Warsaw Genomics
sp. z o.o. spółka komandytowa
ul. Kiwerska 33A / 01-682 Warszawa
tel. 22 65 80 180
Podmiot leczniczy Nr Z-178028-20150909

Charcot-Marie-Tooth disease

First symptoms of Charcot-Marie-Tooth disease are typically observed already in childhood, they include progressive atrophy of motor and sensory neurons. Clinical features include feet deformations (characteristic hollows caused by muscle atrophy), atrophy of the peroneus muscles and decreased Achilles reflex. The most common subtype is 1A, responsible for about 60% of all hereditary neuropathies.

Charcot-Marie-Tooth disease affects one in 2,5000 people.

In this test, using novel technology of genome sequencing, full sequences of the genes responsible for Charcot-Marie-Tooth disease are analyzed.

Genes and genetic syndromes

Gen	Choroba/objawy	Sposób dziedzi-czenia	Znane warianty chorobo-twórcze
AARS	Wczesna encefalopatia padaczkowa, Choroba Charcota-Mariego-Tootha	AD/AR	9
AIFM1	Głuchota	XL	27
AMACR	Niedobór racemazy alpha-metyloacylo-CoA, Zaburzenia syntezy kwasów żółciowych	AR	2
ARHGEF10	Obniżona prędkość przenoszenia impulsów nerwowych	AD	1
ATL1	Kurczowe porażenie kończyn dolnych typ 3, autosomalnie dominujące	AD/AR	23
ATL3	Neuropatria czuciowa	AD	1
BAG3	Kardiomiopatia rozstrzeniowa, Miopatia miofibrylarna	AD	33
BSCL2	Lipodystrofia uogólniona	AR	31
CCT5	Neuropatia czuciowa z porażeniem czterokończynowym	AR	1
COX10	Zespół Leigha, Niedobór kompleksu mitochondrialnego IV	AR	8
COX6A1	Choroba Charcota-Mariego-Tootha	AR	1
CTDP1	Wrodzone zaćmy, niedosłuch i neurodegeneracja	AR	1
DCAF8	Choroba Charcota-Mariego-Tootha	AD	1
DCTN1	Zespół Perryego, Neuropatia motoryczna	AD	12
DHTKD1	Choroba Charcota-Mariego-Tootha	AD/AR	7
DNM2	Choroba Charcota-Marie'a-Tootha	AD/AR	26
DNMT1	Neuropatia czuciowa, Ataksja móżdżkowa	AD	7
DST	Neuropatia czuciowo-autonomiczna	AR	10

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DYNC1H1	Rdzeniowy zanik mięśni, Choroba Charcota-Mariego-Tootha, Niepełnosprawność intelektualna	AD	57
EGR2	Neuropatia, Choroba Charcota-Mariego-Tootha	AD/AR	11
FAM134B	Neuropatia czuciowo-autonomiczna	AR	
FBLN5	Skóra wiotka, zwyrodnienie plamki żółtej związane z wiekiem	AD/AR	11
FGD4	Choroba Charcota-Mariego-Tootha	AR	16
FIG4	Stwardnienie zanikowe boczne, drobnozakrętowość obustronna potyliczna, zespół Yunis-Varon, choroba Charcota-MariegoTootha	AD/AR	25
FXN	Ataksja Friedreicha	AR	13
GAN	Neuropatia aksonalna	AR	15
GARS	Neuropatia, Choroba Charcota-Mariego-Tootha	AD	19
GDAP1	Choroba Charcota-Mariego-Tootha	AD/AR	35
GJB1	Choroba Charcota-Mariego-Tootha	XL	89
GNB4	Choroba Charcota-Mariego-Tootha	AD	3
GNE	Miopatia z ciałkami wtrętowymi	AD/AR	74
HADHB	Niedobór białka trójfunkcyjnego	AR	18
HARS	Zespół Ushera	AR	6
HINT1	Neuropatia aksonalna	AR	9
HK1	Anemia hemolityczna, niesferocytowa z niedoboru heksokinazy	AR	8
HSPB1	Neuropatia, Choroba Charcota-Mariego-Tootha	AD	22
HSPB8	Choroba Charcota-Mariego-Tootha	AD	3
IGHMBP2	Rdzeniowy zanik mięśni, Choroba Charcota-Mariego-Tootha	AR	42
INF2	Stwardnienie kłębuszków nerkowych, Choroba Charcota-Mariego-Tootha	AD	14
KARS	Choroba Charcota-Mariego-Tootha	AR	8
KIF1A	Porażenie spastyczne, Neuropatia neuronu czuciowego	AD/AR	58
KIF1B	Choroba Charcota-Mariego-Tootha	AD	34
KIF5A	Porażenie spastyczne	AD	21
LDB3	Kardiomiopatia rozstrzeniowa, Miopatia miofibrylarna	AD	9
LITAF	Choroba Charcota-Mariego-Tootha	AD	10
LMNA	Zespół serce-ręka, Dystrofia kończynowo-obręczowa, Lipodystrofia, Dystrofia Emery'ego-Dreiffusa, Kardiomiopatia rozstrzeniowa, Progeria Hutchinsona-Gilforda	AD/AR	240
LRSAM1	Choroba Charcota-Mariego-Tootha	AR	11
MARS	Śródmiąższowe choroby płuc i wątroby	AR	8
MED25	Zespół Basel-Vanagait-Smirin-Yosef Choroba Charcota-Mariego-Tootha	AR	4
MFN2	Dziedziczna neuropatia ruchowa i czuciowa, Choroba Charcota-Mariego-Tootha	AD/AR	60
MPZ	Choroba Charcota-Marie'a-Tootha	AD	92
MTMR2	Choroba Charcota-Mariego-Tootha	AR	10
MYOT	Dystrofia mięśniowa kończynowo-obręczowa typ 1A	AD	7

Gen	Choroba/objawy	Sposób dziedzi-czenia	Znane warianty chorobo-twórcze
NDRG1	Choroba Charcota-Mariego-Tootha	AR	3
NEFL	Choroba Charcota-Mariego-Tootha	AD	24
NGF	Neuropatia czuciowo-autonomiczna	AR	1
NTRK1	Niewrażliwość na ból	AR	27
PDK3	Choroba Charcota-Mariego-Tootha	XL	1
PLEKHG5	Rdzeniowy zanik mięśni, Choroba Charcota-Mariego-Tootha	AR	12
PMP22	Choroba Charcota-Mariego-Tootha	AD/AR	33
POLG	Zespół Alpersa typ 4A - deplecja mtDNA	AR	87
PRPS1	Głuchota, zwiększona aktywność syntetazy I fosforybozylopirofosforanu, Zespół Artsa	XL	26
PRX	Choroba Dejerine-Sottasa, Choroba Charcota-Mariego-Tootha	AR	18
RAB7A	Choroba Charcota-Mariego-Tootha	AD	4
REEP1	Porażenie spastyczne, Neuropatia neuronu ruchowego	AD	13
SACS	Ataksja spastyczna	AR	243
SBF1	Choroba Charcota-Mariego-Tootha	AR	5
SBF2	Choroba Charcota-Mariego-Tootha	AR	15
SCN9A	Zespół Dravet	AD/AR	51
SETX	Ataksja z apraksją okoruchową, stwardnienie zanikowe boczne, postać młodzieńcza, ataksja rdzeniowo-móżdżkowa	AD/AR	33
SH3TC2	Choroba Charcota-Mariego-Tootha	AR	56
SLC12A6	Agenezja ciała modzelowatego (Zespół Andermanna)	AR	43
SMAD3	Zespół Loeysa-Dietza	AD	43
SPG11	Porażenie spastyczne, Stwardnienie zanikowe boczne, Choroba Charcota-Mariego-Tootha	AR	143
SPTLC1	Neuropatia czuciowo-autonomiczna	AD	8
SPTLC2	Neuropatria czuciowa i autonomiczna	AD	5
SURF1	Zespół Leigna, Choroba Charcota-Mariego-Tootha	AR	40
TFG	Porażenie czterokończynowe, Neuropatia czuciowo-ruchowa	AR	4
TRIM2	Choroba Charcota-Mariego-Tootha	AR	3
TRPV4	Artropatia-brachydaktylia, Dysplazja kręgosłupowo-nasadowa, Neuropatia czuciowo-ruchowa, Choroba Charcota-Mariego-Tootha	AD	59
TYMP	Zespół deplecji mitochondrialnego DNA	AR	82
VCP	Stwardnienie zanikowe boczne, Choroba Charcota-Mariego-Tootha	AD	17
WNK1	Neuropatia czuciowo-autonomiczna, Pseudohipoaldosteronizm	AD/AR	9
YARS	Choroba Charcota-Mariego-Tootha	AD	6

Methodology

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Information on the test method:

At first, deoxyribonucleic acid (DNA) is isolated from a blood sample or paraffin embedded tissue block. The quantity and quality of the material is determined in spectrophotometric and fluorometric assays. From mechanically or enzymatically fragmented DNA a library is made to be used for determination, sequencing and examination of selected genes. The library is sequenced on a new generation sequencer. Afterwards, sequencing results are subjected to bioinformatics analysis and clinical interpretation. Genetic variants are identified using Burrows-Wheeler Aligner. The test detects 100% of substitutions and 95% of small insertions and deletions.

Information on variant classification:

The study report provides information on variants classified as ‘potentially pathogenic’ and ‘pathogenic’ depending on their suspected clinical significance. The identified variants are classified under the following categories:

Pathogenic variant: the detected change in the gene sequence directly associates with disease development. At the same time, some pathogenic changes may not have full penetration, meaning that a single mutation may not be enough to cause a full-blown disease.

Potentially pathogenic variant: the detected change in the gene sequence may be, with a great probability, associated with disease development however it is not possible to prove this association on the basis of currently available scientific data. Variant pathogenicity confirmation would require additional tests and evidence; it cannot be excluded that further tests might prove that the change has limited or no clinical significance.

Variant of unknown pathogenicity: based on the currently available scientific data it is not possible to determine the significance of the detected change.

Potentially benign variant: the detected change in the gene sequence most probably does not associate with disease development, however based on the currently available scientific data the benignity of the mutation cannot be confirmed. Confirmation of the clinical significance of the variant would require additional tests and evidence; it cannot be excluded that further tests might prove that the detected mutation has clinical significance and would cause disease development.

Benign variant: the detected change does not associate with disease development.

The identified genetic variants are classified based on the guidelines of the American College of Medical Genetics and Genomics and the American Association for Molecular Pathology (S. Richards, Genet Med. 2015 May; 17(5):405-24). In variant classification the following criteria are considered:

- Previous variant identification in persons burdened with the disease
- Variant impact of functional gene product synthesis:
    - Determined through bioinformatics analyses
    - Confirmed by in vitro/in vivo studies
- Variant location (exon/intron, functional domain)
- *De novo*/hereditary change
- Variant incidence in general population (each variant with incidence >5% in line with Exome Sequencing Project, 1000 Genomes Project or Exome Aggregation Consortium is

classified as benign change)
- Variant incidence in general population with relation to patient population

The final classification of variants is made on the basis of the total of the above-mentioned criteria. The data bases include: 1000GP, ClinVar, ConsensusPathDB, Exome Aggregation Consortium, Exome Variant Server, FATHMM, GO (Gene Ontology), GTEx (Genotype-Tissue Expression), GWAS (Genome Wide Association Study), HGMD, KEGG, MetaLR, MetaSVM, MutationAssessor, MutationTaster, OMIM, PolyPhen-2, PROVEAN, SIFT, SnpEff, dbNSFP, UniProt, VEP (Variant Effect Predictor).

Test limitations:

All sequencing technologies have some limitations. Our tests use new generation sequencing (NGS) to examine coding and splicing regions of disease-associated genes. Sequencing techniques and subsequent bioinformatics analyses are aimed at limiting the significance of pseudo-gene sequences, however presence of highly homologous gene sequences may still occasionally disturb the identification of pathogenic alleles, deletions/duplications. The Sanger sequencing method is used to confirm variants with lower quality parameters. Deletion/duplication analyses show qualitative changes in DNA covering at least one exon and always require confirmation with other methods (qPCR or MLPA). The analyses are not designed for detecting certain types of genomic changes, such as translocations, inversions, dynamic mutations (e.g. increased number of trinucleotide repetitions) or mutations in regulatory or intronic regions. In case increased numbers of di- or trinucleotide repetitions are reported, it should be assumed that the exact number of repetitions is not precise. The test is not intended to detect somatic mosaicism and somatic mutation analyses should be made in the context of the germinal DNA sequence.

It is not possible to exclude mutations in genes and regions other than those covered by the test as well as alternations in the gene copy number. The test report includes information on changes in gene sequence identified on the basis of a comparison against current reference sequences maintained in NCBI Nucleotide and Ensembl databases. Tests are developed by *Warsaw Genomics* for clinical objectives. All test results collected are interpreted and analysed by scientific and medical experts of *Warsaw Genomics*.

How to order a test

How to order a test?

A test can be ordered directly through the Warsaw Genomics website. All you have to do is to tick off the required test. We would recommend, however, consulting a doctor prior to test selection. The doctor will help choose the right diagnostic test, explain possibilities and limitations of genetic testing and discus potential results and consequences of testing.

Test execution time: from 4 to 10 weeks. We will provide information on successive stages of the analysis.

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warsaw genomics

1

Medical consultation

The consultation is not obligatory, but we encourage you to consult your doctor, or one of our physicians, prior to ordering the test.

2

Registration

Filling of the test order form .
The form should be filled by the patient or a doctor selected by the patient.

3

Material for analysis

Our genetic tests are performed based on DNA, extracted from the blood sample. In case of cancer somatic profiling, we need the parafin-embedded block of cancer tissue and blood. We also accept DNA shipment by certified medical entities.

4

Sample submission

Blood shoud be collected in a **single, 4ml EDTA tube**. Please see the list of the collaborating laboratories: https://badamygeny.pl/laboratoria
Visit the laboratory with a printed test order form. Alternatively, blood can be shipped by courier. Please enclose the printed test order form.

5

Payment

Bank transfer

After the test has been made

6

Test result

Will be provided to the person that has ordered the test – the patient or doctor selected by the patient.

7

Medical consultation

How to provide material for testing?

Genetic blood tests:

1. Collect a blood sample into a **single** EDTA tube (do not use serum separation and lithium heparin tubes). Blood can be collected at any time with no requirement on fasting:
    - Adult - ca. 4 ml of venous blood for DNA isolation (mix well with anticoagulant and store at temp. 4°C)
    - Child – ca. 4 ml (minimum 2 ml) of venous blood for DNA isolation (mix well with anticoagulant and store at temp. 4°C)
    - Infant – ca. 1.5 - 2 ml of venous blood for DNA isolation (mix well with anticoagulant and store at temp. 4°C)
2. Describe the tube with patient's first and second name and secure it (e.g. with adhesive tape).
3. Pack the secured tube with filled and signed test order form and send it in line with the following instruction: https://badamygeny.pl/docs/instrukcja-wysylki-probki-krwi.pdf
4. In post-transfusion patients blood for genetic tests can be collected not earlier than 2 months after the procedure.

Paraffin embedded tissue blocks for genetic analyses (cancer profiling):

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1. Collect 4 ml of blood into a **single** EDTA tube (do not use serum separation and lithium heparin tubes). Blood sample can be collected at any time, fasting is not required. Mix blood with anticoagulant well and store at temp. 4°C.
2. Describe the tube with patient's first and second name and secure it (e.g. with adhesive tape).
3. **Collect tumour tissue** for test in form of:
    - Paraffin block with embedded tumour tissue and histological preparation (histological slide) facilitating determination of tumour tissue location,
    - Or 4x4x1mm tumour tissue section from paraffin block containing tumour tissue only.
4. Describe the sample with patient's first and second name and protect it (e.g. with adhesive tape).
5. Pack the secured material with filled and signed test order form and send it in line with the following instruction: https://badamygeny.pl/docs/instrukcja-wysylki-probki-krwi.pdf