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Cod: 0638

EVALUATION OF SOME ANTIOXIDANT ENZYME ACTIVITIES (SOD AND GPX) AND THEIR POLYMORPHISMS (MNSOD2 ALA9VAL, GPX1 PRO198LEU) IN FIBROMYALGIA

A. Akbas[1], A. Inanir[2], I. Benli[1], Y. Onder[3], L. Aydogan[1]
[1]*Department of Biochemistry, Gaziosmanpasa University, Medical Faculty, Tokat, Turkey*
[2]*Department of Physical Therapy and Rehabilitation, Gaziosmanpasa University, Medical Faculty, Tokat, Turkey*
[3]*Department of Public Health, Gaziosmanpasa University, Medical Faculty, Tokat, Turkey*

BACKGROUND: Fibromyalgia syndrome (FMS) is a pain syndrome in which common pain in muscle-skeletal system, sleeping disorder and fatigue symptoms coexist. The aim of the present study was to determine superoxide dismutase (SOD) and glutathione peroxidase (GPX) enzyme levels in FMS as well as to investigate possible associations between FMS and Ala9Val polymorphism of MnSOD2 and Pro198Leu polymorphism of GPX1.

METHODS: The study included 127 women FMS patients and 56 healthy women. Total SOD and total GPX enzyme activities were determined in patient and control groups. Enzyme activities were determined based on colorimetric methods. In addition, frequencies of Ala9Val polymorphism of MnSOD2 and Pro198Leu polymorphism of GPX1 were also detected. Genomic DNA samples were extracted from the peripheral leukocytes of the venous blood. Target fragments of the human MnSOD2 Ala9Val and GPX1 Pro198Lgenes were amplified using specific primers. To identify SNPs, genotyping was performed using PCR amplification, and polymorphisms were detected with hybridization probes labeled with fluorescent dyes

RESULTS: SOD enzyme activity was higher in FMS group compared to control ($p < 0.001$). GPX enzyme activity, on the other hand, was not different between FMS and control groups. No significant differences were found between genotype and allele frequencies of GPX1 and MnSOD2 polymorphisms ($p = 0.087$). Frequencies of Ala9Val genotypes of MnSOD were 21.3% for Ala/Ala, 54.3% for Ala/Val, and 24.4% Val/Val in FMS groups, and 28.6% for Ala/Ala, 39.3% for Ala/Val, and 32.1% for Val/Val in control group. Analysis of the data was performed using IBM SPSS Statistics Version 20.

CONCLUSIONS: FMS frequency in adult women in Turkey is 3.6%. Because of higher incidence of FMS in women, patient and control groups in the present study were composed only of women subjects. Elevated total SOD and unchanging total GPX1 activities in FMS patients could be the reason for increased oxidative stress and lipid peroxidation in FMS. Genotype and allele frequencies of Ala9Val polymorphism of MnSOD2 and Pro198Leu polymorphism of GPX1 in FMS have been studied first time in the present study, and no associations were found between them and FMS.
Key Words: Fibromyalgia, SOD, GPX, oxidative stress, polymorphism

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SERUM MMP-2 LEVELS AND MMP-2 GENE POLYMORPHISM IN PRE-ECLAMPSIA

K. Ankush[1], U. Manaktala[1], B. Koner [1], T. Mishra[1]
[1]*Maulana Azad Medical College*

BACKGROUND: Pre-eclampsia affects 3-5% of pregnancies worldwide and increases maternal-fetal morbidity and mortality. Reduced placental perfusion induces the release of biomolecules by the placenta into maternal circulation causing endothelial dysfunction. Zinc dependent matrix metalloproteinase-2(MMP-2) may be upregulated and interacting with circulating factors of oxidative stress and inflammation to produce endothelial dysfunction in pre-eclampsia. Aim: to study the functional polymorphism of MMP-2 gene in pre-eclampsia and its effects on the serum MMP-2 levels in these patients.

METHODS: Fifty pre-eclampsia patients and fifty age and gestation period matched healthy pregnant women with their consent were recruited in the study. Serum MMP-2 levels in all subjects were estimated using standard ELISA kits. MMP-2 gene (g.- 1306 C>T and g.-735 C>T) SNPs were genotyped using whole blood by ASO-PCR.

RESULTS: The pre-eclampsia patients had higher serum levels of MMP-2 compared to the healthy pregnant ($P<0.05$). Although pre-eclampsia were not linked to the MMP-2 genotypes, but the MMP-2 haplotype were associated with significant alteration in the serum MMP-2 concentration in these patients.

CONCLUSIONS: This study results suggest an association of MMP-2 genetic polymorphism and serum levels of MMP-2 to the path physiology of hypertensive disorder of pregnancy.

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FAMILIAL MEDITERRANEAN FEVER: CLINICAL AND GENETIC CHARACTERIZATION OF GEORGIAN FAMILIES

G. Basheleishvili[2], C. Timman[1], K. Kvatadze[2], S. Kavsadze[2], L. Zangurashvili[2], N. Abramishvili[3], N. Kankia[2], M. Lomidze[2], N. Jashiashvili[2], T. Phirtskhalaishvili[2], T. Dzagania[2], D. Metreveli[3], I. Rtskhiladze[2]
[1]*Bernhard-Nocht-Institut for Tropical Medicine*
[2]*Children's Hospital Mrcheveli*
[3]*Medical Center "Mrcheveli"*

BACKGROUND: Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease, characterised by recurrent attacks of fever, serositis and arthritis, which primarily affects non-Ashkenasi Jews, Armenians, Arabs and Turks. A small number of FMF cases are also described in other ethnic groups. Very few data are available on the presence and genetic spectrum of FMF in Georgian patients. The purpose of our study was to find FMF cases in ethnically Georgian patients through genetic testing; to investigate distribution of FMF gene mutation in this ethnic group and to compare mutation distribution in Georgians with population at risk (Jews, Armenians, Arabs and Turks).

METHODS: 104 patients from ethnical Georgians, with clinically suspected diagnosis of FMF, mean age 21.5 year (2-73 year), 59 male, 45 female, underwent molecular genetic studies using polymerase chain reaction. Genetic study was performed in Bernhard-Nocht-Institut for Tropical Medicine, Hamburg, Germany. We also registered clinical manifestations, severity of disease, treatment and its efficacy (using standardised questionnaire) and correlated them with mutation.

RESULTS: FMF gene mutations were found in 104 patients. The M694V Mutation was predominant; it was in 61 patients (58,7%). M68OJ/M694V in 9 patients (8,7%), M694V/R761H in 5 patients (4,8%), M694V/E148Q in 4 patients (3,8%), V726A/E167D in 2 patients (1,9%), other mutations were in 22 patients (21,2%). 56 patients (53,8%), were homozygous M694V/ M694V, 35 patients (33,7%) were compound heterozygotes for M694V and other mutation. Family history of FMF was positive only in 15 (14,4%) cases. Most frequent clinical symptom was fever in 96 patients (91,3%), abdominal pain in 87 patients (84,6%), operation on abdomen in 36 patients (34,6%), arthralgia in 60 patients (57,7%). Renal function was deteriorated in 11 (10,6%) cases, 1 patient (1,0%) were on hemodialysis, renal biopsy (RB) was done in 3 (2,9%) cases. Treatment with colchicine was performed in 37 cases (35,6%).

CONCLUSIONS: FMF is present in ethnical Georgians. Most frequent mutation is M694V. Distribution of mutations is more similar to north African Jews and differs from Armenians in Armenia and Turks. No new mutation was found in Georgian patients.

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ANALYSIS OF MANGANESE SUPEROXIDE DISMUTASE (MNSODALA-9VAL) AND GLUTATHIONE PEROXIDASE (GPX1 PRO 198LEU) GENE POLYMORPHISMS IN VITILIGO

H. Yıldız Seçkin[2], G. Kalkan[2], İ. Bütün[1], A. Akbaş[1], Y. Baş[2], N. Karakuş[3]
[1]*University of Gaziosmanpaşa, Faculty of Medicine, Department of Biochemistry*
[2]*University of Gaziosmanpaşa, Faculty of Medicine, Department of Dermatology*
[3]*University of Gaziosmanpaşa, Faculty of Medicine, Department of Medical Biology*

BACKGROUND: Vitiligo is an autoimmune chronic depigmentation disorder caused by melanocyte loss. Although there have been no specific data related to the etiopathogenesis of the disease; genetic, autoimmune, neural mechanisms, and biochemical factors are the most accused mechanisms. Recent studies have suggested that ROS levels and decreased antioxidant system functions play role in vitiligo pathogenesis. In this study, we aimed to investigate possible associations of Mangan Superoxide dismutase (MnSOD) Ala-9Val and Glutatyon Peroxidase-1 (GPx1) Pro198Leu polymorphisms with vitiligo in Turkish population.

METHODS: Vitiligo clinical types were classified as localized type (32 patients,%56.1), generalized type (22 patients, %38.6), and universal type (3 patients, %5.3).Genomic DNA was extracted from peripheral leukocytes of whole blood and genotyping was performed to identify MnSOD Ala-9Val and GPx1 Pro198Leu polymorphisms by a method based on PCR amplification and detection of polymorphisms with hybridization probes labeled with fluorescent dyes. Genotype and allele frequencies were compared between patients with vitiligo and healthy control subjects.

RESULTS: The frequencies of Ala/Ala, Ala/Val and Val/Val genotypes of MnSODAla-9Val polymorphism in the patients were 21.7%, 46.7% and 31.7%; in the controls were 17.4%, 47.8% and 34%. The frequencies of Pro/Pro, Pro/Leu and Leu/Leu genotypes of GPx1 Pro198Leu polymorphism in the patients were 40%, 48.3% and 11.7%; in the controls were 42%, 39.1% and 18.8%. There was no significant difference between the MnSOD Ala-9Val SNP genotype distributions and allele frequencies of the vitiligo patients and the control group (p=0.919 and p=0.685, respectively). There was also no significant difference between distributions of the genotype or allele frequencies of the GPx1 Pro198Leu SNP of the patient groups and control subjects (p=0.438 and 0.801, respectively).

CONCLUSIONS: This is the first report investigating the possible associations between the MnSOD Ala-9Val and GPx1 Pro198Leu polymorphisms in Turkish population even if no significant difference was found between patient groups and control subjects. Further studies with large cohort on different populations and ethnicities will be able to better clarify the association.

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TUMOR NECROSIS FACTOR (TNF-A) GENE POLYMORPHISMS AND CARDIAC SARCOIDOSIS

E. Manali[1], E. Gialafos [1], F. Triposkiadis [3], V. Kouranos [2], A. Rapti[2], H. Kosmas [3], G. Giamouzis [3], E. Perros [2], M. Gazouli[1]
[1]*National and Kapodistrian University of Athens*
[2]*Outpatient Sarcoidosis Clinic, General Hospital of Chest Diseases "Sotiria", Athens*
[3]*University of Thessaly*

BACKGROUND: The induction of Th1 and suppression of Th2 response is predominant in sarcoidosis granuloma formation and strongly associated with TNF-α production. Polymorphisms in the promoter region of the TNF-α gene result in high and low TNF-α producers. Frequency of the rare TNF-α -308 allele was significantly higher in Japanese patients with cardiac sarcoidosis. Cardiac sarcoidosis (CS) is the leading cause of sarcoidosis mortality and remains underdiagnosed. The identification of genetic predisposition could play a critical role in the identification of underlying subclinical forms of CS. The present study was conducted to investigate possible correlations between the emergence of CS and the -1.031(T/C), -857(C/T), -308(G/A), and -238(G/A) TNF-α gene polymorphisms in a well-defined Greek cohort.

METHODS: One-hundred and seventy three sarcoidosis patients (42 with CS) were recruited. Diagnosis of sarcoidosis was established when clinicoradiological findings were supported by histologic evidence. CS was determined according to standard criteria. DNA was isolated from peripheral blood with the NucleoSpin Blood Kit (Macherey-Nagel, Germany). The -1031(T/C), -857(C/T), -308 (G/A) and the -238 (G/A) polymorphisms of TNFα gene were genotyped as previously described

RESULTS: There was no significant difference between the panel of patients with cardiac and non-cardiac sarcoidosis concerning the -1.031(T/C) and -238(G/A) TNFα polymorphisms. Regarding the -857 (C/T) polymorphism, the TT genotype and the T allele were found to be over-represented in sarcoid patients with CS (p = 0.02 and 0.012, respectively). AA genotype of the -308 (G/A) as well as the A allele were also found significantly more frequently in patients with CS (p = 0.014 and 0.012 respectively). From the investigated TNFα promoter polymorphisms, 9 main haplotypes were deduced. Haplotypes 3 and 5, including A nucleotide position -308, and T nucleotide at position -857 respectively, were significantly over-represented in the sarcoidosis group with cardiac involvement.

CONCLUSIONS: To date, still we do not know what predisposes some sarcoidosis patients to develop cardiac involvement. We showed that TNFα -857T and -308A variants are associated with cardiac involvement in Greek patients with sarcoidosis.

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THE ROLE OF FUNCTIONAL POLYMORPHISMS INVOLVED IN HOMOCYSTEIN METABOLISM

S. Erge[4], S. Karaca[2], N.H. Aksoy[2], T. Kankiliç[1], T. Cesuroglu[3]
[1]*Aksaray University, Faculty of Science and Arts, Biology Department, Aksaray, Turkey*
[2]*Aksaray University, School of Health Science, Aksaray, Turkey*
[3]*Maastricht University, Institute for Public Health Genomics, Maastricht, Netherlands*
[4]*Zirve University, Faculty of Health Science, Department of Nutrition and Dietetics, Gaziantep, Turkey*

BACKGROUND: An increased plasma concentration of total homocysteine (tHcy) is not only an important risk factor for the development of cardiovascular diseases, but it is also has significant impact on development of neurodegenerative disorders, as well as estrogen-related hormonal cancers. Hyperhomocysteinemia is caused by both nutritional and genetic factors. Polymorphisms in the Methylenetetrahydrofolate reductase (MTHFR), Methionine synthase reductase (MTRR) genes are the important risk factors effecting tHcy level. In this study we investigated a relation between functional polymorphisms of MTHFR c.677 C>T (p.Ala222Val), c.1298 A>C (p.Glu429Val) and MTRR c.66 A>G (p.Ile22Met) with plasma homocystein level. Additionaly, Catechol-O-methyltransferase (COMT) variation at position c.472G>A (p.Val158Met) was included, which is important enzyme contributing to homocysteine formation via the methylation of endogenous catecholamines and catechol estrogens.

METHODS: MALDI-TOF based MassArray platform was used for genotyping of n=200 subjects. Multiple statistical analyses were performed to assess the influence of polymorphisms on tHcy.

RESULTS: Total Hcy was higher in males with MTHFR c.677T genotype (p=0.03), while any association were found in females. We unable to find relation between tHcy and variants of MTRR c.66 A>G and MTHFR c.1298 A>C. Significant relation was established with COMT c.472A (p.Met158) allele and tHcy level in females (p=0.01).

CONCLUSIONS: It is known that the c.472AA genotype is related with lower COMT activity in females and could promote a hypercatechol-estrogenic state, which might be implicated in the pathogenesis of mental disorders. The results of our study provides an evidence that the same COMT variant has gender depend influence on tHcy concentration and may be a risk factor for cardiovascular disorders in Turkish women. Our results will hopefully assist in the design of future studies that will investigate contribution of personal characteristics and nutritional factors to homocysteine level in Turkish population.

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CLINICAL CHARACTERISTICS OF GYNECOLOGICAL CANCER IN BRCA MUTATION CARRIERS AND NONCARRIERS

X. Gabaldó Barrios[1], A.I. Sánchez Bermúdez[1], P. Sánchez [1], M.D. Sarabia Meseguer[1], M. Marín Vera[1], J.L. Alonso Romero[1], F. Ruiz-Espejo[1]
[1]*University Hospital Virgen de la Arrixaca, Murcia, Spain*

BACKGROUND: BRCA 1/2 germline mutations are the most common defect that gives rise to hereditary ovarian cancer, accounting for about 10% of cases. Unlike in breast cancer, less is known about the clinical and pathologic features in gynecological tumors in BRCA mutation carriers. We evaluated phenotypes in gynecological tumors considering BRCA-positive patients and BRCA-negative patients.

METHODS: 44 gynecological tumors were selected from Genetic Counselling between April 2007 and January 2014. Diagnosis (histology and stage) were reviewed by a gynecologic pathologist. Information collected included BRCA status, age at diagnosis, affectation with breast cancer, tumor pathology data and stage classification according to the FIGO Staging System (I-II stage or III-IV stage). Median age at diagnosis, affectation with breast cancer and stage were compared for BRCA carriers and noncarriers using a Mann–Whitney U test or chi-square approximation, as appropriate. p values <0.05 were considered statistically significant.

RESULTS: Of all cases, 16 were BRCA-positive (36.4%) and 28 were BRCA-negative (63.6%). Median age at diagnosis was 54 (13-76) among BRCA carriers and 47 (19-73) among noncarriers (p=0.138). Breast and ovarian cancer in the same patient was in 10 cases (62.5%) among BRCA carriers and 9 cases (32.1%) among noncarriers (p=0.051). Tumor pathology data within BRCA carriers: 11(78.6%) serous, 0(0%) mucinous, 1(7.1%) endometroid, 0(0%) clear cell, 1(7.1%) transitional cell, 1(7.1%) mullerian tumor, 0(0%) endometrial cancer and 2 cases unknown; within noncarriers: 6(30%) serous, 6(30%) mucinous, 4(20%) endometroid, 1(5%) clear cell, 0(0%) transitional cell, 0(0%) mullerian tumor, 3(15%) endometrial cancer and 8 cases unknown. Regarding clinical stage, among BRCA-positive: 0(0%) stage I-II, 8(100%) stage III-IV and 8 cases unknown; among noncarriers: 13(65%) stage I-II, 7(35%) stage III-IV and 8 cases unknown (p=0.002).

CONCLUSIONS: Within BRCA mutation carriers, there are more cases of breast and ovarian cancer in the same patient, the majority of all cancers are serous, mucinous tumors and endometrial cancers are uncommon and have higher stage tumors than within noncarriers. The age at diagnosis not differ between BRCA mutation carriers and noncarriers.

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A188D NEW MUTATION OF GCK GENE CAUSES MODY TYPE 2 IN A LARGE SPANISH FAMILY OVER THREE GENERATIONS

E. Gastaldo[3], C. Fajardo[1], A. Zuniga[2], M. Ortiz[2], I. Aleixandre[2]
[1]*Servicio de Endocrinologia, Hospital Univ. de la Ribera, Alzira, Valencia, Spain*
[2]*Servicio de Genetica, Hospital Univ. de la Ribera, Alzira, Valencia, Spain*
[3]*Servicio de Pediatria, Hospital Univ. de la Ribera, Alzira, Valencia, Spain*

BACKGROUND: MODY is a monogenic disease which accounts for 2–5% of all diabetes cases. The most frequent form is HNF-1alfa-MODY (MODY type 3), which is caused by mutations in the HNF1A gene encoding hepatic nuclear factor 1alfa. The second most frequent form is GCK-MODY (MODY type 2), which has been shown to be the result of mutations in the GCK gene (7p15.3-p15.1) that encode a protein glucokinase. Heterozygous inactivating mutations cause GCK-MODY, which mostly presents with mild hyperglycemia and is inherited in an autosomal dominant fashion. Homozygous or compound heterozygous inactivating GCK mutations result in a more severe phenotype presenting at birth as permanent neonatal diabetes mellitus. Heterozygous activating GCK mutations, in contrast, cause persistent hyperinsulinemic hypoglycemia of infancy. We report a novel heterozygous inactivating GCK gene mutation in a nonobese family diagnosed with diabetes over three generations. Index case was a three-years-old infant with a hyperglycemia (115 mg/dl). Her family history was strongly positive for diabetes. The patient's mother, her grandfather, and several members on her mother's side were diagnosed with diabetes. This clinical presentation was highly suggestive of GCK-MODY.

METHODS: Therefore, a mutation analysis of the GCK gene was initiated. Genomic DNA of the patient was isolated, and PCR amplification of the pancreas-specific exon 1a as well as of exons 2–10 of the GCK gene was performed. Sequencing of the PCR products identified a novel mutation p.Ala188Asp (c.563C>A; NM_000162.2) encoded by exon 5 of GCK gene.

RESULTS: Carrier screening of clinically affected family members revealed the same mutation in large pedigree.

CONCLUSIONS: Because of the typical clinical symptoms and the cosegregation of the phenotype with the genotype, we conclude that this novel mutation is a pathogenic one and not a polymorphism without an effect on protein function. The identification of a GCK gene mutation is important for the correct and definite diagnosis of GCK-MODY. It also helps the clinician to predict the clinical course of the disease and to advise appropriate therapy. Since only mild fasting hyperglycemia and no diabetes-related complications are usually present, diet is sufficient as a therapeutic approach in most cases.

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ANALYSIS OF GENOTOXIC EFFECTS OF INHALATION ANESTHETICS IN BRONCHOALVEOLAR CELLS USING COMET ASSAY

Z. Cukurova[1], A. Gedikbasi[1], S. Ozturk[2], H. Cetingok[1], G. Eren[1], D. Ozturk[2], O. Hergunsel[1], K. Cefle[2], S. Palanduz[2]
[1]*Bakirkoy Dr.Sadi Konuk Training and Research Hospital*
[2]*Istanbul University, Istanbul Faculty of Medicine, Division of Medical Genetics*

BACKGROUND: The single-cell gel electrophoresis (comet) assay is a sensitive and powerful method for determining DNA strand breaks, a significant indicator of genotoxic and cytotoxic effects on cells. Sevoflourane and desflourane are preferred inhalation anesthetics in general anesthesia because of providing quick induction and recovery. In this study, we aimed to determine of DNA damage by comet assay in patients under sevoflurane and desflourane anesthesia. To the best of our knowledge, this is the first paper that has been studied in the bronchoalveolar lavage (BAL) cells.

METHODS: Forty eight patients who planned to have disc herniation surgery were included. BAL fluid and blood were taken immediately after administrating anesthesia and at the end of the surgery. Comet assay was applied to study genotoxic properties of two inhalation anesthetics in human BAL cells. We measured as total comet length, comet height, comet area, tail length. The images were measured and saved with TriTek Comet Score freeware v1.5. DNA damage in blood cells was measured quantitatively with 8-hydroxy-2'-deoxyguanosine (8-OHdG) test using ELISA. Comet assay parameters and 8-OHdG levels were analyzed statistically in order to investigate the genotoxic effects and to compare the effects of two different inhalation anesthetics.

RESULTS: We found that comet length and tail length increased in BAL fluid cells taken after inhalation anesthesia from sevoflourane and desflourane groups (279,81±84,52 and 368,25±46,81 258,55±27,95 p=0,016 and 320,21±53,09, p=0,026, respectively). When two drugs were compared, mean comet length, mean comet height and mean comet area of sevoflourane group was found to be significantly higher than those of desflourane group (p=0,046, p=0,016, p=0,013, respectively). A time-dependent increase of 8-OHdG level was observed in the peripheral blood cells (p=0,046).

CONCLUSIONS: We found significantly DNA damage in BAL fluid with comet assay following inhalation in both groups. Inhalation anesthetics may have genotoxic potential. The observed genotoxic effects in the BAL cells may cause any long-term effect in patients requiring repeated surgery in later life. The possible mutagenic effects of genotoxicty must be considered.

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STUDIES OF GENETIC VARIATION OF G6PD GENE IN A TUNISIAN PATIENTS WITH G6PD DEFICIENCY

F. Ghoul[1]
[1]*PhD Student*

BACKGROUND: The glucose-6-phosphate dehydrogenase (G6PD) deficiency, also called favism, a genetic enzyme deficiency disease. This is the most common deficiency in the world:it involves more than 420 million people. It primarily affects African populations, Mediterranean and Far East. The main clinical manifestation of this deficit is hemolysis, which can be acute or chronic or neonatal jaundice in the newborn (Kaddari,2004). The G6PD gene is X-linked. The G6PD gene is highly polymorphic; over 400 variants have been identified by the identification of mutations in the gene. Among these variants non-deficit presented by the variants B+ and A+ with normal enzyme activity and loss variants presented by the variants B and A- obtained by additional mutations in the genes of normal enzymes B+ and A+ are distinguished. In this study we looked for possible mutations in a subpopulation of Tunisian patients with G6PD deficiency.

METHODS: Our study focused on 40 blood samples, 20 control patients without deficit in G6PD and 20 patients with G6PD deficiency, from Tunisian people of different origins. The age of these patients ranged from a few days (newborn) to 70 years. DNA extraction was performed on blood leucocytes by proteinase K lysis followed by protein salting-out and ethanol precipitation and by affinity chromatography. DNA amplification was done by conventional PCR using specific primer pairs flanking each G6PD exon or group of exons. The amplified product of exons 6,7 and 8 from three deficient and one control patients were sequenced using the ABI Prism 3100 Avant-Genetic Analyzer and Big Dye Terminators technology (Applied Biosystems/Hitachi).

RESULTS: We have succeeded in this work to identify the 9 exons of G6PD (exon 2 to exon 10) by conventional PCR amplification of exon 2 based on the variation of the hybridization temperature. PCR results revealed bands of the expected sizes for each exon or group of exons. Alignment blasting sequences showed Sequencing of exons 6, 7 and 8 has allowed us to detect three types of mutation (substitution and insertion). four substitutions in patient 1 these mutations are located in exon 6 which encoded for the catalytic site of the G6PD enzyme, the analysis of the protein sequence indicated that two silent mutations are found and the two others have caused a substitution of amino acids. We observed also one insertion in exon 6 in patient 2; this mutation caused a modification of a large part of the sequence of amino acids. For both exons 7 and 8 we found no mutations.

CONCLUSIONS: We conclude that most mutations found in exon 6, who encoded for the catalytic and the substrate binding sites of the enzyme of G6PD. Any point mutation in this exon, which can alter the amino acid sequence, can influence on the enzyme activity and cause the deficit. The substitutions of bases at these exons have been described in the literature. The insertion appear beings that have not been described by researchers.

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INVESTIGATION OF PARAOXANASE ENZYME POLYMORPHISM IN PATIENTS WITH ALOPECIA AREATA

A. Gurel[3], G. Kalkan[4], M. Kulac[1], H. Ozyurt[2], H. Erdogan[5], F. Tulubas[3], B. Topcu[6]
[1] *Department of Dermatology, Faculty of Medicine, Namik Kemal University, Tekirdag, Turkey*
[2]*Department of Biochemistry, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey*
[3]*Department of Biochemistry, Faculty of Medicine, Namik Kemal University, Tekirdag, Turkey*
[4]*Department of Dermatology, Faculty of Medicine, Gaziosmanpaşa University, Tokat, Turkey*
[5]*Department of Physiology, Faculty of Medicine, Namik Kemal University, Tekirdag, Turkey*
[6]*Departments of Biostatistics, Faculty of Medicine, Namık Kemal University, Tekirdağ, Turkey*

BACKGROUND: We evaluated the relationship between polymorphisms of the paraoxonase 1 (PON 1) gene and the risk of alopesia areata (AA) disease in Turkish patients.

METHODS: Our study included 223 volunteers, classified into two groups: 104 healthy volunteers and 119 AA patients aged 60.0 ± 9.7 and 64.3 ± 12.3 years, respectively. Polymorphisms of the PON1 gene were determined using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) techniques.

RESULTS: There was no significant difference between the PON1 genotype distribution in the two groups of AA and controls.

CONCLUSIONS: The polymorphisms of the PON 1 gene studied are not related to increased risk of AA in the Turkish population.

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THE FREQUENCY OF FAMILIAL MEDITERRANEAN FEVER GENE MUTATIONS AND GENOTYPES AT KOCAELI

E. Kale[1], H. Sezikli[1], C. Yakicier[2]
[1]*Department of Central Laboratory, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey*
[2]*Department of Molecular Biology and Genetics, Faculty of Medicine, Acıbadem University, Istanbul, Turkey*

BACKGROUND: In this study we have retrospectively analysed the mutation spectrum of the 293 Familial Mediterranean fever patients referred to Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey, Department of Central Laboratory over a period of one years between March 2013 and February 2014 were investigated.

METHODS: We analyzed the pyrin domain of MEFV gene in 293 Turkish patients by PCR-analysis and direct sequencing

RESULTS: We have found 10 different mutations, including rare mutations such as K695R and 21 different genotypes showing the heterogeneity of MEFV Mutations in North West Anatolia. We found at least one mutation in 139 of 293 (47.44%) patients; homozygous R202Q and M694V; 1 had 3 mutations; 22 had 2 homozygous mutations, 28 had 2 compound heterozygous mutations; 89 had 1 mutation and 154 had none of the mutations covered in the tests. The most frequent genotypes are M694V/Wt, E148Q/Wt and M680I/Wt found in 34 (24.46 %), 20 (14.38 %) and 10 (7.19 %) patients respectively. Interestingly, among the genotypes carrying two or more mutations most common ones are M680I /M694V (9 patient, 6.47 %) and the genotype of all 1 patients with three mutations is R202Q/R202Q/M694 (0.72 %). The allelic frequency of the M694V (48.16 %), V726A (16.23 %), E148Q (15.18 %), M680I (12.56 %) mutations were the most frequent.

CONCLUSIONS: Our study is reflecting the mutational heterogeneity of MEFV and summarize mutational spectrum of Kocaeli regions.

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GENETIC SCREENING OF MEDULLARY THYROID CANCER IN ALGERIAN PATIENTS

K. Sifi[1], N. Abadi[1], a.K. Lezzar[2], K. Boudaoud[2], N. Nouri[2], S. hanachi[1], K. Benmebarek [1], C. Benlatreche [1]

[1]*Biochemistry Service, Ibn Badis Hospital, Constantine, Algeria, Laboratory of Biology and Molecular Genetics, Faculty of Medicine, University 3 Constantine Algeria*

[2]*Endocrinology Service, Ibn Badis Hospital, Faculty of Medicine, Constantine, Algeria*

BACKGROUND: Medullary Thyroid Carcinoma (MTC) can occur in hereditary (25%) or sporadic form (75%). In the hereditary forms, MTC is the major component of the Multiple Endocrine Neoplasia Syndrome type 2 (MEN 2). MEN 2, which includes MEN2A (Multiple Endocrine Neoplasia Syndrome type 2A) , MEN 2B (Multiple Endocrine Neoplasia Syndrome type 2B) and FMTC (Familial medullary thyroid cancer) is caused by autosomal dominant gain-of-function mutations of RET proto-oncogene. Early prophylactic total thyroidectomy before the development of MTC is currently the only curative treatment. The aims of this study: Determine the frequency and the localization of the detected RET proto-oncogene changes in MTC case index and their relatives.- Present the phenotype–genotype correlation in Algerian MEN2 families.

METHODS: DNA was extracted from the peripheral blood lymphocytes of a total of 40 persons, including 25 MTC probands and 15 of their unaffected kindred's. Exon 8, 9, 10, 11, 13, 14, 15 and 16 of the RET gene were amplified by PCR and sequenced. Informed consent was obtained from all subjects.

RESULTS: The C634Y RET exon11 germline mutation was detected in 8% of our MTC index cases and in 46.66% of their relatives. In MEN2, RET G691S/S904S haplotype is more frequent. In relatives G691S and S904S polymorphisms identical to those of MEN2 index cases were found but in the homozygous state, suggesting that this haplotype have a modifying effect on the age of onset of MTC in MEN2A. That is what was observed in our relatives. In sporadic MTC, the exon 11 non synonymous G691S SNP, was strongly present. Several studies have shown that this SNP is associated with predisposition to sporadic MTC. In our patients, the C634Y mutation was significantly associated with the presence of pheochromocytoma, which is consistent with the literature data.

CONCLUSIONS: The identification of the C634Y mutation allowed us to offer to the mutated case index and their relatives prophylactic thyroidectomy.

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FAMILIAL MEDITERRANEAN FEVER: CLINICAL AND GENETIC CHARACTERIZATION OF AZERBAIJAN FAMILIES

S. Kavsadze[2], T. Christian[1], B. Giorgi[2], K. Kvatadze[2], L. Zangurashvili[2], N. Kankia[2], M. Lomidze[2], N. Abramishvili[2], N. Jashiashvili[2], T. Dzagania[2], T. Phirtskhalaishvili[2], D. Metreveli[2], I. Rtskhiladze[2], I. Rtskhiladze[2]
[1]*Bernhard-Nocht-Institut for Tropical Medicine*
[2]*Children's Hospital Mrcheveli*

BACKGROUND: Familial Mediterranean Fever (FMF) is an autosomal recessive hereditary disease, characterised by recurrent attacks of fever, serositis and arthritis, which primarily affects non-Ashkenasi Jews, Armenians, Arabs and Turks. A small number of FMF cases are also described in other ethnic groups. Very few data are available on the presence and genetic spectrum of FMF in Azerbaijan patients. The purpose of our study was to find FMF cases in ethnically Azerbaijan patients through genetic testing; to investigate distribution of FMF gene mutation in this ethnic group and to compare mutation distribution in Azerbaijan with populations at risk.

METHODS: 10 ethnical Azerbaijan patients with clinically suspected diagnosis of FMF, mean age 19,2 year (4-45 year), 7 male, 3 female, underwent molecular genetic studies using polymerase chain reaction. Genetic study was performed in Bernhard-Nocht-Institut for Tropical Medicine, Hamburg, Germany.We also registered clinical manifestations, severity of disease, treatment and its efficacy (using standardised questionnaire) and correlated them with mutation.

RESULTS: FMF gene mutations were found in 10 patients; The M694V Mutation was present in 2 patients (20%). M680J/M6994V in 1 patient (10%), M694V/R761H in 1 patient (10%), Other mutations were in 6 patients (60%). 4 patients (40%) were homozygous M694V/ M694V, 3 patients (30%) were compound heterozygotes for M694V and other mutation. Family history of FMF was positive only in 2 (20%) cases. Most frequent clinical symptom was abdominal pain and fever in 9 patients (90%). Arthralgia was present in 4 patients (40%). Renal function was deteriorated in 2 (20%) cases, 1 patient were on hemodialysis. Treatment with colchicine was performed in 3 cases (30%).

CONCLUSIONS: FMF is present in ethnical Azerbaijans. Most frequent mutation is M694V. Distribution of mutations is more similar to north African Jews and differs from Armenians in Armenia and Turks. No new mutation was found in Azerbaijan patients.

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MOLECULAR GENETIC DIAGNOSTICS OF HUNTINGTON DISEASE IN CROATIAN PATIENTS

H. Ljubić[1], A. Merkler[1], D. Caban[1], A. Acman Barišić [1], S. Telarović[2], J. Sertić[1]
[1]*Department of Laboratory Diagnostics, University Hospital Centre Zagreb, Zagreb, Croatia*
[2]*Department of Neurology, University Hospital Centre Zagreb, Zagreb, Croatia*

BACKGROUND: Huntington disease (HD) is an autosomal dominant, neurodegenerative disorder, characterized by progressive motor, cognitive and psychiatric disturbances. Incidence of HD approximates 3-10 persons in 100 000 in populations of Western European descent. First symptoms of HD usually appear between 35 to 50 years of age, and life expectancy after onset is about 15 to 20 years. More than 99% of HD cases are associated with an expansion of a CAG trinucleotide repeat region in the first exon in the HTT gene. Polymorphic CCG region close to CAG tract can be used to exclude HD diagnosis in certain number of patients.

METHODS: Genomic DNA of 177 patients referred for HD testing was extracted from peripheral blood by salting-out method. Reverse oligonucleotide primers used for PCR amplification of CAG and CCG triplet repeat region were labelled with 6-carboxyfluorescein (6-FAM) fluorescent dye at the 5' end. Denatured fluorescently labelled PCR products mixed with LIZ size standard were analyzed using capillary electrophoresis in POP-7 polymer and AB Genetic Analyzer 3130xl instrument (Applied Biosystems, Foster city, CA).

RESULTS: DNA samples of 177 patients with suspicion of HD clinical diagnosis or referred for predictive testing were analyzed. Fragmentary analysis was performed for CAG repeats, and in case of CAG homoallelism, CCG and CAGCCG repeat PCR products. Expanded allele was detected in 78 (44.1%) patients, ranging from 36 to 62 CAG repeats. Intermediate allele was detected in eight patients. In 10 out of 27 patients (37%) homozygous for normal number of CAG repeats, HD diagnosis was excluded using additional analysis of CCG and CAGCCG fragments. Capillary electrophoresis method, which can separate alleles with one CAG repeat difference, together with additional CCG and CAGCCG repeat analysis showed 24.3% increase in diagnostic specificity.

CONCLUSIONS: Fragmentary analysis by capillary electrophoresis is recommended in genetic diagnostics of HD because of its accuracy and diagnostic specificity. Confirmation/exclusion of HD on molecular genetic level is very important in patients with atypical clinical presentation and for the purpose of predictive testing of HD patient's close family members.

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ASSOCIATION OF PARAOXONASE 1 POLYMORPHISMS (L55M AND Q192R) WITH DYSLIPIDEMIA AND NEPHROPATHY IN A TUNISIAN POPULATION WITH TYPE 1 DIABETES: A 4-YEAR FOLLOW-UP STUDY

F. Ons[1], S. Triki [1], I. Hellara [1], F. Neffati[1], M.F. Najjar[1]
[1]*Laboratoire de Biochimie-Toxicologie, Hôpital Universitaire Fattouma Bourguiba, Monastir, Tunisie*

BACKGROUND: Paraoxonase 1 (PON1) polymorphisms have been associated with susceptibility to macro and microvascular complications in diabetes. We purpose to study the association of PON1 L55M and Q192R polymorphisms with diabetes complications in a Tunisian young population with type 1 diabetes (T1D).

METHODS: Our study included 32 children (20 boys and 12 girls) with T1D, aged 12.5 ± 3.9 years who were followed up during a period of 4 years (2010-2013). All patients have a clinical examination and laboratory measurements in 2010 (T0) and in 2013 (T4). Glucose, total cholesterol (TC), triglycerides (TG), cholesterol-HDL (c-HDL) and cholesterol-LDL (c-LDL) were determined by enzymatic methods. Microalbuminuria and creatinine were measured respectively by immunoturbidimetric and kinetic Jaffé methods. Estimated glomerular filtration rate was determined by MDRD formula. Genotyping of PON1 gene was assessed by multiplex PCR followed by restriction fragment-length polymorphism.

RESULTS: A significant increase in TC, c-HDL, c-LDL, and in microalbuminuria was observed in patients at T4. The frequency of dyslipidemia, microalbuminuria and renal failure in this population increased significantly ($p < 0.001$), respectively from 3.1 to 43.7 %; from 3.1 to 21.8 % and from zero to 12.5 %. Frequencies of dyslipidemia, microalbuminuria and renal failure were significantly higher in LM, in QR genotypes and in LMQR haplotype. The association of these three complications was significantly more frequent in patients with LMQR ($p < 0.001$).

CONCLUSIONS: LM, QR genotypes and their combined effect seem to be associated to dyslipidemia and nephropathy in T1D. Additional studies are needed to evaluate the role of PON1 haplotypes in diabetes complications.

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POMPE DISEASE DUE TO IVS10+1G>A MUTATION OF GAA GENE IN A PATIENT OF MOROCCAN ORIGIN

G. Pi[2], A. Zuniga[1], M. Ortiz[1], I. Aleixandre[1]
[1]*Servicio de Genetica, Hospital Univ. de la Ribera, Alzira, Valencia, Spain*
[2]*Servicio de Pediatria, Hospital Univ. de la Ribera, Alzira, Valencia, Spain*

BACKGROUND: Infantile-onset glycogen storage disease type II (GSD-II; OMIM #232300) is one of the causes of infantile sudden death. Affected infants can appear normal at birth, but soon develop generalized muscle weakness, areflexia, macroglossia, hepatomegaly and massive cardiomegaly. Most patients die of cardiorespiratory failure prior to 2 years of age. GSD-II is an autosomal recessive disorder, caused by deficient activity of lysosomal acid alfa-glucosidase (acid maltase) (GAA). It is an enzyme responsible for the degradation of glycogen in lysosomes. GSD-II encompasses a wide range of clinical phenotypes, which correlate with residual GAA enzyme activity, and the most severe one is the infantile-onset form.

METHODS: We describe a case of a one-month-old male infant with diagnosis of Pompe disease. Patient was born at full-term by a G1P1 healthy mother. Parents were non consanguineous (but of the same village) and of Moroccan origin. She had a birth body weight of 2550g and a normal Apgar score 8-9. After birth, frequent respiratory distress, feeding difficulties and poor weight gain were noticed by her parents. She was sent to our hospital because of fever and respiratory distress. She was poorly-nourished, acyanosis, weak crying, and protruding tongue. Flaccid extremities with frog position and decreased deep tendon reflexes were found on neurological examination. Chest films showed cardiomegaly with a cardiothoracic ratio of about 80% and hepatomegaly. An ECG revealed a short PR interval, high QRS voltage, ST-T changes and prominent Q wave in the left precordial leads. The echocardiogram demonstrated biventricular and inter-ventricular hypertrophy but no left ventricular outflow tract obstruction.

RESULTS: Pompe disease was confirmed by deficient activity of acid alfa-glucosidase (GAA) (0.283 units, control 1.203 units). This activity was also decreased in her parents (father 0.620 units, mother 0.412 units). The patient died of cardiopulmonary failure, aspiration pneumonia and hypertrophic cardiomyopathy at 8 months of age. Genetic studies show that patient was carrier of a mutation in GAA gene: IVS10+1G>A in homozygosis. Both parents were heterozygous carriers.

CONCLUSIONS: Prenatal analysis in amniotic fluid of pregnant mother results in a foetus non-carrier of this mutation.

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HIGH PREVALANCE OF MEFV R202Q MUTATIONS IN PATIENTS WHO ARE EVALUATED FOR FAMILIAL MEDITERRANEAN FEVER

A. Akbaş[2], İ. Bütün[2], İ. Benli[2], L. Aydoğan[2], Y. Önder[1], Z.C. Özmen[2]
[1]*Department of Public Health, Gaziosmanpasa University Medical Faculty, Tokat, Turkey*
[2]*Gaziosmanpasa University, School of Medicine, Department of Biochemistry, Tokat, Turkey*

BACKGROUND: Familial Mediterranean Fever (FMF) is an autoinflammatory disesae characterized by recurrent attacks of fever, peritonitis, pleuritis and arthritis. Mediterranean Fever gene (MEFV gene) was identified on the short arm of the chromosome 16, as the responsible gene for FMF, which codes for pyrin protein. More than 50 mutations have been described, and the most common mutations are M694V, V726A, M694I, M680I, and E148Q. We investigated the prevalence of 10 common MEFV mutations in Tokat region, in patients who are being evaluated for FMF because of their complaints and/or clinical findings.

METHODS: 619 patients with abdominal pain, arthritis/arthralgia and fever were included in the study. A744S, E148Q, F479L, K695R, M680I (G/A), M694I, M694V, R202Q, R652H ve V726A mutations were screened in the MEFV gene. TIB Molbiol LightSNiP reagents and Roche LightCycler 480II Real-Time PCR were used.

RESULTS: Frequencies of the mutations were as follows: 44.91% R202Q (10.82% homozygous); 22.46% M694V (4.04% homozygous); 10.82% E148Q (3.55% homozygous); 8.24% V726A (0.16% homozygous); 1.78% A744S; 0.48% K695R; 0.32% F479L; 0.16% M680I(G/A). There were not any R652H and M694I mutations. Frequencies of the allelles for R202Q was 27.86%; M694V 13.24%; E148Q 7.18%; V726A 4.20%; A744S 0.88%; K695R 0.24%; F479L 0.16%; M680I(G/A) 0.08%. 71.89% of the subjects had at least one mutation. 19 different genotype were detected. High linkage disequilibrium between R202Q and M694V were found (D'=0,922; r2=0,3359).

CONCLUSIONS: R202Q mutation was the most frequent between all genotypes. This finding and also the high linkage disequilibrium may lead to further studies about the association and the gentoyping.
Key words: FMF, MEFV, R202Q, M694V, linkage disequilibrium

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ANALYSIS OF MANGANESE SUPEROXIDE DISMUTASE (MNSOD ALA-9VAL) AND GLUTATHIONE PEROXIDASE (GPX1 PRO 197 LEU) GENE POLYMORPHISMS IN ALOPECIA AREATA

G. Kalkan[2], İ. Benli[1], A. Akbaş[1], H. Yıldız Seçkin[2], Y. Baş[2], N. Karakus[3], İ. Bütün[1], H. Özyurt[1]
[1]*Gaziosmanpasa University, School of Medicine, Department of Biochemistry, Tokat*
[2]*Gaziosmanpasa University, School of Medicine, Department of Dermatology, Tokat*
[3]*Gaziosmanpasa University, School of Medicine, Department of Medical Biology, Tokat*

BACKGROUND: Alopecia areata is chronic inflammatory disorder that is assumed to be a tissue-specific, T-cell mediated autoimmune disease of the hair follicle, clinically characterized by well defined patches of nonscarring hair loss. The exact aetiopathogenesis of AA remains unknown. The role of the oxidative stress in AA has been studied by several researchers in a few studies with conflicting results. These results suggested that lipid peroxidation and alterations in the oxidant- antioxidant enzymatic system may play a role in the pathogenesis of AA. Therefore, in this study, we aimed to examine to investigate possible associations between the MnSOD Ala-9Val and GPx1 Pro198Leu polymorphisms and AA susceptibility and disease progression in Turkish population.

METHODS: The study group consisted of 119 unrelated patients with AA (68 male and 51 female; mean age: 32.55±9.606 standard deviation [SD] years), and 104 (54 male and 50 female; mean age: 32.28±11.908 SD years) unrelated healthy controls with no scalp lesions in their personal history or on clinical examination. Genotyping was performed to identify MnSOD Ala-9Val and GPx1 Pro198Leu polymorphisms by a method based on PCR amplification and detection of polymorphisms with hybridization probes labeled with fluorescent dyes. Genotype and allele frequencies were compared between patients with AA and 104 healthy control subjects.

RESULTS: There was no significant difference between the MnSOD Ala-9Val SNP genotype distributions and allele frequencies of the AA patients and the control group (P = 0.168 and p=0,820, respectively). There was not any association between clinical and demographical features of the study patients with AA and MnSOD Ala-9Val and GPx1 Pro198Leu polymorphism genotypes except gender.

CONCLUSIONS: This is the first report examining the possible associations between the MnSOD Ala-9Val and GPx1 Pro198Leu polymorphisms and AA susceptibility and in Turkish population even if no significant difference was found between patient groups and control subjects. Additional studies with larger populations will be necessitated in order to better illuminate the association.
Key Words: AA, MnSOD Ala-9Val, GPx1 Pro198Leu, polymorphism

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THE POSSIBILITIES OF Y-HAPLOGROUP PREDICTION IN THE SLOVAK POPULATION

E. Petrejcikova[1], D. Hronska[1], D. Gabrikova[1], J. Bernasovska[1], I. Boronova[1], M. Mydlarova Blascakova[1]
[1]*University of Presov in Presov, Faculty of Humanities and Natural Sciences, Department of Biology*

BACKGROUND: Determination of Y-chromosomal haplogroups can explain the geographic and ethnic origin of the Slovak population. Y-chromosomal lineages are established by SNP and STRs, which provide the corresponding haplogroup and haplotype, respectively. The purpose of our study was to describe and compare the possibilities of prediction of paternal lineages in the Slovak population from Y-STR polymorphisms, when Y-SNP data is not available.

METHODS: The efficiency of three software (Athey`s Haplogroup Predictor, Cullen`s Haplogroup Predictor and YPredictor by Vadim Urasin) for Y-haplogroup prediction was tested with 298 samples of know haplotypes in the Slovak population. Y-haplotypes were identified by analyze of 11 Y-STR markers (DYS391, DYS389I, DYS439, DYS389II, DYS438, DYS437, DYS19, DYS392, DYS393, DYS390, DYS385a/b). Capillary electrophoresis was performed on a MegaBACE® 1000 Genetic Analyzer.

RESULTS: Our results showed the inaccuracies in prediction of the 18 haplotypes (6.04%). The Slovak population displays a majority of Eurasian lineages, mainly represented by Y-haplogroup R1a (34.64%), followed by R1b (18.21%) and I2a (16.07%). Other paternal lineages have been observed at frequencies lower than 10%.

CONCLUSIONS: Prediction of paternal lineages using Y-STR haplotypes is quick and easy method and may help to estimate the population of origin. But the proportion of error in Y-haplogroup prediction cannot be ignored and Y-SNP analysis is necessary to precisely define a phylogenetic branch on the Y-chromosome. We assume haplogroup prediction inaccuracies could be reduced by increasing the number of Y-STR haplotypes in the database.
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ELLIS VAN-CREVELD SYNDROME: MOLECULAR DIAGNOSIS AND CARRIER TESTING

G. Pi[1], A. Zıniga[1], M. Ortiz[1]
[1]*Hospital Universitario De La Ribera, Alzira, Valencia, Spain*

BACKGROUND: Ellis-van Creveld syndrome (EVC, #225500) is an autosomal recessive skeletal dysplasia characterized by disproportionate short stature with acromesomelic shortening of limbs, short ribs, and postaxial polydactyly of hands and feet. Tooth abnormalities, multiple oral frenulae, hypoplastic nails, congenital heart defects, typically an atrial or atrioventricular septal defect, are other common features in this syndrome. EVC, also called chondroectodermal dysplasia, is caused by mutations of the EVC1 and EVC2 genes positioned on chromosome 4p16 and has been described as a “ciliopathie”.

METHODS: We present a case of a six-month-old male infant with bilateral polydactyly of hands and inward deviation of the right eye (OD). He was delivered normally at term, was the second son of non-consanguineous couple, a 28-year old healthy father and 22-year-old healthy mother. No other family members had similar hand deformity or defect in the position of eyeball. Ocular examination revealed right isotropy of about 90 PD deviation with left eye fixating and cross fixation on side gaze. He had no abduction deficit. Nystagmus was absent. Cycloplegic refraction in both eyes was +1.0 D. On physical examination, his weight was 3.8 kg, height 48.5 cm and head circumference 36 cm (all below 2SD). The chest circumference was 31 cm (below 2SD) and trunk of normal size. Each upper limb was 20 cm, while each lower limb was 16.5 cm (both below 2SD). The arm span was 43 cm (below 2SD). The arms and legs were short, clubby and shortened out of proportion to the trunk. The hands were wider than normal and feet were square shaped. Bilateral postaxial polydactyly of hands were present. Her digits were proportionately short compared to her hands. Fingernails and toenails were markedly hypoplastic. He had a fusion of the upper lip to the maxillary gingival margin that produced a V-notch in the middle of the lip and had a lip tie.

RESULTS: Genetic study of EVC1 and EVC2 was performed. All exons and intronic adjacent regions were sequenced for both genes. Parents and brother were studied and results were: father was carrier of W884X mutation, and mother and brother were carriers of S1220X mutation.

CONCLUSIONS: Patient was a compound heterozygous with W884X mutation in exon 15 of EVC1 and S1220X in exon 22 of EVC1.

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FREQUENCY OF HFE GENE C282Y, H63D, S65C MUTATIONS IN THE MIDDLE BLACK SEA REGION IN TURKEY

Ş. Şahin[1], A. Akbaş[1], L. Aydoğan[1], İ. Benli[1], İ. Bütün[1]
[1]*University of Gaziosmanpaşa, Faculty of Medicine, Department of Biochemistry*

BACKGROUND: Hereditary Hemochromatosis (HH), one of the most common inherited disorders, is characterized by iron overload. Three common mutations have been identified in the HFE (High Fe) gene, C282Y, H63D, S65C. The aim of the present study was to determine the prevalence of these three mutations in Tokat region, and investigate if there is an association with the serum iron (SI), serum ferritin (SF) levels, total iron binding capacity (TIBC), saturation of transferrin (%TS).

METHODS: The study was conducted in the 70 local areas in the province of Tokat, with about 530 000 inhabitants. The study population of 1095 subjects was selected random sampling method among them. HFE C282Y, H63D and S65C SNPs, genotyping was performed using the LightMix kit. SI, UIBC, SF were determined by an autoanalyzer. TIBC and %TS were calculated.

RESULTS: Mean age of the male and female subjects were 41.17±17.69 and 41.56±16.27, respectively. We could not detect any homoygous mutation for C282Y. Frequency of H63D/H63D and S65C/S65C were 2.19% and 0.37%, respectively. The most common heterozygous form was the wt/H63D (16.62%). Wt/H63D genotype was found higher in male (19.22%) than female (14.08%). There was not any compound mutation. Allelle frequncies of C282Y, H63D, S65C was 0.41%, 10.5% and 0.73%. SI levels were higher in men with wt/C282Y (176.4 ± 86.37 µg/dL) and H63D/H63D (180.86 ± 60.42 µg/dL) genotypes then the men with wt/wt (125.64 ± 68.97 µg/dL). TIBC levels were as follows, wt/C282Y: 349.2 ± 88.51; wt/S65C: 338.14 ± 33.34; wt/wt: 388.41 ± 114.94. SF in men with the wt/C282Y genotype were higher (166.97 ± 104.91 ng/mL) then the wt/wt (103.66 ± 105.79). %TS values were also elevated in wt/C282Y (49.15 ± 14.86) and H63D/H63D (44.99 ± 4.97) , while it is 32.20 ± 13.05 in wt/wt. SI and %TS levels in female subjects with wt/C282Y (124.5 ± 71.79; 32.59 ± 6.42, respectively) were higher then the wt/wt (91.22 ± 49.79; 22.82 ± 10.72, respectively). TIBC values were only higher in wt/H63D (414.13 ± 110.94) when compared with wt/wt (409.96 ± 116.81) in females.

CONCLUSIONS: In our region, HFE mutations were associated with the iron parameters, even it is not statistically significant, the results may be considered as remarkable.

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HLA CLASS I AND II POLYMORPHISMS AND ANTHROPOLOGICAL ASPECTS IN THE COASTAL CENTRAL REGION OF TUNISIA

K. Sakly[4], I. Bannour[2], M. Tlijani[2], A. Ben Bnina[2], S. Chartaoui[2], O. Kallala[2], S. Aloui[1], A. Soussi[2], M. Fadli[3], M. El May[1], N. Sakly[2]

[1]*Department of Nephrology, University Hospital F.B., Monastir, Tunisa*
[2]*Laboratory of Immunology, University Hospital F.B., Monastir, Tunisa*
[3]*Lagitre Laboratory, One Lambda, Milano, Italy*
[4]*Research unit 03-UR/07/02, University of Monastir, Faculty of Pharmacy, Monastir, Tunisia*

BACKGROUND: HLA polymorphism is very useful to curry out anthropologic studies which deals with the genetic relationships between populations. It is well documented that populations with very similar HLA antigen frequencies are clearly derived from a common ancestry and it was shown that the HLA polymorphism is very informative to reconstruct past human migration events. The aim of this study was to investigate HLA class I and class II polymorphisms in the population of the coastal central region of Tunisia and to compare it with other local and Mediterranean populations.

METHODS: The HLA typing has been conducted for 150 unrelated Tunisian donors (sex ratio 1; mean age: 36.42 ±11.8 years; range: 20-59 years) from the coastal central region of Tunisia using microlymphocytotoxicity for the class I (A and B) and molecular biology (polymerase chain reaction-sequence specific primers) for the class II (DRB1 and DQB1). The data were analysed with Arlequin. Phylogenetic tree was constructed using DISPAN.

RESULTS: The most frequent HLA class I antigens were A2 (24.6%), A1 (10.3%) and A3 (8%), while the most frequent B antigens were B50 (11.67 %), followed by B44 (9.33%) and B51 (9%). Among HLA class II DRB1 alleles, the most frequent were HLA-DRB1*07 (19.67%), DRB1*13 (15.33%) and DRB1*03 (13.3%); for DQB1, they were DQB1*02 (30.67%) and DQB1*03 (28%) and DQB1*06 (2%). Furthermore, extended haplotypes analysis revealed that A2-B50/DRB1*07-DQB1*02 and A2-B44/DRB1*7-DQB1*02 were the most frequent in our population with the frequencies of 2.95% and 2.33%, respectively.

CONCLUSIONS: Our study showed the close relatedness of our series with other Tunisian populations. The HLA-A-B-DRB1-DQB1 extended haplotypes found in our population reflect common characteristics with other Mediterranean background. Phylogenetic analyses indicate that individuals from the coastal central region of Tunisia are very close to other Tunisians, to their North African neighbors (Moroccans and Algerians) and to western Europeans, particularly Iberians (Spaniards and Portuguese). These observations are consistent with recognized historical, geographical, cultural, ethnic and linguistic relationships between these populations.

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PREVALENCE OF BRCA MUTATION CARRIERS WITH BREAST CANCER WITHOUT FAMILY HISTORY OF CANCER. ARE PHYSICIAN RECOMMENDATIONS FOR BRCA1/2 TESTING APPROPRIATE?

X. Gabaldó Barrios[1], A. Sánchez Bermúdez[1], A. Sarabia Meseguer[1], P. Sánchez [1], M. Marín Vera[1], J.L. Alonso Romero[1], F. Ruiz-Espejo[1]
[1]*University Hospital Virgen de la Arrixaca, Murcia, Spain*

BACKGROUND: Germline mutations in BRCA1 or BRCA2 are associated with a significantly increased risk for both breast cancer and ovarian cancer. In general, testing is offered to a woman who has a probability of ten percent or greater for being positive for a mutation. The SEOM criteria consider early age of diagnosis (before age 40) and family history of cancer. We estimate the proportion of BRCA mutation carriers among women without family history of cancer diagnosed at age<30, <35, <40. Moreover, we estimate the proportion among triple negative breast cancers diagnosed at age 40 or younger without family history of cancer.

METHODS: 87 cases diagnosed at age 40 or younger without family history of breast and ovarian cancer in first- or second-degree relatives was selected from Genetic Counselling between April 2007 and January 2014. Were determined the triple negative status in these cases if her medical records indicated that her breast carcinoma was negative for ER, PR and HER2. Genomic DNA was extracted using QIamp genomic DNA Mini kit (Qiagen Group).DNA was amplified by PCR using primers specific for the coding sequence and exon/ intron boundaries and sequencing by BigDye Terminator V3.1 Cycle Sequencing Kit on a 3130 Genetic Analyzer (Applied Biosystems). Both forward and reverse strands were sequenced. Large genomic rearrangements (LGRs) were performed by multiplex ligation-dependent probe amplification (MLPA) technique.

RESULTS: Of all breast cancer cases studied, 18 cases were diagnosed at age<30 (20.7%), 30 cases between 31-35 years old (34.5%) and 39 cases between 36-40 years old (44.8%). 14 of the 87 cases were triple negative (16.1%). The prevalence of mutation carriers was 4/18 cases (22.2%) for breast cancers diagnosed at <30 years old, 10/48 cases (20.8%) for these diagnosed at age <35 and 17/87 (19.5%) for these diagnosed at age <40. The prevalence of cases BRCA positives in triple negative breast cancers diagnosed at age 40 or younger was 6/14(42.9%).

CONCLUSIONS: The SEOM criteria regarding age at diagnosis is optimal, is not necessary to lower the cutoff age for early-onset breast cancer. The trend of the results indicates that it would be added as criteria triple negative status without a family history of breast and ovarian cancer.

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ASSOCIATION BETWEEN DEPRESSION AND POLYMORPHISMS OF THE TRYPTOPHAN HYDROXYLASE (TPH) GENE IN THE TUNISIAN POPULATION

M.A. Sayadi[2], I. Azizi[2], A. Ezzaher[2], A. Mechri[3], F. Neffati[2], W. Douki[2], L. Gaha[3], M.F. Najjar[2], A. Malafosse[1]

[1]*Division of Medical Genetics, Department of Genetic Medicine and Development, University Hospitals of Geneva, Switzerland*

[2]*Laboratory of Biochemistry-Toxicology, Monastir University Hospital, Tunisia*

[3]*Research Laboratory "Vulnerability to Psychotic disorders LR 05 ES 10", Department of Psychiatry, Monastir University Hospital, Tunisia*

BACKGROUND: The purpose of this work was to study the association between the (Tryptophane Hydorxylase) TPH A218C polymorphism and depression in Tunisian patients and to explore their relation to clinical and therapeutic characteristics of this disease.

METHODS: Our study included 200 depressive patients and 187 controls aged 44.5±13.5 and 37.9±12.9 years, respectively. TPH gene polymorphism were determined by PCR-RFLP (Restriction fragment length polymorphism).

RESULTS: Significant difference was detected in the distribution of the genotype frequencies of TPH A218C polymorphisms (χ^2=15.81, df=2, p<10-3) between patients and controls. We showed significant association between depression and TPH A218C polymorphism. After adjustment for confounder factors (Gender and drugs consumption), this association remained significant. AC Genotype is more frequent in control compared to patients (n= 99/65 respectively). Indeed, significant association was noted between depression and AC genotype (OR 2.21, CI 95% 1.15–4.23, p=0.016; OR 2.42, CI 95% 1.25-4.68 p=0.009 before and after adjustment). No significant association was found for depression and the AA and CC genotypes. There were no significant differences in gender, age at onset and treatment among all genotypes.

CONCLUSIONS: Depression was significantly associated with TPH A218C polymorphism, suggesting that the AC polymorphism may play a role for protection against depression. There was no significant association between the clinical and therapeutic characteristics of this population and this polymorphism. Further studies are required to clarify the implication of TPH A218C polymorphism in the pathophysiology of depression.

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PREVALENCE THE RAD51C IN BRCAX

A.I. Sánchez Bermúdez[1], X. Gabaldó Barrios[1], M.D. Sarabia Meseguer[1], E. Serrano Santos[1], M. Marín Vera[1], G. Marín Zafra[1], J.L. Alonso Romero[1], F. Ruiz-Espejo[1]
[1]*Clinical University Hospital Virgen de la Arrixaca*

BACKGROUND: A high percentage of breast cancer cases with high familial aggregation are not explained by alterations in genes BRCA1, BRCA2 and CHEK2 (BRCAX families). Recently, it has been postulated involvement RAD51C gene like a predictor of cancer risk in hereditary breast and ovarian cancer (HBOC). The objective of this study is determining the prevalence RAD51C gene mutation in our population.

METHODS: It has done a cross-sectional study on patients who meet criteria for high or moderate risk of HBOC syndrome and in who not has been found any gene variant in BRCA1, BRCA2 and CHEK2 associated with increased risk. Mutation screening of index cases was made by sequencing study (polymerase chain reaction (PCR) and capillary electrophoresis). To evaluate the pathogenicity of variants, bioinformatics and family cosegregation studies were realized and databases were consulted.

RESULTS: We selected 213 index cases with suspected HBOC during 2007-2012. In total BRCA1 and BRCA2 mutations were found in 42 families, a 19.72% of cases. The rest of 171 cases were categorized like BRCAX. At the moment, the study of the gene RAD51C has been realized in 24 families BRCAX. Four gene variants in RAD51C have been found. The variants c.-26C>T and c.904+34T>C are located in intronic regions and it´s described in the database dbSNP(NCBI) as non pathogenic variants. The other two variants are found in exonic regions and it´s described in the literature as pathogenic (c.404C>T exon2) and Variants of Uncertain Significance (c.859T>C exon6). The mutation c.404C>T has been described in a proband with a triple negative breast cancer at age 67 and an ovarian cancer at 73. Her mother and her sister died of pancreatic cancer at age of 77 and 65, respectively. The variant c.859T>C has been described in a proband with breast cancer at age 39. Her mother suffered CO at age 68.

CONCLUSIONS: The mutation c.404C>T has been described in a proband who developed breast and ovarian cancer, data consistent with other published studies, which shows a higher percentage of RAD51C mutations in families where breast cancer and ovarian cancer coexist. Although it is early to draw conclusions, the finding of a pathogenic variant puts us in a mutational frequency of 4% in our population´s study.

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ALPHA1-ANTITRYPSIN DEFICIENCY CONFIRMED BY QUANTIFICATION AND PHENOTYPING (PI*ZZ) IN DISCREPANCY WITH GENOTYPING RESULTS (M/Z)

M. Štefanović[1], A. Tešija Kuna[1], I. Vukasović[1], N. Vrkić[1]
[1]*Clinical Institute of Chemistry, University Hospital Sestre Milosrdnice*

BACKGROUND: Alpha1-antitrypsin (A1AT) is a plasmatic glycoprotein, primary inhibitor of the serine protease leukocyte elastase. It is highly polymorphic protein, and some variations within A1AT gene are associated with decreased serum concentrations or dysfunctional protein, causing A1AT deficiency. Besides common M allele, there are two most common disease associated alleles: Pi*S and Pi*Z. Patients with homozygous or compound heterozygous combination of Pi*S (codon E288V) or/and Pi*Z (codon E366K) alleles have low or insufficient A1AT concentration. That increases the risk for uncontrolled proteolytic damage in lower respiratory tract and developing chronic obstructive respiratory disease, or in the case of Z allele, of liver damage caused by inclusions of polymerized protein.

METHODS: Methods used in our laboratory are in concordance with common laboratory procedure testing for A1AT deficiency and involves quantification of protein (immunoturbidimetry), genotyping (realtime PCR - melting curve analysis, LightCycler, Roche, Switzerland) of most common Pi*S and Pi*Z alleles and confirmation by phenotyping (semi-automated method of isoelectric focusing with immunofixation, Sebia, France). Here we present male patient, 42 years old, with symptoms of chronic obstructive respiratory disease for whom laboratory testing for suspected A1AT deficiency was requested. A1AT serum concentration (0.14 g/L) corresponded to determined PiZZ phenotype, but both was in discordance with genotyping results (Pi*S: M/M and Pi*Z: M/Z).

RESULTS: All results were confirmed on repeated testing. This discrepancy between A1AT concentration, genotype, and phenotype could be consistent with the presence of a Z allele and a null allele (Z/null) that would not be detected by either phenotyping or genotyping. Determined PiZZ phenotype, however, is clinically more compatible with the low A1AT concentration and observed clinical symptoms than M/Z genotype.

CONCLUSIONS: We concluded this case as genotyping method inability to detect rare deficient variant (possible null allele). Consistency of A1AT concentration with clinical symptoms and determined phenotype is considered sufficient for diagnostic purpose, although scientific proof of rare variant is still to be confirmed by A1AT gene sequencing.

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OTX2 GENE INVOLVEMENT IN EYE MALFORMATIONS

E. Tejedor Hernández[1], T. Vendrell Bayona[2], N. Castells Sarrret[2], A. Fernández Rodríguez[2], A. Plaja[2], M. Mosquera Parrado[1]

[1]*Department of Clinical Biochemistry, Hospital Universitari Vall d´Hebron, Barcelona, Spain*

[2]*Department of Genetics, Hospital Universitari Vall d´Hebron, Barcelona, Spain*

BACKGROUND: Severe eye malformations are a rare group of developmental disorders with a live birth prevalence of 1 per 10,000. At the severe end of the spectrum are anophthalmia and extreme microphthalmia. Our patient, a 2 year-old male presented right anophthalmia and left microphthalmia with absence of both optic nerves, ventriculomegaly, Blake cyst and cerebellar vermis abnormality. Percentile length 3 and occipito-frontal head circumference (OFC) at -2SD. He was the fourth child of healthy non-consanguineous parents with no known family history of malformations. Pregnancy follow-up was almost nonexistent, but at the third trimester a bilateral ventriculomegaly was observed. At the 41th weeks of pregnancy the child was born with a birth weight of 3180 g, length of 50 cm and OFC of 35 cm.

METHODS: High resolution array comparative genomic hybridization (a-CGH) (Agilent G4827A CGH ISCA v2, 8x60K), was performed according to the manufacture's protocols. Subsequently to the identification of a deletion, we confirmed results and performed familiar study with CNV-specific BAC-FISH applying the probe RP11-10p7 (14q22.3, SO, [hg19] 55968549-56129687) and marker RP11-123m6 (14q.32.2, SG).

RESULTS: a-CGH analysis identified a heterozygous deletion of approximately 1.67Mb in 14q22.3, involving 9 genes, 5 of them described on the OMIM database: KTN1, KINECTIN, PELI2, OTX2 and EXOC5. FISH analysis showed the same 14q22.3 deletion in the mother.

CONCLUSIONS: Heterozygous mutation in the OTX2 gene is related to syndromic microphthalmia type 5 (OMIM 610125). Heterozygous loss of function of OTX2 gene accounts for about 2-8% in patients with anophthalmia and/or severe microphthalmia and commonly occurs de novo in affected children. Our patient inherited the mutation from her normal mother. Since almost 35% of the cases OTX2 mutations are inherited from a normal parent, it has been suggested that OTX2 mutations alone may not lead to full expression of the phenotype. Additional genetic factors, environmental and stochastic variation on development have been invoked as coadjutant factors to full expression of OTX2 malfunction phenotypic effects.

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TRANSTHYRETIN-RELATED FAMILIAL AMYLOID POLYNEUROPATHY DUE TO V30M MUTATION IN TTR GENE IN YOUNG PATIENT

B. Lopez-Pesquera[1], A. Zuniga[1], J.A. Dominguez-Moran[1], M. Ortiz[1]
[1]*Hospital Universitario De La Ribera*

BACKGROUND: Hereditary amyloidoses are a clinically and genetically heterogeneous group of autosomal dominantly inherited diseases characterized by the deposit of unsoluble protein fibrils in the extracellular matrix. Transthyretin-related Familial Amyloid Polyneuropathy (TTR-FAP, OMIM #105210) is a hereditary amyloidosis, caused by amyloid formation and destabilization of the transthyretin tetramer. The disease is autosomal dominant, caused by mutations in the TTR gene. Patients with transthyretin amyloidosis typically present with polyneuropathy, carpal tunnel syndrome, autonomic insufficiency, cardiomyopathy, and gastrointestinal features, occasionally accompanied by vitreous opacities and renal insufficiency. In later stages of the disease severe diarrhea with malabsorption, cachexia, incapacitating neuropathy, severe cardiac disturbances, and marked orthostatic hypotension dominate the clinical picture. Death usually occurs 5 to 15 years after onset of symptoms.

METHODS: We present the case of a 35 year old male of Portuguese origin who came to the service of Neurology by weakness in limbs. Paternal grandfather died at age of 35 y.o. and father at 55 y.o. of paramyloidosis. The patient starts clinic of hyperalgesia in the soles of the feet of three years of evolution, accompanied by loss of sensitivity as well as weakness in lower limbs with distal dominance.Physical examination it reveals is a marked hypesthesia to knees, loss of strength in the lower limbs with distal gradient. Abolition of aquileos and kneecap osteotendinous reflexes. Ulcerative lesions in the toes. There were any other finds of interest in the rest of the neurological examination.
The genetic study from DNA obtained from a sample of peripheral blood, performing the analysis of the TTR gene by automatic sequencing all exons and intronic adjacent regions.

RESULTS: The result is the detection in compous heterozygosity of p.Gly6Ser mutations (NP_000362.1; described as a polymorphism in Caucasian population) and the mutation p.Val30Met (NP_000362.1). The p.Val30Met mutation is described as pathogenic and cause of amyloid polyneuropathy given the character an autosomal dominant disease.

CONCLUSIONS: With the genetic diagnostic confirmation the patient was referred to his reference hospital for liver transplantation.

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