XIII. AZIZ SANCAR INSTITUTE OF EXPERIMENTAL MEDICINE DAYS
XIII. AZİZ SANCAR DENEYSEL TIP ARAŞTIRMA ENSTİTÜSÜ GÜNLERİ

Omics Technologies in Life Sciences: From Genome to Therapy
Yaşam Bilimlerinde Omik Teknolojileri: Genomdan Tedaviye

December 21-22, 2021
21-22 Aralık 2021

ORAL PRESENTATIONS
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[SS-01]
Anesthetics Change microRNA Levels in Blood Samples of Bypass Patients and in Blood and Sperm Tissues of Mice

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ABSTRACT

Objective: The increasing burden of births of children with autism has made research on diagnosis and molecular mechanisms the focus of attention of large laboratories around the world. Through detection of non-coding RNA (miRNA), we observed that reduced levels of six miRNAs (miR-19a, miR-126, mir-150, miR 3613, miR-361 and miR-499) that are passed on from parents to offspring are associated with the development of autism (1). The close association of the levels of these six miRNAs with behavioral traits could be a valuable marker in identifying risk factors. Evidence in the literature suggests that some patients with autism spectrum disorder (ASD) exhibit altered responses to pain and general anesthesia (2). In this study, we propose that anesthetics alter the levels of these six miRNAs in humans and mice.

Materials and Methods: Propofol was administered as an anesthetic to patients (n=20) who underwent bypass surgery. Blood samples were taken the day before and the day after surgery. On the other hand, we used two-month-old male mice (Balb/C) administered ketamine + xylazine intraperitoneally. Two time points were determined: one week and one month after anesthesia administration, blood and sperm RNAs were collected and analyzed by qPCR.

Results: MiR-19a levels show a significant increase after one day of anesthesia in patients compared to the preoperative period. In addition, other variations were observed where miR-361 and miR 499 levels increased and miR-126, mir-150 and miR-3613 decreased. In mice, the expression levels of miR-19a, miR-126, miR-150, miR 499, miR-361, miR-3613 at two stages differed compared to controls.

Conclusion: Propofol is widely used for anesthesia in surgical patients (3). While xylazine is an anesthetic that acts on pre-synaptic and post-synaptic nerve endings; Ketamine is classified as an NMDA receptor antagonist (4). In previous studies, these anesthetics; It has been shown to have inhibitory effects and anti-inflammatory effects on the cardiovascular and parasympathetic systems and has a protective role in many organs. Cardiac miRNAs have been shown to be released into the circulation after myocardial injury and can be used as biomarkers of perioperative myocardial injury (5,6,7). Our results suggest that these six miRNAs are affected by general anesthesia and the significant increase in miR-19a expression induced by propofol has a protective effect in myocardial tissue.

Keywords: anesthesia, bypass surgery, miRNA, autism, sperm, blood

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[SS-02]
Association of the *ECE-1b* rs213045 and rs2038089 Polymorphisms in the Prevalence of Hypertension in CAD Patients

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ABSTRACT
Objective: Endothelin (ET) is one of the most vasoconstrictor proteins in the human body and has regulatory role in vascular tone and blood pressure (1).ECE-1 is the major enzyme in the biosynthesis of ET-1 and ET-1 levels increase when *ECE-1* gene is over-expressed (2).Therefore, ECE-1 inhibitors are also being investigated in the new therapeutic approaches to hypertension. *ECE-1b*-C338A(rs213045) polymorphism is found in the promoter region of *ECE-1*b and leading to changes in the gene expression. Previous studies have found association between rs213045 polymorphism and hypertension, coronary artery disease(CAD),carotid atherosclerosis and ischemic stroke (1-6).*ECE-1b*-rs2038089 is an intronic polymorphism and found to be associated with atherosclerosis in hypertensive males previously (6).The purpose of this study is to investigate the association of rs213045 and rs2038089 polymorphisms in *ECE-1b* gene with hypertension in CAD patients.

Material and Method: Study groups were comprised of hypertensive(n=190) and non-hypertensive CAD patients(n=176). Polymorphisms in *ECE-1b* gene was determined by Real-Time PCR method.

Results: The serum triglyceride, glucose and HbA1c levels were found higher in hypertensive group than non-hypertensive CAD patients ($p<0.01$).The frequency of rs2038089 (A>G)-GG genotype was found higher in hypertensives versus non-hypertensives (20.1% vs 12.5%,respectively,$p=0.05$).Hypertension was found more common in males than female patients(65.3% vs 34.7%,respectively,$p=0.010$).In men with ≥50 ages, rs2038089-rare GG- genotype ($p=0.042$) and G-allele frequency($p=0.035$) were higher in the hypertensive group, however this association was not observed in males with <50 ages and in females. Genotypes and allel distributions of rs213045 (C>A)-polymorphism were not statistically different between hypertensive and non-hypertensive patients.

Conclusion: Our findings indicate that the rs2038089 (A>G)-GG genotype may be associated with hypertension in patients with CAD, and this relationship may be related to age and gender.

Keywords: endothelin, ECE-1b, polymorphism, hypertension, CAD

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[SS-03]
Determining the Relationship of XPO1 Mutations to the Pathogenesis of CLL

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ABSTRACT

Objective: iDEP (Integrated Differential Expression and Pathway Analysis) is a web application that combines 63 R/Bioconductor packages, 2 web services, and extensive annotation and pathway databases for humans and 220 plant and animal species. The workflow is created by downloading the customized R code and related pathway files (1).

The study used NCBI Gene Expression Omnibus (GEO) datasets, a public, functional genomic data repository that supports MIAME-compliant data submissions (2). We aimed to identify the cellular pathways disrupted in response to the E571K XPO1 mutation, which is the most frequently observed mutation in CLL patients, using the iDEP program, through the high-throughput mRNA sequencing dataset (GSE163370) of chronic lymphocytic leukemia (CLL) cells containing E571K XPO1 mutations.

Material and Method: Exportin 1 (XPO1/CRM1) is an important mediator of nuclear transport associated with many cancers, including CLL. The GSE163370 dataset, in which unbiased RNA sequencing of B-CLL cells from CLL patients with E571K XPO1 mutation (n=3) was performed and the results were compared with XPO1-wt IgVH-U CLL cells (n=4), were evaluated through the Integrated Differential Expression and Pathway Analysis program, iDEP (2).

Results: We used the first 1000 genes in hierarchical clustering, sorting the genes by their standard deviations across all samples. Comparison of XPO1-wt IgVH-U CLL cells with CLL cells containing the E571K XPO1 mutation (Cut-off Z-score: 4) (Figure 1).

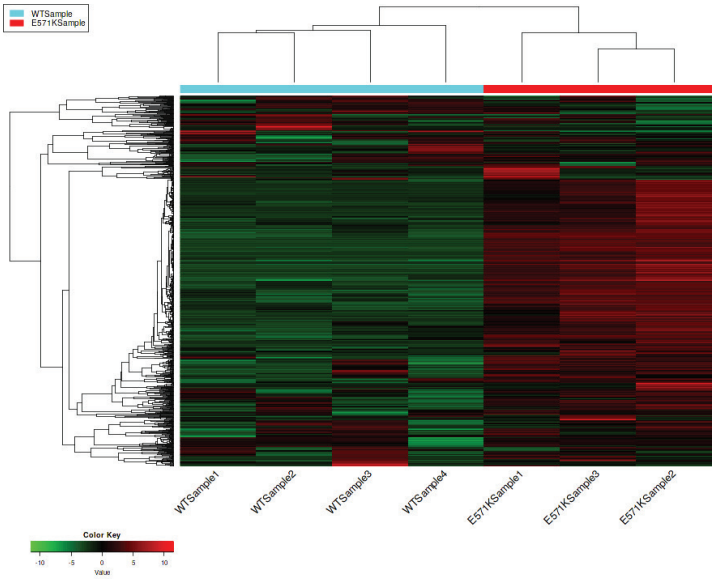

Figure 1: Hierarchical clustering

With the DESeq2 package, we identified 920 genes up-regulated and 62 down-regulated genes relative to the false-discovery rate threshold (FDR < 0.1 and fold change > 2) (Figure 2).

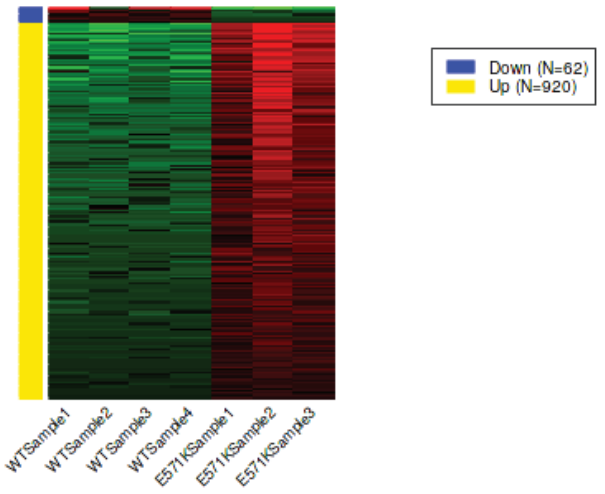

Figure 2: Differential expression analysis data using DESeq2

Enriched GO Biological Process terms associated with genes upregulated in DEGs were identified. Upregulated genes were found to be involved in immune response, cell activation, regulation of stimulus response, cell surface receptor signaling pathway and leukocyte activation.

In our study, coexpression networks and submodules were identified using WGCNA over the 1000 most variable genes, and enriched pathways were shown between all genes in the selected module for XPO1-wt IgVH-U CLL patients and CLL patients with E571K XPO1 mutation (Figure 3).

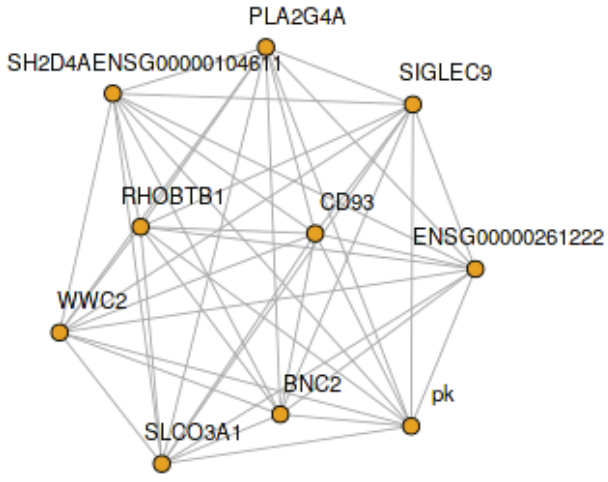

Figure 3: Gene coexpression network

Conclusion: As a result, PLA2G4A, SIGLEC9, RHOBTB1, CD93, WWC2, SLCO3A1, BNC2 candidate genes that may be associated with CLL to identify therapeutic targets through the coexpression network in the selected module were identified. Thus, according to the results of the co-expression network, we believe that the determination of new gene regulations and functions related to CLL samples carrying XPO1 mutations can be a guide to elucidate the pathogenesis of the disease.

Keywords: CLL, RNA sequencing, iDEP, pathogenesis

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[SS-04]
Investigation of Variants Causing Hot Water Epilepsy by Whole Exome Sequencing Approach

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ABSTRACT

Epilepsy, with an average frequency of 1% in the population, is a common neurological condition characterized by spontaneous recurrent seizures. Epilepsies can be categorized as generalized or partial depending on the extent of the brain region involved. Hot water epilepsies (HWE) comprise an interesting class of partial epilepsies that occur when hot water is poured over the head. HWEs also belong to the reflex epilepsy group, in which a certain trigger or stimulus brings on seizures. HWE is a rare condition and its etiopathogenesis has not been clearly elucidated yet. Our study aims to reveal the genetic factors contributing to HWE. 10 patients, whose clinical evaluations had been performed by the

Istanbul University Faculty of Medicine, Department of Neurology were included in this study. The blood derived DNA was subjected to whole exome sequencing (WES) and analyzed by our in house sequencing pipeline. Rare variants in epilepsy related genes were prioritized. One variant in sodium channel gene *SCN2A* (NM_001040142.2:c.463A>G) and two variants in *SCN9A* (NM_001365536.1:c.3391G>T and NM_001365536:1:c.164C>T) were detected in three unrelated individuals. All three identified variants cause missense variation and have not been previously reported in the literature. The variants determined within the scope of the study reside on genes that encode subunits of sodium channels that may be involved in channelopathies. It is speculated that disruptions in the sodium-potassium ATPase channel may be related to the molecular etiopathogenesis of the disease. The analysis of the patients for novel genes and copy number variations are ongoing.

Keywords: hot water epilepsy, whole-exome sequencing, sodium channel gene family

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[SS-05]
Candidate Variant Detection by Whole Exome Sequencing in Two Cases with Congenital Hemolytic Anemia

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ABSTRACT

Objective: Rare congenital hemolytic anemia (CHA) is a very heterogeneous group of diseases caused by the shortening of the normal life span of erythrocytes for various reasons (1). In this group, which shows genetic and clinical heterogeneity, the underlying genetic changes may be complex and may also occur due to compound heterozygosity inherited from asymptomatic parents (2). In this study, it was aimed to determine the genetic variations causing the disease in two index cases followed with the suspicion of CHA and not diagnosed with conventional diagnostic approaches.

Material and Method: Whole exome sequencing (WES) was performed in the index cases (HA-1 and HA-2) who was followed up with the suspicion of congenital hemolytic anemia. Raw data was aligned to hg38 reference genome with BWA and SAMtools to generate variant list. For the selection of candidate genes; exonic missense, nonsense, stop-loss, frameshift and splice-site variants were filtered. Remaining variants were prioritized according to their MAF score (<0.05, reported by 1000Genomes, ExAC, gnomAD). To predict the potential consequences of variations; PolyPhen, Provean, MutPred, Mutation taster and SIFT's scores were used. For the clinical interpretation of candidate variants OMIM, ClinVar's known reports (benign/pathogenic/uncertain) predictions, and conservation scores (CADD) were evaluated.

Results: As a result of exome sequencing analysis, a combined heterozygous variant was detected in HA-1 whose parents were consanguineous, one causing a missense and the other a frameshift mutation (NM_001321761.1, p.Arg101Trp and p.Pro248fs). *CDIN1* (*C15orf41*) gene has been associated with autosomal recessive congenital dyserythropoietic anemia type1b (CDA-type1b) and homozygous or combined heterozygous variations in this gene

have been held responsible for ineffective erythropoiesis of erythroblasts in the bone marrow. *CDIN1* is predicted to function as a nuclease but the specific activity remains to be shown (3). HA-2, IVS1-110G>A variation, which was detected in the *HBB* gene in the first place due to a family history of thalassemia, was far from explaining the patient's clinic. As a result of WES analysis, heterozygous stop-gain variation (NM_001291366.1, p.Trp459*) in the *PERM1* gene was detected. *PERM1* is a new candidate gene that can be associated with congenital dyserythropoietic anemia type3 (CDA-type3).

Conclusion: These findings may be effective in finding candidate genes/variants by whole exome sequencing and informatic analysis for patients with congenital hemolytic anemia that could not be diagnosed by conventional laboratory tests and clinical examination.

Keywords: congenital hemolytic anemia, WES, red blood cell disorders, *CDIN1*, *PERM1*

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[SS-06]
Lenfoma ve İmmünyetmezliğe Sahip İndeks Olguda Somatik ve Germline Varyasyonların Ekzom Dizi Analizi ile Analizi

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ÖZ

Amaç: Bu çalışmanın amacı, ailevi kanser yatkınlığı düşünülen ailede tanı ve remisyon örneklerinde tüm ekzom dizilemesi yapılarak "germline" /somatik kanser yatkınlık genlerinin saptanmasıdır.

Gereç ve Yöntem: Çalışmaya, immün yetmezlik ve DLBCL (Diffuse Large B Cell Lymphoma) kliniğine sahip indeks olgu, immün yetmezlik şüphesi bulunan erkek kardeşi ve akraba evliliği olan ebeveynler dahil edildi. İndeks olgusunun tanı (FFPE) ve remisyon (periferik kan) örneklerinden elde edilen DNA örneğinden tüm ekzom dizlemesi yapıldı. Ham veri BWA ile hg38 referans genoma hizalandı ve GATK [1] ve Vep [2] algoritmaları kullanılarak VCF dosyası oluşturuldu ve annotasyonu yapıldı. Aday gen seçimi için 1000G [3], ExAC [4] ve GnomAD [5] veritanlarında bulunan minör allel frekansı (MAF) sıklığı, korunmuşlık skorları (CADD) [6] ve tahmin araçlarının sonuçları kullanıldı. Ayrıca, aday gen önceliklendirilmesi için PECAN [7] veritabanı da kullanıldı. Bulunan varyasyonların validasyonu Sanger dizileme yöntemi ile yapıldı.

Bulgular: İndeks olgunun tüm ekzom verisinde MAF<0.05 olan homozigot ekzonik varyantlar (n=265) incelendiğinde, grubumuzun literatür taraması ile oluşturduğu immün yetmezlik genleri arasında bulunan *RAG2* geninde mutasyon bulunduğu tespit edilmiştir. Bu mutasyon Clinvar [8] veritabanında immünyetmezlik ile ilişkili patojenik mutasyon olarak raporlanmaktadır. Ayrıca, literatürde heterozigot durumda kansere yatkınlık oluşturduğu öne sürülen [9] *NBN* geninin indekste heterozigot, babanın taşıyıcı ve erkek kardeşin yabanıl tipte

olduğu tespit edilmiştir. Somatik ekzom verisi incelendiğinde, kanser yolakları ile ilişkilendirilen genlerde aday mutasyonlar tespit edilmiştir.

Sonuç: İndeks olguda saptana *RAG2* mutasyonu, hastanın immün yetmezliğini açıklamaktadır. *RAG2* mutasyonunun lenfomaya yatkınlık ile ilişkisini raporlayan literatür bulunmamaktadır. *RAG2* mutasyonunun homozigot olmasına rağmen lenfoma geliştirmeyen erkek kardeşten farklı olarak, indeks olgu kansere yatkınlık adayı olan heterozigot *NBN* mutasyonu içermektedir.

Anahtar Kelimeler: DLBCL, immün yetmezlik, germline

Bu çalışma İstanbul Üniversitesi Bilimsel Araştırmalar Proje Birimi tarafından desteklenmiştir (Proje No: 37127).

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[SS-07]
Protez Enfeksiyonunda Mikroarray Yöntemi ile Bakteri İdentifikasyonu

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ÖZ

Amaç: Çalışmanın amacı, bakteri DNA'sını temel alan mikroarray analizi kullanılarak ortaya konacak bakteri identifikasyonu ile protez çevresi infeksiyonlar için klasik tedavi protokolleri açısından yüksek duyarlı ve kısa süreli tanı uygulaması sağlamaktır.

Gereç ve Yöntem: Helsinki-Finlandiya merkezli Mobidiag şirketinin geliştirdiği Prove-it Bone&Joint kitlerinde uygulanan PCR, hibridizasyon ve kendi yazılımları ile uygulanan "microarray" ile 3,5 saatte bakteri belirlenmesi yapıldı. PCR ve hibridizasyon prosedürleri kite özel olup farklı bileşenler içermektedir. Eklem sıvısından DNA izole etme yöntemi, Zymo Research Şirketinin ZR Fungal/Bacterial DNA Miniprep kiti prosedürü uygulanarak yapıldı.

Bulgular: 41 hastadan alınan numuneler üzerinde yapılan çalışma sonuçlarına göre 32 (%78) hastada pozitif 9 (%22) hastada ise negatif sonuçlar elde edilmiştir. Mikroarray cihazı ile bakteriler işaretlenip tanınmaya çalışılmakta ve belli bir sayının üstünde kaldı ise klinik olarak anlamlı kabul edilmektedir. Klinik olarak değerlendirildiğinde hastalarda 2 aşamalı yapılan revizyon cerrahisi sonrası klinik ve biyokimyasal parametreler ele alındığında 34 hastanın (%84) enfeksiyonun ortadan kaldırıldığı izlenmiştir. Literatürde de 2 aşamalı revizyon başarısı %80-90 aralığında verilmektedir. Elde ettiğimiz klinik başarı oranı literatürle uyumludur.

Sonuç: Çalışmamızda elde ettiğimiz sonuçlarla Microarray yönteminin aşırı hassas bir teknik olduğu en küçük bir bulaştan etkilendiği görülmektedir. İncelenen yapı DNA dır . DNA nın incelenmesi için öncelikle PCR ile miktarının artırılması gerekmektedir. Mikroarray yönteminde en küçük bir kontaminasyon sonuçları etkileyebilmektedir. Over diagnose ihtimali mikroarray yönteminde her zaman akılda tutulmalıdır. Ancak yanlış negatiflik oldukça düşüktür (% 4.1).

Anahtar Kelimeler: protez çevresi, enfeksiyon, DNA, microarray

Bu çalışma İstanbul Üniversitesi Bilimsel Araştırmalar Proje Birimi tarafından desteklenmiştir (Proje No: 29121).

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[SS-08]
Multi-omics Feature Grouping for Breast Adenocarcinoma

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ABSTRACT

Objective: In this study, we attempt to combine 3 -omics data (miRNA, methylation, and mRNA), downloaded from the The Cancer Genome Atlas (TCGA) for breast cancer. We aim to learn the hidden relationships within these -omics data via incorporating biological domain knowledge, and use this information to group the features which in turn will increase the classification performance.

Material and Method: Raw read counts of RNA-Seq and miRNA-Seq data were normalized using the edgeR TMM method. Beta values of DNA methylation data (Illumina Human Methylation 450) were downloaded from XenaBrowser. We used the molecular subtypes (LumA, LumB, Her2 and Basal). Differentially expressed data between these subgroups were identified with exactTest. By applying the grouping function, highly correlated

CpGs and miRNAs were selected. Then genes which were highly correlated with both CpGs and miRNAs were identified.

Results: 188 such groups were identified by using our grouping function. Each group contains one miRNA, one CpG and their correlated genes. The first group contains hsa.let.7c as miRNA, cg02389084 as CpG and KDM1A, ZNF263, ANLN, DCN, ARHGAP31 genes.

Conclusion: For each CpG and miRNA pair, we created a group that contains the features from the gene expression data that are highly correlated with both features of the pair. As a future work, we plan to calculate the scores of those groups and hence generate rankings of those identified groups. In summary, we believe that this approach has a potential to decipher the underlying disease development and progression mechanisms.

Keywords: multi-omics, data integration, breast cancer

[SS-09]
In Silico Evaluation of the Relationship Between Skin Cancer and WWC1

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ABSTRACT

Objective: It was aimed to evaluate the possible relationship of KIBRA(WWC1), one of the proteins responsible for activating the core kinase cassette of the Hippo pathway, with skin cancer by in silico analysis method.

Materials and Methods: Quantitative datas from total of 968 skin cancer samples(S), including metastatic melanoma(MM)(DFCI, Nature Medicine 2019; n=144), skin melanoma(SM)(TCGA, Pan Cancer Atlas; n=448), basal cell carcinoma(BCC)(UNIGE, Nat Genet 2016; n=293) and cutaneous squamous cell carcinoma(CSCC)(UCSF, NPJ Genome Med 2021; n=83), were clinically evaluated by using cBioportal for Cancer Genomics (https://www.cbioportal.org/). The obtained findings of WWC1 expression from GSE115791 and GSE183115 data sets were compared by using GEO (https://www.ncbi.nlm.nih.gov/geo/).

Results: Mutations in the WWC1 were found in 6.4%(61/968) of all samples, 6.7%(39/592) of all MS; 8%(45/448) of DM and 2.8%(4/144) of MM. 5.9%(22/376) of all non-melanoma(NM) skin cancer samples(NMSCS), 10.8%(9/83) of CSCC and 4.4%(13/293) of BCC have WWC1 mutation. In addition, 74.4%(29/39) of MS with WWC1 mutations are metastatic with primary and survival rates of 15.4%(6/39) and 48.7%(19/39), respectively WWC1 expression of MM(n=3) was higher(logFc=0,01) than primary melanoma(n=3)(p=0.002) according to the findings obtained GSE115791 dataset. According to the findings obtained from GSE183115 WWC1 expression of nevus (n=4) was found higher(logFc=0.6) than melanoma(n=5) (p=0.003).

Conclusion: The findings demonstrate the potential of WWC1 to be effective in the progression of melanoma. The possible changes in the structure of KIBRA caused by mutations are predicted that elucidating the protein by means of programs that model its structure can create ideas for future studies.

Keywords: melanoma, KIBRA protein, computational biology