidelines for sequence variant interpretation.** Hum Mutat. 2018 Nov;39(11):1614-1622. doi: 10.1002/humu.23645. (PMID: [30311389](#)) PMCID: PMC6225902.
- Miller DT, Lee K, Gordon AS, Amendola LM, Adelman K, Bale SJ, Chung WK, Gollob MH, Harrison SM, Herman GE, Hershberger RE, Klein TE, McKelvey K, Richards CS, Vlangos CN, Stewart DR, Watson MS, Martin CL; ACMG Secondary Findings Working Group. **Recommendations for reporting of secondary findings in clinical exome and genome sequencing, 2021 update: a policy statement of the American College of Medical Genetics and Genomics (ACMG).** Genet Med. 2021 May 20. doi: 10.1038/s41436-021-01171-4. Epub ahead of print. (PMID: [34012069](#))
- Miller DT, Lee K, Chung WK, Gordon AS, Herman GE, Klein TE, Stewart DR, Amendola LM, Adelman K, Bale SJ, Gollob MH, Harrison SM, Hershberger RE, McKelvey K, Richards CS, Vlangos CN, Watson MS, Martin CL; ACMG Secondary Findings Working Group. **ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the**



Υπογεγραμμένο ηλεκτρονικά από

- Γεωργία Πεπέ, MSc Μοριακός Βιολόγος, ΑΜΚΑ:09038403029

- Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255

Genekor Ιατρική Α.Ε. | Μια εταιρεία πιστοποιημένη με EN ISO 9001:2015 (Αρ.πιστοποιητικού: 041150049) και διαπιστευμένη για αριθμό εξετάσεων με ELOT EN ISO 15189:2012 (Αρ. Πιστοποιητικού: 822)



Cerebrum DX *Mito*

Genekor Medical S.A. | 52, Spaton Ave., 15344, Gerakas, Athens, Greece ,G.E.MI. nr: 0007856001000
email: info@genekor.com, www.genekor.com | Tel. (+30) 210 6032138 Fax. (+30) 210 6032148
Scientific Director: George Nasioulas PhD

Name: -

Barcode : -

American College of Medical Genetics and Genomics (ACMG). Genet Med. 2021 May 20. doi: 10.1038/s41436-021-01172-3.
Epub ahead of print. ([PMID: 34012068](https://pubmed.ncbi.nlm.nih.gov/34012068/))



Υπογεγραμμένο ηλεκτρονικά από - Γεωργία Πεπέ, MSc Μοριακός Βιολόγος, ΑΜΚΑ:09038403029

- Γιώργος Νασιούλας, PhD Μοριακός Βιολόγος, Επιστημονικός Διευθυντής, ΑΜΚΑ:26025301255

Genekor Ιατρική Α.Ε. | Μια εταιρεία πιστοποιημένη με EN ISO 9001:2015 (Αρ.πιστοποιητικού: 041150049) και διαπιστευμένη για αριθμό εξετάσεων με ELOT EN ISO 15189:2012 (Αρ. Πιστοποιητικού: 822)