MEDIPOL
İSTANBUL MEDİPOL UNIVERSITY
GENETIC DISEASES ASSESSMENT CENTER

EXOM/GENOME SEQUENCE ANALYSIS ANAMNESIS AND CONSENT FORM

PATIENT AND DOCTOR INFORMATION		Date: ... / ... / ...
Barcode	Patient	Name and surname : ..... ID / Passport Number : ..... DOB : ... / ... / ... Gender: ☐ Female ☐ Male Mobile phone : ..... E-mail : ..... Sampling Date : ... / ... / ...
	Doctor	Name and surname : ..... Mobile phone : ..... E-mail : .....

REQUIRED TEST

☐ Whole Exome Sequence Analysis ☐ Clinical Exome Sequence Analysis ☐ Whole Genome Analysis

TEST INFORMATION

☐ Solo (Single) ☐ Duo (Dual) ☐ Trio (Triple) ☐ Trio Plus (If additional family members are included)

ADDITIONAL FAMILY SAMPLE INFORMATION (Fill in Duo, Trio and Trio Plus options)		
Barcode	Father	Name and surname : ..... DOB : ... / ... / ... Sampling Date : ... / ... / ... ☐ Symptomatic ☐ Asymptomatic
Barcode	Mother	Name and surname : ..... DOB : ... / ... / ... Sampling Date : ... / ... / ... ☐ Symptomatic ☐ Asymptomatic
Barcode	Other Family Member (Duo, Trio Plus)	Name and surname : ..... Proximity : ..... DOB : ... / ... / ... Sampling Date : ... / ... / ... ☐ Symptomatic ☐ Asymptomatic

SAMPLE TYPE

☐ Blood EDTA (2-5 ml) ☐ Purified DNA (At least 1 µg) ☐ Other (please specify) .....
(Please indicate the gestational week in prenatal samples)

CLINIC INFORMATIONS (Accurate clinical findings are necessary for the correct interpretation of test results.)

Clinical Indications/Findings: .....

Age of Onset of Findings: .....

Prenatal History (USG/Screening Test etc.): .....

Natal History: Birth Weight: ..... Birth Length: ..... Head Circumference at Birth: ..... Week of Birth: .....

Physical Examination Findings: Height: ..... Weight: ..... Head circumference: .....

DIAGNOSIS/PREDIAGNOSIS

Diagnosis/Pre-diagnosis: .....

Diseases you want to be examined: .....

FAMILY HISTORY

Consanguineous Marriage ☐ Yes ☐ No Affected sibling ☐ Yes ☐ No

Degree of Parental Closeness (Same village, nearby village etc. Please specify if there are any):

Genetic Diseases in the 1st, 2nd and 3rd Degree Relatives of the Patient: .....

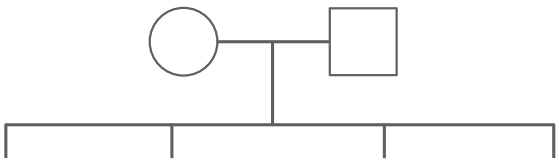
LABORATORY RESULTS

Chromosome Analysis/CGH Array: .....

Other Genetic Tests: .....

Other Laboratory Results (Biochemistry, MRI, CT, USG, ECO, EEG, EMG, Pathology etc.): .....

DRAW PEDIGREE



Mark for phenotype information. (The findings in the table are taken from "Human Phenotype Ontology (HPO)".
You can write the findings that are not included in the table in the "Other" field.)

A. Mouth, Throat and Ear	E. Hematology and Immunology	5. Neuromuscular anomalies
1. Iconductive hearing loss	1. Anemia	5.1 Hyperreflexia
2. External ear malformation	2. Abnormal hemoglobin	5.2 Muscular hypotonia
3. Tooth color anomalies	3. Abnormal Coagulation	5.3 Muscular hypertonia
4. Hypodontia	4. Immunodeficiency	5.4 Spasticity
5. Sensorineural hearing loss	5. Neutropenia	6. Other
6. Cleft lip/palate	6. Pancytopenia	6.1 Regional seizures
B. Skin and Skeleton	7. Splenomegaly	6.2 Headache / Migraine
1. Skin findings	8. Thrombocytopenia	6.3 Dementia
1.1 Abnormal skin pigmentation	F. Cardiovascular	6.4 Encephalopathy
1.2 Abnormal hair structure	1. Angioedema	6.5 Febrile seizures
1.3 Abnormal nail structure	2. Aortic Coarctation	6.6 Stroke
1.4 Hyperextensible leather	3. Arrhythmia	6.7 Generalized seizures
1.5 Ichthyosis	4. Atrial septum defect	6.8 Craniosynostosis
2. Skeleton	5. Aortic dilatation	6.9 Macrocephaly
2.1 Abnormal limb morphology	6. Dilated cardiomyopathy	6.10 Microcephaly
2.2 Abnormal skeletal system	7. Tetralogy of Fallot	6.11 Neuropathy
2.3 Abnormal vertebral column	8. Hypertension	I. Oncology
2.4 Joint hypermobility	9. Hypertrophic Cardiomyopathy	1. Adenomatous polyposis
2.5 Multiple joint contractures	10. Hypotension	2. Lung neoplasm
2.6 Polydactyly	11. Stroke	3. Skin neoplasm
2.7 Scoliosis	12. Heart and great vessel malformation	4. Pheochromocytoma
2.8 Syndactyly	13. Lymphedema	5. Colorectal Carcinoma
2.9 Talipes equinovarus	14. Myocardial infarction	6. Leukemia
C. Gastrointestinal, Genitourinary,Endocrine	15. Vasculitis	7. Breast carcinoma
1. Endocrinological diseases	16. Ventricular septum defect	8. Myelofibrosis
1.1 Diabetes disease	G. Metabolism	9. Paraganglioma
1.2 Hypo/hyperparathyroidism	1. Anomalous creatine kinase	J. Prenatal and Development
1.3 Hypo/hyperthyroidism	2. Increase in CSF lactate level	1. Growth Retardation
2. Gastrointestinal	3. Hypoglycemia	2. Dysmorphic facial features
2.1 Aganglionic megacolon	4. Hyperalanineemia	3. Hemihypertrophy
2.2 Diarrhea	5. Ketosis	4. Hydrops fetalis
2.3 Gastroschisis	6. Lactic acidosis	5. Intrauterine growth restriction
2.4 Obesity	7. Organicaciduria	6. Short stature
2.5 Hepatomegaly	8. Decrease in plasma carnitine level	7. Oligohydramnios
2.6 Liver failure	9. Increase in serum pyruvate level	8. Overgrowth
2.7 Constipation	H. Neurology	9. Premature birth
2.8 Pyloric Stenosis	1. Brain imaging	10. Polyhydramnios
2.9 Vomiting	1.2 Abnormal myelination	11. Tall length
2.10 Elevated hepatic transaminase	1.3 Abnormal cortical structure	K. Reproduction
3. Genitourinary	1.4 Brain atrophy	1. Abnormal external genitalia
3.1 Abnormal kidney morphology	1.5 Heterotop	2. Abnormal internal genitalia
3.2 Abnormal urinary system	1.6 Hidrosefali	3. Hypogonadism
3.3 Hydronephrosis	1.7 Holoprozensefali	4. Hypospadias
3.4 Renal agenesis	1.8 Korpus kallozum agenezisi	5. Infertility
3.5 Renal cyst	1.9 Lizensefali	L. Other (not listed)
D. Eye	1.11 Serebellar hipoplazi	1.
1. Blepharospasm	2. Davranışsal Anomaliler	2.
2. Glaucoma	2.1 Lack of attention	3.
3. Visual impairment	2.2 Autism	
4. Cataract	2.3 Psychiatric diseases	
5. Coloboma	3. Developmental Retardation	
6. Microphthalmia	3.1 Developmental regression	
7. Nystagmus	3.2 Intellectual disability	
8. Ophthalmoplegia	3.3 Delay in speech	
9. Optic atrophy	3.4 Delay in motor development	
10. Ptosis	4. Movement anomalies	
11. Retinitis pigmentosa	4.1 Ataxia	
12. Retinoblastoma	4.2 Chorea	
13. Strabismus	4.3 Dystonia	
	4.4 Parkinsonism	

DEFINITIONS AND GENERAL INFORMATION;

WHAT IS WHOLE EXOME, CLINICAL EXOME AND WHOLE GENOME SEQUENCE ANALYSIS?

Whole Exome Sequencing (WES) is one of the comprehensive and reliable genetic tests; that allows the detection of genetic disease-causing changes. The functional regions of DNA, the hereditary material responsible for protein production, are called exons. In whole-exome sequencing analysis, all of the protein-producing exons of approximately 20 thousand genes in human DNA constituting approximately 1% of human DNA are sequenced using the new generation sequencing technology (New Generation Sequencing System NGS). Clinical exome sequence analysis focuses on genes with known disease-causing effects instead of approximately 20 thousand genes as in the whole exome sequence analysis test, and all protein-producing parts of approximately 6700 genes are tried to be sequenced. The whole genetic material of human DNA, coding or noncoding for protein, is called Genome. Genome analyzes examine many different types of changes in the genome.

TEST REPORTS

The information we obtain as a result of these tests is compared with the reference human genome in order to determine genetic differences. Changes obtained after comparison are classified according to ACMG (American College of Medical Genetics) criteria[1]. According to the patient's clinical findings, pathogenic, possibly pathogenic, and variants of uncertain clinical significance (VUS) in genes are reported using the Human Phenotype Ontology database (HPO). Variants of uncertain clinical significance are preferably reported depending on the patient's clinic, frequency in the healthy population, in-house frequency, and other factors. Whole Exome Sequencing (WES), Clinical Exome, and Whole Genome Sequence Analysis (WGS) are performed in line with the patient's clinical findings. While the carriers that may be compatible with the patient's clinic are reported, other carriers are not reported. In case of requests for carrier tests, it is recommended to contact a Medical Geneticist.

INCIDENTAL FINDINGS

Genetic changes that do not match the patient's clinical findings may also be detected in the analysis. These findings are called incidental findings. In line with the consent of the patient or patient's parents; Among the random changes, pathogenic, possibly pathogenic variants in the genes included in the ACMG guideline are indicated in the report[2]. In trio (patient, mother, and father) analysis, incidental findings are analyzed only in index cases. In order to determine the carrier status of the parents of the coincidental findings defined in the index case (individual patient), new consent should be requested. Incidental findings are not examined in prenatal samples.

USING SAMPLES OF FAMILY MEMBERS IN ANALYSIS

In whole-exome and whole-genome analyses, the patient's data analysis is performed together with the data of the biological mother and father in order to increase the diagnosis rates. This analysis is called trio analysis. In these analyses, genetic changes that are not found in the so-called "de novo" parents but found in the patient are detected. In addition, trio analyses allow a more accurate assessment of the disease-causing potential of some variants of uncertain clinical significance in the patient. Data from other family members also may be included in these analyses (trio plus). Double analysis in which only the sick/healthy sibling or spouses are included with the patient is called "duo analysis".

TECHNICAL LIMITATIONS

Analyses are performed based on current data in line with the patient's clinical findings. The accuracy and completeness of the description of clinical, laboratory, and imaging findings are essential. Detailed questioning of family history is one of the other factors affecting the analyses. Single nucleotide changes and small deletions and insertions can be detected with high accuracy using Whole Exome, Clinical Exome, and Whole Genome Sequence Analysis. Although genetic changes such as large deletions, duplications, and copy number variations (CNV) can be identified by the employed bioinformatics methods, they need to be confirmed by additional methods. Most probably, it is recommended to rule out such genetic alterations through microarray analysis. Due to technical limitations, Whole Exome, Clinical Exome, and Whole Genome Sequence Analysis may not cover the whole targeted region. Statistical information about the scope of the individual analysis is given in the patient's report as a table.

Testing does not exclude genetic variants that may be out of coverage. The physician evaluates the patient's result based on clinical findings and current data. In case of incompatibility, the findings in the anamnesis form are reviewed again. Additional findings, if any, should be reported to our center. Classification of genetic changes according to ACMG criteria may change with new information added. In addition, the phenotype of genes with unknown association with the disease can be identified in the future. For these reasons, the analysis of patients whose diagnosis cannot be made definitively should be done annually. Additional findings detected in patients may help in making the diagnosis. In these cases, reanalysis may be requested.

[1] Richards S, et al. 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.

[2] Miller, D.T., Lee, K., Chung, W.K. et al. ACMG SF v3.0 list for reporting of secondary findings in clinical exome and genome sequencing: a policy statement of the American College of Medical Genetics and Genomics (ACMG). Genet Med (2021). https://doi.org/10.1038/s41436-021-01172-3

I have read and understood the Definitions and General Information form. Signature of the Patient/Patient's Parent

GENETIC ANALYSIS CONSENT FORM

Note: For Whole Exome, Clinical Exome, and Whole Genome Sequence Analysis, written consent from the patient and signing of the form are mandatory. In this consent, approval of the test study must be obtained by the patient/patient representative or the patient's physician.

Your doctor has recommended that you (or someone you have custody of or accompany) have this genetic analysis to clarify the following diagnostic/clinical findings:

.....

(The name of the disease to be examined will be filled by the doctor)

The research material is mostly blood samples. Taking a blood sample does not pose any health risk to the patient. Sometimes it may cause an injury at the place where the blood is drawn or, rarely, nerve/vascular damage may occur. Another risk is mixing samples. All necessary precautions are taken to prevent such errors from occurring.

SIGNIFICANCE OF RESULTS

The genetic test to be performed is only for the disease/indication mentioned above. This test does not guarantee that you and/or your future children will be completely healthy. In case of negative test results, other genetic or non-genetic diseases may occur. Genetic tests are new and developing tests compared to other laboratory tests. Most of these DNA-based tests are based on foreign databases, and most of these diseases do not have mutation profiles and/or polymorphic features defined for the Turkish population. For these reasons, it may not always be possible to reach accurate and precise results in diagnosing single-gene diseases.

In these tests, which are quite complex due to their structure, there is a possibility that sufficient cell/DNA replication cannot be achieved and/or the result is incorrect. The results obtained may not be 100% accurate due to rare genetic variations in the individual's DNA or the complexity of the tests (detailed multi-step). (The acceptable error rate for all laboratories is known to be approximately 1 in 1000 samples.) Re-sampling may be required when the DNA is insufficient and/or confirmation of the diagnosis is required.

The number of viable cells/DNA must be at the desired level in genetic tests. When not enough cells/DNA are obtained or not of the desired quality, resampling may be requested, and the test will be repeated (free of charge). In the presence of any suspicious findings, additional testing from the parents may be recommended (paid).

The specified times for obtaining the test results are given according to the average test result time under normal conditions. Analysis may be concluded earlier or later due to patient or laboratory factors. For this reason, it should be kept in mind that the reported test time is given as an estimation and that a phone call must be made before getting results. In some cases, there may be situations where the biological relationships specified in genetic tests performed on family members do not match with the actual biological relationships. When family members are analyzed, the correct interpretation of the results depends on the accuracy of their assumed relationships. If there is any doubt about kinship, the patient will not be informed about this issue. However, an exception can be made when it is absolutely essential to complete the required test, or it is mandatory to do so under the legal regulations.

Signature of the Patient/Patient's Parent

(Please read carefully)

"I have received, read, and understood the written explanation of the genetic analysis. Statements about the disease were made to me." .... (The above statement will be written precisely by the patient/patient representative)
I was given explanations about the genetic basis of the disease, the possibility of prevention/treatment, the purpose, scope, and importance of the planned genetic test(s), as well as any risks associated with blood sample collection. All my questions were answered, and sufficient reflection time was allowed.
I give my consent to handling the samples; collection, storage, and destruction of the samples at the end of the legal period by the Genetic Diseases Assessment Center following the provisions of the "Regulation on Personal Health Data" published in the Official Newsletter No. 30808.
If deemed necessary, test results can be used to inform or test my family members.
I consent to store the data obtained by the patient's sample and test throughout the legal process.
The test results can also be used in researching, diagnosing, and improving the treatment of genetic diseases. In this case, personal data is anonymized or encrypted (nicknamed). I consent to the storage and use of my pseudonymized or anonymized test results in a statistical database for scientific purposes and to improve and facilitate the diagnosis of genetic changes and diseases in other patients.
Test results are essential for medical research and studies for physicians, scientists, and researchers to investigate genetic diseases and improve their diagnosis and treatment. I consent to share and process the results stored in the database with doctors, scientists, and researchers, provided that my identity information is not included.

Per my signature below, I consent to genetic analysis and taking the necessary blood sample for the disease/clinical findings mentioned above. I have been told that I can withdraw my full or partial consent at any time, without giving any reason, and that I have the right (right not to know) information about the test results. I understand that I can request the destruction of non-anonymous test materials (including all collected components) and all results collected until then.

I understand that anonymous reports and sample materials cannot be destroyed at my request once anonymized. Therefore, I accept that any right to the report and material after anonymization belongs to Istanbul Medipol University Genetic Assessment Center.

Incidental Findings

I agree and consent to reporting incidental findings detected in Whole Exome, Clinical Exome, and Whole Genome Sequence Analysis.

☐ Yes ☐ No

I have read and understood all of the above explanations and information texts and the risks described. I agree to be tested.

Name, Surname, Date
Signature of Patient/Patient Parent

Name, Surname, Date
Doctor's Signature