complex, GEMIN4 participates in the mature process of microRNAs, the target RNA recognition and repression. Recently, a T>C transition (rs7813) in GEMIN4 gene was described, in which, the C variant was associated with cellular growth inhibition in vitro. Our purpose was to investigate the influence of the GEMIN4 rs7813 (T>C) functional polymorphism in the overall survival of RCC patients.
Material and Methods: A follow-up study (60 months) was undertaken to evaluate the overall survival, in 13 patients (67.4% males and 32.6% females), with histopathologically confirmed RCC, with a median age of 62 years. Genotyping of GEMIN4 rs7813 (T>C) genetic polymorphism was performed by Real-Time PCR allelic discrimination method.
Results: The frequency of the TT, CT and CC genotypes were 43.5%, 44.9% and 11.6%, respectively. Median estimated overall survival was significantly lower in heterozygous patients compared with patients carriers of CC/TT genotypes (50 versus 57 months, Log Rank test P=0.016). Furthermore, multivariate Cox regression model using age, gender and metastasis at diagnosis as covariants, demonstrated a higher risk of death by cancer in heterozygous patients (hazard ratio- HR= 5.1, 95%CI: 1.43-18.07, P= 0.012).
Conclusions: Our results suggest that GEMIN4 rs7813 CT genotype may contribute to a higher risk of death by cancer in heterozygous patients. Thus, abnormality in GEMIN4 protein might result in the differential expression of some miRNAs that are related to CCR. Further studies are needed to evaluate the association reported here, in particular large well-designed studies of ethnically diverse populations and functional studies on RCC cells may help clarify which variants are truly causal for this disease

A new mutation of the KCNQ1 gene causing long QT syndrome.

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Introduction: Long QT syndrome (LQTS) is a congenital cardiac disorder which is life threatening condition with ventricular arrhythmia. Two phenotypic variants have been defined. Autosomal dominant Romano-Ward syndrome (RWS) which is more common and autosomal recessive Jervelland Lange Nielsen syndrome accompanies sensorineural deafness which is rare. The prevalence is between 1:200 – 1:500. Repetitive syncope attacks and sudden deaths as a result of torsades de pointes type ventricular arrhythmias can occur especially during sympathetic hyperactivity. 5000 deaths occur in USA every year as a consequence of this syndrome.
Case: Proband (index case), 27 years old male, directed to the Medical Genetics policlinic with LQTS diagnosis. The patient had repetitive syncope and anxiety complaints. Chest pain, tachycardia and sudden syncopes generally occur after exercise. Parents of the patient aren't relatives, the father died at the age of 50 from LQTS(?). The patient has brothers and nephews who had syncope attacks or died after an effort.Genetic analysis of KCNQ1 gene demonstrated heterozygote c.1088_1089dupGAGGCAGAAGCA mutation in exon 8.
Discussion:The RWS diagnosis is made using the characteristic ECG findings, clinic and family history of the patient and the molecular genetic analysis results. If there is a QT interval prolongation in ECG during a syncope attack, first of all acquired causes must be considered. It has been known that electrolyte balance disorders like hypopotassemia, hypomagnesemia and hypocalcemia, antiarrhythmic drugs (quinidine, procainamide, sotalol, ibutilide, amiodarone, bepridil), antibiotics (erythromycin, clarithromycin,clindamycin), antidepressants (desipramine, nortriptyline, amitriptyline) and antihistaminics (terfenadine, astemizole) can cause deadly arrhythmias by prolonging the QT interval. We eliminated these factors in our patient.
The mutations in 13 different genes can be related to RWS. The most common genes and their contribution rates to the syndrome are as the following: KCNQ1 (%46), KCNH2 (%38), SCN5A (%13), KCNE1 (%2), KCNE2 (%1); and less frequently; CAV3, SCN4B, AKAP9, SNTA1, KCNJ5, ANK2, KCNJ2, CACNA1C.
We have performed the molecular genetic analysis of KCNQ1 gene which includes the most common mutations in RWS. The KCNQ1 gene is localized on the 11p15.5-p15.4 chromosome. This gene encodes the α subunit of the inwardly rectifying potassium channels (KIR). Abnormal gene product causes a decrease in KIR channel functions. In certain databases, over 470 mutation including missense, nonsense, splice, site, frame shift and deletion/duplication mutations has been notified in KCNQ1 gene.
In this case, heterozygote c.1088_1089dupGAGGCAGAAGCA mutation has been defined in exon 8 of KCNQ1 gene and this mutation has not been defined in the literature before. In literature, mutations in the KCNQ1 gene detected with deletion/duplication analysis have been reported in %46 of the RWS cases. These mutations results in the clipping errors in the mRNA.
With the information about new mutations, it will be possible to identify the LQTS type, arrange the prophylactic treatment and give information about the drugs which their use should be avoided

Influence of CYP2C9 genetic polymorphisms on the warfarin anticoagulant

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Warfarin has been one of the most used oral anticoagulant drugs over the last 60 years in the

prevention of thromboembolic disease complications. Due to its narrow therapeutic range, bleeding complications or recurrent thrombosis may occur, especially during the initial phase of treatment. Management of anticoagulation therapy is challenging due to a large variability in the dose-response relationship, which is partly caused by genetic polymorphisms. S-warfarin is the most active isomer and it is majorly metabolized by CYP2C9, an enzyme from the CYP450 family. CYP450 isoforms are frequently affected by single nucleotide polymorphisms (SNPs), and several papers have reported that these variations may alter warfarin metabolism and could lead to severe adverse reactions. The aim of this study was to perform a systematic review of the clinical evidence about CYP2C9 genetic polymorphisms and how they could affect the outcome of warfarin anticoagulant therapy.
A systematic review of studies retrieved through a MEDLINE database search was performed, in order to evaluate the effect of CYP2C9 SNPs in the anticoagulant therapy with warfarin. Papers publish before January 2012, which fulfilled the inclusion/exclusion criteria were included. Methodological quality was assessed with Downs&Back checklist.
In Caucasians the presence of CYP2C9 *2 and *3 alleles was more frequently associated with therapeutic variation, while in Asians this is mostly due to the presence of CYP2C9*3 allele. In Africans the presence of CYP2C9 *5,*6,*8,*9 and *11 alleles proved to influence warfarin metabolism. While in Hispanics, the presence VKORC1 variations seem to influence with a larger impact than those from CYP2C9.
CYP2C9 genetic polymorphisms influences warfarin metabolism, but the outcome can differ within different ethnic populations. Dosage adjustment based on patient's genetics profile, may have advantages in warfarin anticoagulant therapy by reducing the risk of hemorrhage or avoid the absence of anticoagulant affect.

The role of OCT1, ABCB1, ABCG2 and CYP4F3 gene expressions in the therapeutic outcome of chronic myeloid leukemia

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Imatinib, the selective BCR-ABL tyrosine kinase inhibitor, has represented the first line of treatment for chronic myeloid leukaemia (CML) since 2001. Although the majority of patients respond well to treatment with imatinib, primary resistance occurs in 25% and secondary resistance in 20-25% of the patients. Mutations within the kinase domain and BCR-ABL gene amplification account for the majority of these cases. However, increasing number of studies indicate an important role of imatinib pharmacokinetics in the development of resistance. Imatinib is a substrate for OCT1, which transports the drug into the target cells and for ABCB1 and ABCG2, which have a role in elimination of imatinib from the cells. Studies have shown that patients with suboptimal response to imatinib often have low OCT1 activity. The aim of our study was to determine expressions of the genes, encoding for OCT1, ABCB1 and ABCG2 transporters in granulocytes and peripheral blood mononuclear cells (PBMCs) of CML patients and to correlate them with the therapeutic outcomes of the disease. Since some studies have shown a significant difference in expression of CYP4F3 between patients who responded well to the imatinib therapy and those with primary and secondary resistance, we also determined the influence of CYP4F3 on the development of imatinib resistance. Our results show, that the outcome of imatinib treatment is influenced by ABCG2 and CYP4F3 expressions, but not by OCT1 expression. The expression of OCT1 did not differ significantly between patients with optimal response to imatinib and those who didn't reach major molecular response in 18 months. However the expressions of ABCG2 and CYP4F3 were significantly higher in the PBMCs of the patients with suboptimal response (p= 0.048 and 0.036 respectively). The expressions in granulocytes did not differ significantly. Currently, no test in clinical use can predict which patients will develop a resistance in the future. Our results suggest that determination of ABCG2 and CYP4F3 gene expressions could help to identify patients in risk of developing imatinib resistance before the beginning of the treatment, but the results should be confirmed on a larger group of patients.

Allele frequency and genotype distribution of CYP2C9, VKORC1СYP4F2, CYP2D6, CYP1A2*1F, GGCX, NAT2, GSTP1 polymorphisms in Kazakh population

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Objective: Determination of the allelic variants of xenobiotic biotransformation genes is important not only for personalized drug prescription. The knowledge of the allele frequency distribution in different populations may be taken into account when preferred medication regimen is selected. The frequency of CYP2C9, VKORC1, CYP4F2, GGCX, CYP2D6, NAT2, GSTP1, CYP1A2 gene polymorphisms studied in the world populations, except for several regions, including Central Asia.
Materials and methods. Using Real-Time PCR and direct sequencing based methods, the current study assessed the frequencies of 11 polymorphisms from genes encoding enzymes involved in drug metabolism in 444 healthy individuals from different regions of Kazakhstan.
Results: Allele frequencies were derived for CYP2C9*2 (0,02), CYP2C9*3 (0,03) VKORC1 1542 и VKORC1 1173 (0,72), СYP4F2 (0,31), GGCX (0,04) , CYP2D6*4 (0,07), CYP2D6*3 (0,01), NAT2*5 (0,54), GSTP1 (0,27), CYP1A2*1F (0,35). All alleles were in Hardy – Weinberg