

Genes Associated with Cancer, Schizophrenia and Type 2 Diabetes in the Circassian and Chechen Populations in Jordan

Rana Dajani^{1,2}, *Tarek Salah*¹, *Seba Jamal Shbailat*¹, *Zhi Wei*³,
*Manal Daas*¹, *Hakon Hakonarson*^{4,5}

Abstract

Background and Aims: Diabetes afflicts 16% of Jordanian citizens over the age of 18 years and is the fifth main cause of death in Jordan. We aimed to explore single nucleotide polymorphisms (SNPs) identified by GWAS study for potential associations with other diseases.

Methods: We manually searched the National Center for Biotechnology Information for all genes related to the annotated nominally significant single nucleotide polymorphisms ($p < 0.05$) found in a previous genome-wide association study. This study included 34 diabetes cases and 106 controls for the Circassians and 34 diabetes cases and 110 controls for the Chechens.

Results: Our research revealed 20 genes associated with cancer and 6 genes associated with schizophrenia in the Circassian population, and 2 genes associated with cancer and 7 genes associated with schizophrenia in the Chechen population. These genes may have a pathogenetic association with type 2 diabetes mellitus.

Conclusion: The results from this pilot study demonstrates that multiple genetic factors that underlie type 2 diabetes may be associated with cancer and schizophrenia in the Chechen and Circassian populations in Jordan.

Keywords: GWAS, type 2 diabetes, Cancer, Schizophrenia, Circassian, Chechen.

(*J Med J* 2018; Vol. 52 (1):59-75)

Received

Oct. 8, 2017

Accepted

July 3, 2017

Introduction

Diabetes is one of the most common non-communicable diseases globally. The International Diabetes Federation estimates that diabetes is currently affecting more than 425

million people, of which one-third are people older than 65 years.¹ Type 2 diabetes is the most common type of diabetes, accounting for around 90% of all cases of diabetes.¹ Diabetes type two is the fifth leading cause of death in Jordan and afflicts 16 percent of Jordanian

1. Department of Biology and Biotechnology, The Hashemite University, Zarqa, Jordan.
2. Radcliffe Institute for Advanced Studies, Harvard University, Cambridge, MA, USA.
3. New Jersey Institute of Technology, Newark, New Jersey, USA.
4. Center for Applied Genomics, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA.
5. Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA.

* Correspondence should be addressed to:

Rana Dajani

Department of Biology and Biotechnology, The Hashemite University, Zarqa, Jordan.

E-mail: rdajani@hu.edu.jo

citizens over the age of 18. According to a study conducted by the Heart and Capillary Disease Prevention Directorate (HCDP) of the Ministry of Health in Jordan, in 2011, another 23.8 percent of Jordanians over 18 years old were on the brink of developing diabetes. The possibility of diabetes prevalence in Jordan is 30.5 percent among both children and adults.

Despite extensive research efforts for more than a decade, the genetic basis of common human diseases such as type 2 diabetes remains largely unknown, although there have been some notable successes.² Genome-wide association studies (GWASs) are a powerful approach to identifying novel susceptibility genes for complex diseases.^{3,4} A GWAS is defined as any study of genetic variation across the entire human genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight), or the presence or absence of a disease or condition (such as type 2 diabetes).⁵ GWASs are based on the hypothesis that common diseases are caused by a limited number of common genetic variants. Although it has been difficult to discover the functional significance of loci discovered, the GWAS still remains a way to discover genetic risk factors for complex diseases.⁶⁻⁸ However, most GWASs have been performed on European populations.⁵⁻⁸ There is a need to conduct GWASs on different ethnic populations to discover novel risk factors for these populations, and, perhaps more importantly, to apply the discoveries on these and other populations worldwide.

Both the Circassians and the Chechens are ethnic groups indigenous to the North Caucasus.⁹⁻¹² They are descendants of ancient origins.^{11,13} Previous analyses of classical genetic markers such as blood groups and serum proteins have shown statistically

significant genetic diversity in the Caucasus.^{9,10} This genetic diversity has been confirmed by mitochondrial DNA and Y chromosome analyses.^{11,13}

Under military pressure, a large group of Circassians and Chechens immigrated to Jordan 140 years ago. Generally, the Circassians and Chechens in Jordan are endogamous communities¹⁴ and, therefore, represent unique populations genetically distinct from the majority Arab population in Jordan.

Based on predictions from population genetic theory, isolated populations such as the Circassians and Chechens in Jordan, which have undergone severe bottlenecks or have remained small for a long time, have extensive linkage disequilibrium compared to outbred populations. Linkage disequilibrium mapping is useful in genetic studies of complex diseases. So far, the method has been used to locate a number of candidate regions that may harbor risk genes. Identification of these novel genetic risk factors have the potential to help us explore new biology and develop innovative treatments to reduce disease burden and promote good health.

In Circassians in Jordan, the prevalence of impaired fasting glycemia and diabetes was found to be 18.5% and 9.6%, respectively.¹⁵ In Chechens in Jordan, the prevalence of impaired fasting glycemia and diabetes was found to be 14.6% and 10.1%, respectively.¹⁵ In both ethnicities, the prevalence of impaired fasting glycemia and diabetes was significantly higher in men, older age groups, those were married, those with a lower level of education, past smokers, and those with obesity. Moreover, a low level of high-density lipoprotein (HDL) was the most common metabolic abnormality observed in the Circassian and Chechen populations in Jordan.¹⁶⁻¹⁸

A GWAS on the Circassians and the Chechens in Jordan has been performed previously.¹⁹ It was shown that *JAG1* and *MLXIP* are associated with type 2 diabetes in these two populations.¹⁹ A copy-number variation region (CNVR) associated with type 2 diabetes has also been identified in gene *AKND1* in these populations.²⁰ The objective of the present study was to further explore significant single nucleotide polymorphisms (SNPs) found in the original GWAS study¹⁹ for potential associations with other diseases.

Materials and Methods

Subject and sample collection

This study has been approved by the Institutional Review Board (IRB) at the National Center for Diabetes, Endocrinology and Genetics in Amman, Jordan. This study was based on data obtained from a previously conducted GWAS.¹⁹ In that study, a random sample of both sexes in the Chechen population in Jordan (N = 144) and a random sample of both sexes in the Circassian population in Jordan (N = 140) were recruited, and participants signed a written consent form indicating their acceptance to participate in the study. Each participant filled out a survey that included pedigree information. If any parent, grandparent or great-grandparent of an individual was not of Chechen or Circassian ethnicity (depending on the study group), he/she was excluded from the study.

A subject was considered diabetic if he/she was previously diagnosed as a patient, or if his/her fasting serum glucose was at least 7 mmol/L (126 mg/dL), in accordance with the American Diabetes Association (ADA) guidelines. Impaired fasting glucose was defined as a fasting serum glucose level of ≥ 6.1 mmol/L (100 mg/dL) but < 7 mmol/L

(126mg/dL). Glycemic control was assessed using HbA1c. Patients with previously diagnosed diabetes who had a HbA1c $> 7\%$ were considered to have “unsatisfactory” glycemic control.¹ as performed in the original GWAS study.¹⁹

Sample collection

Nine milliliters of whole blood were drawn from each subject in ethylenediamine tetraacetic acid (EDTA) tubes by a vacutainer system. Genomic DNA was isolated from whole blood samples using the phenol-chloroform protocol, as performed in the original GWAS study.¹⁹

Illumina Infinium data files

We used files produced by high-throughput, genome-wide SNP genotyping using the Infinium OmniExpress BeadChip (Illumina) at the Center for Applied Genomics at the Children’s Hospital of Philadelphia (CHOP) in Pennsylvania, USA. These files consisted of intensity data that were loaded directly into Illumina’s genotype analysis software, BeadStudio. A bead pool manifest created from the laboratory information management system (LIMS) database containing all the BeadChip data was loaded into BeadStudio along with the intensity data for the samples. BeadStudio uses a normalization algorithm to minimize BeadChip to BeadChip variability. Once the normalization was complete, the clustering algorithm was run to evaluate cluster positions for each locus and to assign individual genotypes. Each locus was given an overall score, which was based on the quality of the clustering, and each individual genotype call was given a GenCall score. GenCall scores are a quality metric that ranges from 0 to 1. They were calculated using information from the clustering of the samples. The location of each

genotype relative to its assigned cluster determined its GenCall score. as performed in the original GWAS study.¹⁹

Statistical analysis

All statistical tests for association were carried out using the software package PLINK (<http://pngu.mgh.harvard.edu/~purcell/plink/index.shtml>). Principal components analysis was carried out using Eigenstrat 3.0 (<http://genepath.med.harvard.edu/~reich/Software.htm>). The single marker analysis for the genome-wide data was carried out using logistic regression on allele counts, with the first 10 principle components as covariates. Odds ratios with the corresponding 95% confidence intervals and *p*-values were calculated for the association analysis.

Genes related to SNPs from the GWAS data

In order to identify genes related to SNPs from the previous GWAS data,¹⁹ we performed a manual search of the National Center for Biotechnology Information (NCBI) database for all genes related to our list of the annotated nominally significant SNPs ($p < 0.05$). If we did not find evidence in the database discussing our exact SNPs, we used a multi-step search technique, starting with identification of the SNP, then determining its location and the related gene. Then, we searched the National Institute of Health (NIH) database for studies that discussed the related gene and whether it was connected to type 2 diabetes. After that, we described the full name of the gene, its function, if known, and major disease associations based on the NIH database.

Results

Sample population

Information about the sample population after quality control (QC) is summarized in

Table 1, as reported in the original study.¹⁹ Specifically, for the Chechens, there were 34 diabetes cases and 110 controls, of which 61 were male and 85 were female. A total of 640,236 SNPs from this Chechen population passed QC. For the Circassians, there were 34 diabetes cases and 106 controls, of which 61 were male and 79 were female. A total of 643,776 SNPs from this Circassian population passed QC.

Table 1. Ethnic distribution of participants with type 2 diabetes (cases) and those without (controls) following quality control

Ethnicity	Control	Case	Total
Chechen	110	34	144
Circassian	106	34	140
Total	216	68	284

Table 2. Single nucleotide polymorphisms (SNPs) found in the Circassian population by a genome-wide association study¹⁹ and their associated genes related to schizophrenia

SNP	Associated gene	References
rs1341322, rs10789050	<i>DABI</i>	21, 22
rs2469358	<i>CSMD1</i>	24, 26
rs573514	<i>ADRA1A</i>	27
rs1623372, rs4733130, rs17719687	<i>NRG1, NRG2, NRG3</i>	28
rs7284103, rs7290713, rs11704261, rs4999923	<i>SYN3</i>	29, 30
rs35524	<i>MEGF10</i>	31, 32

Genes associated with schizophrenia

As shown in Table 2, results revealed that SNPs carried on 6 genes associated with type 2 diabetes in the Circassians were also associated

with schizophrenia. These genes were *DABI*, *CSMD1*, *ADRA1A*, *NRG1*, *NRG2*, *NRG3*, *SYN3* and *MEGF10*. The results for the Chechen population are shown in Table 3, revealing that SNPs carried on 7 genes associated with type 2 diabetes in the Chechens were also associated with schizophrenia. These genes were *DABI*, *CSMD1*, *NAVI*, *GRM7*, *CNTNAP2*, *GRIA4* and *ZDHHC8*. Among these genes associated with schizophrenia, the Disabled-1 (*DABI*) and CUB and Sushi multiple domain 1 (*CSMD1*) genes were common between the Circassians and the Chechens.

Table 3. Single nucleotide polymorphisms (SNPs) found in the Chechen population by a genome-wide association study¹⁹ and their associated genes related to schizophrenia

SNP	Associated gene	References
rs3768171	<i>DABI</i>	21-23
rs17066250	<i>CSMD1</i>	24-26
rs504988	<i>NAVI</i>	33
rs162782, rs162769, rs3804820	<i>GRM7</i>	34-36
rs10250801	<i>CNTNAP2</i>	37-38
rs17391295	<i>GRIA4</i>	39, 40
rs175174	<i>ZDHHC8</i>	41-43

Genes associated with cancer

We found that SNPs located on 20 genes associated with type 2 diabetes in the Circassian population were also associated with cancer (Table 4). We found two genes in the Chechen population, *DCC* and *CHSY1*, correlated with the occurrence of colorectal cancer (Table 5). However, overall, no specific type of cancer dominated.

While no single SNP met the genome-wide significance criteria of $p < 5 \times 10^{-8}$ in either

population, detailed results for the top hits for the Circassians are provided in the supplementary file, containing 471 SNPs with $p < 1e-2$. Detailed results for the top hits for the Chechens are provided in the supplementary file, containing 540 SNPs with $p < 1e-3$.

Table 4. Single nucleotide polymorphisms (SNPs) found in the Circassian population by a genome-wide association study¹⁹ and their associated genes related to cancer

SNP	Associated gene	References
rs10493757	<i>LPAR3</i>	44, 45
rs2993549, rs4951436	<i>DTL</i>	46, 47
rs2813703	<i>ESRRG</i>	48, 49
rs11127131	<i>BRE</i>	50-52
rs11124283	<i>BIRC6</i>	53
rs2579600	<i>SCTR</i>	54
rs11708944	<i>TP63</i>	55, 56
rs498221	<i>ERGIC1</i>	57
rs10487888	<i>BRAF</i>	58
rs3739915	<i>TTF1</i>	59, 60
rs19808560	<i>KIN</i>	61
rs11258848	<i>FRMD4A</i>	62
rs3750996	<i>STIM1</i>	63, 64
rs883752	<i>CD82</i>	65, 66
rs1044370	<i>LIMAI</i>	67, 68
rs7139030	<i>NTN4</i>	69, 70
rs9318227	<i>KLF12</i>	71
rs13329643, rs782918	<i>RORA</i>	72, 73
rs2233456	<i>NOL3</i>	74
rs16996073	<i>PAK7</i>	75, 76

Discussion

GWASs have been a very successful approach for identifying disease susceptibility loci for many diseases and traits. In 2016, the GWAS catalog contained 24,218 unique SNP-trait associations from 2,518 publications in

337 different journals (www.ebi.ac.uk/gwas;¹⁹). In a previous study, we performed a GWAS of the Chechen and Circassian populations in Jordan, in search for novel susceptibility genes for type 2 diabetes. While no single SNP met genome-wide significance criteria at a level of $p < 5 \times 10^{-8}$ in either population, multiple SNPs demonstrated a suggestive association with type 2 diabetes in this data set of over 600,000 SNPs.¹⁹

Table 5. Single nucleotide polymorphisms (SNPs) found in the Chechen population by a genome-wide association study¹⁹ and their associated genes related to Colorectal cancer

SNP	Associated gene	References
rs4940189	<i>DCC</i>	44-46
rs12148369	<i>CHSY1</i>	47

In the present study, our search revealed that SNPs carried on 6 genes in Circassians and 7 genes in Chechens were associated with schizophrenia. Among these genes, the Disabled-1 (*DABI*) and CUB and Sushi multiple domain 1 (*CSMD1*) genes were shared by both the Circassians and Chechens.

Genes associated with schizophrenia shared by both the Circassians and Chechens

Disabled-1 (*DABI*) is a protein coding, Dab, reelin signal transducer, homolog 1 (*Drosophila*). In mice, the Disabled-1 gene (*Dab1*) plays a central role in brain development, directing the migration of cortical neurons (previously formed) to reach their proper layer. The mouse gene (*Dab1*) is similar to its human orthologue (*DABI*), and the protein encoded by *Dab1* is thought to be a

signal transducer that interacts with protein kinase pathways to regulate neuronal positioning in the developing brain. The gene is associated with central nervous system (CNS) disorders.²¹⁻²³

Another gene, *CSMD1* (CUB and Sushi multiple domain 1) is protein-coding. It is associated with breast, colorectal and skin carcinoma as well as schizophrenia.²⁴⁻²⁶ It is interesting that *CSMD1* is associated with both schizophrenia and cancer and in the two populations.

Other genes associated with schizophrenia in the Circassian population

ADARI, or the adrenoceptor alpha 1A gene, codes alpha-1-adrenergic receptors (alpha-1-ARs), which are members of the G protein-coupled receptor superfamily. They activate mitogenic responses and regulate growth and proliferation of many cells.²⁷

NRG1, *NRG2*, and *NRG3* are neuregulin 1 genes that code a 44-kD glycoprotein that interacts with the NEU/ERBB2 receptor tyrosine kinase to increase its phosphorylation on tyrosine residues. This protein is a signaling protein that mediates cell-cell interactions and plays critical roles in the growth and development of multiple organ systems. An extraordinary variety of different isoforms are produced from this gene through alternative promoter usage and splicing. These isoforms exhibit tissue-specific expression and differ significantly in their structures. The isoforms are classified into types I, II, III, IV, V and VI. Gene dysregulation has been linked to diseases such as cancer, schizophrenia and bipolar disorder (BPD).²⁸

SYN3 is the synapsin III gene, is protein-coding, and is a member of the synapsin gene family. Synapsins encode neuronal phosphoproteins which associate with the

cytoplasmic surface of synaptic vesicles. Its family members are characterized by common protein domains, and they are implicated in synaptogenesis and the modulation of neurotransmitter release, suggesting a potential role in several neuropsychiatric diseases. The protein encoded by *SYN3* shares the synapsin family domain model, with domains A, C, and E exhibiting the highest degree of conservation. The protein contains a unique domain J, located between domains C and E. Based on this gene's localization to 22q12.3, a possible schizophrenia susceptibility locus, and the established neurobiological roles of the synapsins, this family member may represent a candidate gene for schizophrenia. The *TIMP3* gene is located within an intron of this gene and is transcribed in the opposite direction.^{29,30} *MEGF10* (multiple EGF-like-domains 10 gene) is also protein-coding. This gene encodes a member of the multiple epidermal growth factor-like domains protein family. The encoded protein plays a role in cell adhesion, motility and proliferation, and is a critical mediator of apoptotic cell phagocytosis as well as amyloid-beta peptide uptake in the brain. Expression of this gene may be associated with schizophrenia, and mutations in this gene are a cause of early-onset myopathy, areflexia, respiratory distress, and dysphagia (EMARDD), as well as congenital myopathy with minicores.^{31,32}

Other genes associated with schizophrenia in the Chechen population

The gene *NAVI* (neuron navigator 1) is protein-coding. It is expressed predominantly in the nervous system. The encoded protein contains coiled-coil domains and a conserved AAA domain characteristic for ATPases associated with a variety of cellular activities. The exact function of this gene is not known, but it is

thought to play a role in neuronal development and regeneration.³³

GRM7 is a protein-coding gene, also called glutamate receptor, metabotropic 7. Glutamatergic neurotransmission is involved in most aspects of normal brain function and may be perturbed in many neuropathologic conditions. The metabotropic glutamate receptors are a family of G protein-coupled receptors that have been divided into three groups on the basis of sequence homology, putative signal transduction mechanisms, and pharmacologic properties. Group I includes GRM1 and GRM5 receptors, and these have been shown to activate phospholipase C. Group II includes GRM2 and GRM3 receptors, while Group III includes GRM4, GRM6, GRM7 and GRM8 receptors. Groups II and III receptors are linked to the inhibition of the cyclic AMP cascade, but differ in their agonist selectivities.³⁴⁻³⁶

CNTNAP2, or the contactin-associated protein-like 2 gene, encodes a member of the neurexin family which functions in the vertebrate nervous system as cell adhesion molecules and receptors. This gene has been implicated in multiple neurodevelopmental disorders, including Gilles de la Tourette syndrome, schizophrenia, epilepsy, autism, attention deficit and hyperactivity disorder (ADHD) and mental retardation.^{37,38}

The gene *GRIA4* (glutamate receptor, ionotropic, AMPA4) is protein-coding. Glutamate receptors are the predominant excitatory neurotransmitter receptors in the mammalian brain and are activated in a variety of normal neurophysiologic processes. These receptors are heteromeric protein complexes composed of multiple subunits, arranged to

form ligand-gated ion channels. The classification of glutamate receptors is based on their activation by different pharmacologic agonists. The subunit encoded by this *GRIA4* belongs to a family of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate)-sensitive glutamate receptors, and is subject to RNA editing (AGA->GGA; R->G). Alternative splicing of this gene results in transcript variants encoding different isoforms, which may vary in their signal transduction properties. Some haplotypes of this gene show a positive association with schizophrenia.^{39,40}

ZDHHC8 is the protein-coding zinc finger, DHHC-type containing 8 gene. It encodes a four-transmembrane protein that is a member of the zinc finger DHHC domain-containing protein family. The encoded protein may function as a palmitoyltransferase. Defects in this gene may be associated with a susceptibility to schizophrenia.⁴¹⁻⁴³

Genes associated with cancer in the Circassian population

There were twenty genes associated with cancer found in the Circassian population. *LPAR3*, or the lysophosphatidic acid receptor 3 gene, codes for a member of the G protein-coupled receptor family, as well as the EDG family of proteins. This protein functions as a cellular receptor for lysophosphatidic acid and mediates lysophosphatidic acid-evoked calcium mobilization. This receptor couples predominantly to G(q/11) alpha proteins.^{44,45}

ESRRG, or the estrogen-related receptor gamma gene, encodes a member of the estrogen receptor-related receptor (ESRR) family, which belongs to the nuclear hormone receptor superfamily. All members of the ESRR family share an almost identical DNA binding domain, which is composed of two C4-type zinc finger

motifs. The ESRR members are orphan nuclear receptors; they bind to the estrogen response element and steroidogenic factor 1 response element, and activate genes controlled by both response elements in the absence of any ligands. The ESRR family is closely related to the estrogen receptor (ER) family. They share target genes, co-regulators and promoters, and, by targeting the same set of genes, the ESRRs seem to interfere with the ER-mediated estrogen response in various ways. It has been reported that the protein encoded by this gene functions as a transcriptional activator of DNA cytosine-5-methyltransferase 1 (*DNMT1*) expression by direct binding to its response elements in the *DNMT1* promoters, modulates cell proliferation and estrogen signaling in breast cancer, and negatively regulates bone morphogenetic protein 2-induced osteoblast differentiation and bone formation.^{48,49}

BIRC6 encodes a protein with a BIR (baculoviral inhibition of apoptosis protein repeat) domain and a UBCc (ubiquitin-conjugating enzyme E2, catalytic) domain. This protein inhibits apoptosis by facilitating the degradation of apoptotic proteins by ubiquitination. BIRC6 protein is also associated with cancer recurrence and chemoresistance in non-small-cell lung cancer.⁵³

The *SCTR* (secretin receptor) gene encodes a G protein-coupled receptor that belongs to the glucagon-VIP-secretin receptor family. It binds secretin, which is the most potent regulator of pancreatic bicarbonate, electrolyte and volume secretion. Secretin and its receptor are suggested to be involved in pancreatic cancer and autism.⁵⁴

TP63, or the tumor protein p63 gene, encodes a member of the p53 family of

transcription factors. An animal model, p63 $-/-$ mice, has been useful in defining the role this protein in the development and maintenance of stratified epithelial tissues. The p63 $-/-$ mice have several developmental defects which include the lack of limbs and other tissues, such as teeth and mammary glands, which develop as a result of interactions between mesenchyme and epithelium.^{55,56}

ERGIC1 (endoplasmic reticulum-golgi intermediate compartment 1), encodes a cycling membrane protein which is an endoplasmic reticulum-golgi intermediate compartment (ERGIC) protein that interacts with other members of this protein family to increase their turnover. Furthermore, *ERGIC1* gene was shown to be highly expressed in prostate cancer tissues.⁵⁷ The high mRNA expression of *ERGIC1* was associated with the expression of two oncogenes; androgen receptor (AR) and v-ets avian erythroblastosis virus E26 oncogene homolog (ERG).⁵⁷

The *BRAF* gene (v-raf murine sarcoma viral oncogene homolog B) encodes a protein belonging to the raf/mil family of serine/threonine protein kinases. This protein plays a role in regulating the MAP kinase/ERK signaling pathway, which affects cell division, differentiation and secretion. Mutations in this gene are associated with cardiofaciocutaneous syndrome, a disease characterized by heart defects, mental retardation and a distinctive facial appearance. Mutations in this gene have also been associated with various cancers, including non-Hodgkin's lymphoma, colorectal cancer, malignant melanoma, thyroid carcinoma, non-small cell lung carcinoma, and adenocarcinoma of the lung. A pseudogene, which is located on chromosome X, has been identified for this gene.⁵⁸

TTF1 (the transcription termination factor, RNA polymerase I gene) encodes a transcription termination factor that is localized to the nucleolus and plays a critical role in ribosomal gene transcription. The encoded protein mediates the termination of RNA polymerase I transcription by binding to Sal box terminator elements downstream of pre-rRNA coding regions.^{59,60}

KIN (antigenic determinant of recA protein homolog) encodes a nuclear protein that forms intranuclear foci during proliferation and is redistributed in the nucleoplasm during the cell cycle. Short-wave ultraviolet light provokes the relocalization of the protein, suggesting its participation in the cellular response to DNA damage.⁶¹

FRMD4A gene codes for FERM domain containing protein 4A. *FRMD4A* upregulation in human squamous cell carcinoma promotes tumor growth and metastasis and is associated with poor prognosis.⁶²

STIM1, the stromal interaction molecule 1 gene, encodes a type 1 transmembrane protein that mediates Ca^{2+} influx after depletion of intracellular Ca^{2+} stores by gating of store-operated Ca^{2+} influx channels (SOCs). It is one of several genes located in the imprinted gene domain of 11p15.5, an important tumor-suppressor gene region. Alterations in this region have been associated with Beckwith-Wiedemann syndrome, Wilms tumor, rhabdomyosarcoma, adrenocortical carcinoma, as well as lung, ovarian, and breast cancers. *STIM1* gene may play a role in the occurrence of malignancies and diseases that involve the imprinted gene domain of 11p15.5 region as well as the occurrence of early hematopoiesis, by mediating attachment to stromal cells. For

example, mutations in this gene are also associated with fatal classic Kaposi sarcoma, immunodeficiency due to defects in store-operated calcium entry (SOCE) in fibroblasts, ectodermal dysplasia and tubular aggregate myopathy. This gene is oriented in a head-to-tail configuration with the ribonucleotide reductase 1 gene (RRM1), with the 3' end of this gene situated 1.6 kb from the 5' end of the RRM1 gene.^{63,64}

CD82 codes a metastasis suppressor gene product that is a membrane glycoprotein and a member of the transmembrane 4 superfamily. Expression of this gene has been shown to be downregulated in tumor progression of human cancers and can be activated by p53 through a consensus binding sequence in the promoter. Its expression and that of p53 are strongly correlated, and the loss of expression of these two proteins is associated with poor survival for prostate cancer patients.^{65,66}

LIM1, the LIM domain and actin binding 1 gene, encodes a cytoskeleton-associated protein that inhibits actin filament depolymerization and cross-links filaments in bundles. It is downregulated in some cancer cell lines. Alternatively, spliced transcript variants encoding different isoforms have been described for this gene, and expression of some of the variants may be independently regulated.^{67,68}

NTN4 (the netrin 4 gene) encodes NTN4, which belongs to a family of proteins related to laminins.^{69,70}

KLF12 (the Kruppel-like factor 12 gene) encodes a protein that is a member of the Kruppel-like zinc finger protein family. This protein can repress expression of the Activator protein-2 alpha (AP-2 alpha) gene by binding to

a specific site in the AP-2 alpha gene promoter. AP-2 alpha is a developmentally regulated transcription factor and important regulator of gene expression during vertebrate development and carcinogenesis. Repression by the encoded protein requires binding with a corepressor, CtBP1.⁷¹

RORA (RAR-related orphan receptor A gene) encodes a protein that is a member of the NR1 subfamily of nuclear hormone receptors. It can bind as a monomer or as a homodimer to hormone response elements upstream of several genes to enhance the expression of those genes. The specific functions of this protein are not known, but it has been shown to interact with NM23-2, a nucleoside diphosphate kinase involved in organogenesis and differentiation, as well as with NM23-1, the product of a tumor metastasis suppressor candidate gene.^{72,73}

PAK7 encodes the p21 protein (Cdc42/Rac)-activated kinase 7, a member of the PAK family of Ser/Thr protein kinases. PAK family members are known to be effectors of Rac/Cdc42 GTPases, which have been implicated in the regulation of cytoskeletal dynamics, proliferation, and cell survival signaling. This kinase contains a CDC42/Rac1 interactive binding (CRIB) motif, and has been shown to bind CDC42 in the presence of GTP. This kinase is predominantly expressed in the brain. It is capable of promoting neurite outgrowth, and thus may play a role in neurite development. It is also associated with microtubule networks and induces microtubule stabilization. The subcellular localization of this kinase is tightly regulated during cell cycle progression.^{75,76}

Other genes include *DTL* (the denticleless E3 ubiquitin protein ligase homolog gene) (*Drosophila*), which encodes protein and is

associated with various types of cancer, including colon cancer.^{46,47} The gene *BRE* (brain and reproductive organ-expressed) is a tumor promotor.⁵⁰⁻⁵² *NOL3* encodes nucleolar protein 3 (apoptosis repressor with CARD domain), an anti-apoptotic protein that has been shown to downregulate the enzyme activities of caspase 2, caspase 8 and tumor protein p53.⁷⁴

Genes associated with cancer in the Chechen population

The two genes in the Chechen population associated with cancer were *DCC* and *CHSY1*. *DCC* is a protein-coding gene, deleted in colorectal carcinoma. This gene encodes a netrin 1 receptor. The transmembrane protein is a member of the immunoglobulin superfamily of cell adhesion molecules, and mediates axon guidance of neuronal growth cones towards sources of netrin 1 ligand. The cytoplasmic tail interacts with the tyrosine kinases Src and focal adhesion kinase (FAK, also known as PTK2) to mediate axon attraction. The protein partially localizes to lipid rafts, and induces apoptosis in the absence of ligand. The protein functions as a tumor suppressor, and is frequently mutated or downregulated in colorectal cancer and esophageal carcinoma.⁷⁷⁻⁷⁹

CHSY1, the gene chondroitin sulfate synthase 1, encodes a member of the chondroitin N-acetylgalactosaminyltransferase family. These enzymes possess dual glucuronyltransferase and galactosaminyltransferase activity and play critical roles in the biosynthesis of chondroitin sulfate, a glycosaminoglycan involved in many biological processes including cell proliferation and morphogenesis. Decreased expression of this gene may play a role in colorectal cancer, and mutations in this gene are a cause of temtamy preaxial brachydactyly syndrome.⁸⁰

Disease prevalence in Circassians and Chechens in Jordan

It is worth mentioning that an analysis of the prevalence of cancer in the Circassian and Chechen populations in Jordan showed a higher prevalence of colorectal cancer in Circassians. Both Circassians and Chechens had a higher prevalence of breast cancer and, to a lesser extent, lung cancer compared to Arab Jordanians.⁸¹

Future studies should focus on other ethnic groups and investigate the association of genetic variants in diabetes with other diseases. Moreover, the studies should examine the effect of diabetes medication on the treatment of other diseases, and explore whether or not combination therapy can be applied.

Conclusion

In the present study, our search revealed SNPs carried on 6 genes in the Circassians and 7 genes in the Chechens are associated with schizophrenia. Among these genes, Disabled-1 (*DABI*) and CUB and Sushi multiple domain 1 (*CSMD1*) were common between the Circassians and the Chechens. *CSMD1* is associated with both cancer and schizophrenia. We also found that SNPs located on 20 genes in the Circassians and 2 genes in the Chechens are associated with cancer. However, overall, no specific type of cancer dominated.

Taken together, the results from this pilot study demonstrate that multiple genetic factors that underlie type 2 diabetes are also associated with cancer and schizophrenia in the Chechen and Circassian populations in Jordan.

Acknowledgments

This research was funded by the King Hussein Institute for Biotechnology and Cancer and the Higher Council for Science and

Technology in Amman, Jordan. We would like to thank the Circassian and Chechen communities for their cooperation in conducting this study.

References

1. Karuranga S, Fernandes JR, Huang Y, Malanda B. IDF Diabetes Atlas, 8th ed. Brussels, Belgium: International Diabetes Federation 2017.
2. Hirschhorn JN, Daly MJ. Genome-wide association studies for common diseases and complex traits. *Nature reviews. Genetics* 2005; 6 (2): 95-108.
3. Barrett JC, Cardon LR. Evaluating coverage of genome-wide association studies. *Nature genetics* 2006; 38 (6): 659-662.
4. Pe'er I, de Bakker PI, Maller J, Yelensky R, Altshuler D, Daly MJ. Evaluating and improving power in whole-genome association studies using fixed marker sets. *Nature genetics* 2006; 38(6): 663-667.
5. Freimer NB, Sabatti C. Human genetics: variants in common diseases. *Nature* 2007; 445(7130): 828-831.
6. Liu JZ, Mcrae AF, Nyholt DR, Medland SE, Wray NR, Brown KM, Hayward NK, Montgomery GW, Visscher PM, Martin NG. A versatile gene-based test for genome-wide association studies. *The American Journal of Human Genetics* 2010; 87 (1): 139-145.
7. Parra E, Below J, Krithika S, Valladares A, Barta J, Cox N, Hanis C, Wachter N, Garcia-Mena J, Hu P. Genome-wide association study of type 2 diabetes in a sample from Mexico City and a meta-analysis of a Mexican-American sample from Starr County, Texas. *Diabetologia* 2011; 54 (8): 2038-2046.
8. Subramanian A, Tamayo P, Mootha VK, Mukherjee S, Ebert BL, Gillette MA, Paulovich A, Pomeroy SL, Golub TR, Lander ES. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proceedings of the National Academy of Sciences* 2005; 102 (43): 15545-15550.
9. Barbujani G, Nasidze IS, Whitehead GN. Genetic diversity in the Caucasus. *Human biology* 1994; 66(4): 639-668.
10. Barbujani G, Whitehead GN, Bertorelle G, Nasidze IS. Testing hypotheses on processes of genetic and linguistic change in the Caucasus. *Human biology* 1994; 66 (5): 843-864.
11. Nasidze I, Ling E, Quinque D, Dupanloup I, Cordaux R, Rychkov S, Naumova O, Zhukova O, Sarraf-Zadegan N, Naderi G. Mitochondrial DNA and Y-chromosome variation in the Caucasus. *Annals of human genetics* 2004; 68 (3): 205-221.
12. Bulayeva KB. Overview of genetic-epidemiological studies in ethnically and demographically diverse isolates of Dagestan, Northern Caucasus, Russia. *Croatian medical journal* 2006; 47 (4): 641-648.
13. Nasidze I, Stoneking M. Mitochondrial DNA variation and language replacements in the Caucasus. *Proceedings of the Royal Society of London B: Biological Sciences* 2001; 268 (1472): 1197-1206.
14. Kailani W. Chechens in the Middle East: between original and host cultures. *Caspian Studies Program. Paper presented at seminar*, 2002.
15. Dajani R, Khader YS, Fatahalla R, El-Khateeb M, Shiyab AH, Hakooz N. Diabetes mellitus in genetically isolated populations in Jordan: prevalence, awareness, glycemic control, and associated factors. *Journal of Diabetes and its Complications* 2012; 26 (3): 175-180.
16. Dajani R, Khader YS, Hakooz N, Fatahalla R, Qadani F. Metabolic syndrome between two ethnic minority groups (Circassians and Chechens) and the original inhabitants of Jordan. *Endocrine* 2013; 43(1): 112-119.
17. Shishani K, Dajani R, Khader Y. Hypertension risk assessment in the largest ethnic groups in Jordan. *Journal of immigrant and minority health* 2013; 15 (1): 43-48.
18. Tayyem RF, Dajani R, Khader YS, Abu-Mweis SS, Fatahalla R, Bawadi HA. Nutrient intake and lifestyle factors by diabetes status of Circassians and Chechans in Jordan. *Ethnicity & disease* 2014; 24 (2): 200-206.
19. MacArthur J, Bowler E, Cerezo M, Gil L, Hall P, Hastings E, Junkins H, McMahon A, Milano A, Morales J, Pendlington MZ, Welter D, Burdett T, Hindorf L, Flicek P, Cunningham F, Parkinson H. The new NHGRI-EBI Catalog of published genome-wide association studies (GWAS Catalog). *Nucleic Acids Research* 2016, 45 (D1), D896-D901.
20. Dajani R, Li J, Wei Z, March ME, Xia Q, Khader Y, Hakooz N, Fatahalla R, El-Khateeb M, Arafat A, Saleh T, Dajani AR, Al-Abbadi Z, Abdul Qader M, Shiyab AH, Bateiha A, Ajlouni K, Hakonarson H. Genome-wide association study identifies novel type II diabetes risk loci

- in Jordan subpopulations. *PeerJ* 2017; 5, e3618.
21. Dajani R, Li J, Wei Z, Glessner JT, Chang X, Cardinale CJ, Pellegrino R, Wang T, Hakooz N, Khader Y, Sheshani A, Zandaki D, Hakonarson H. CNV Analysis Associates AKNAD1 with Type-2 Diabetes in Jordan Subpopulations. *Scientific Reports* 2015; 5: 13391.
 22. Verbrugge P, Bouwer S, Wiltshire S, Carter K, Chandler D, Cooper M, Morar B, Razif MF, Henders A, Badcock JC. Impact of the reelin signaling cascade (ligands–receptors–adaptor complex) on cognition in schizophrenia. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2012; 159 (4): 392-404.
 23. Costa E, Davis J, Grayson DR, Guidotti A, Pappas GD, Pesold C. Dendritic spine hypoplasticity and downregulation of reelin and GABAergic tone in schizophrenia vulnerability. *Neurobiology of disease* 2001; 8(5): 723-742.
 24. Impagnatiello F, Guidotti AR, Pesold C, Dwivedi Y, Caruncho H, Pisu MG, Uzunov DP, Smalheiser NR, Davis JM, Pandey GN. A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proceedings of the National Academy of Sciences* 1998; 95(26): 15718-15723.
 25. Donohoe G, Walters J, Hargreaves A, Rose E, Morris D, Fahey C, Bellini S, Cummins E, Giegling I, Hartmann A. Neuropsychological effects of the CSMD1 genome-wide associated schizophrenia risk variant rs10503253. *Genes, Brain and Behavior* 2013; 12(2): 203-209.
 26. Håvik B, Le Hellard S, Rietschel M, Lybæk H, Djurovic S, Mattheisen M, Mühleisen TW, Degenhardt F, Priebe L, Maier W. The complement control-related genes CSMD1 and CSMD2 associate to schizophrenia. *Biological psychiatry* 2011; 70(1): 35-42.
 27. Shull AY, Clendenning ML, Ghoshal-Gupta S, Farrell CL, Vangapandu HV, Dudas L, Wilkerson BJ, Buckhaults PJ. Somatic mutations, allele loss, and DNA methylation of the Cub and Sushi Multiple Domains 1 (CSMD1) gene reveals association with early age of diagnosis in colorectal cancer patients. *PloS one* 2013; 8 (3): e58731.
 28. Fallin MD, Lasseter VK, Liu Y, Avramopoulos D, McGrath J, Wolyniec PS, Nestadt G, Liang KY, Chen PL, Valle D, Pulver AE. Linkage and association on 8p21.2-p21.1 in schizophrenia. *American journal of medical genetics. Part B, Neuropsychiatric genetics: the official publication of the International Society of Psychiatric Genetics* 2011; 156 (2): 188-197.
 29. Hatzimanolis A, McGrath J, Wang R, Li T, Wong P, Nestadt G, Wolyniec P, Valle D, Pulver A, Avramopoulos D. Multiple variants aggregate in the neuregulin signaling pathway in a subset of schizophrenia patients. *Translational psychiatry* 2013; 3 (5): e264.
 30. Chen Q, Che R, Wang X, O'Neill FA, Walsh D, Tang W, Shi Y, He L, Kendler KS, Chen X. Association and expression study of synapsin III and schizophrenia. *Neuroscience letters* 2009; 465 (3): 248-251.
 31. Imai K, Harada S, Kawanishi Y, Tachikawa H, Okubo T, Suzuki T. Polymorphisms in the Promoter and Coding Regions of the Synapsin III Gene. *Neuropsychobiology* 2001; 43 (4): 237-241.
 32. Chen X, Wang X, Chen Q, Williamson V, van den Oord E, Maher BS, O'Neill FA, Walsh, D, Kendler KS. MEGF10 association with schizophrenia. *Biological psychiatry* 2008; 63 (5): 441-448.
 33. Chen X, Sun C, Chen Q, O'Neill FA, Walsh D, Fanous AH, Chowdari KV, Nimgaonkar VL, Scott A, Schwab SG. Apoptotic engulfment pathway and schizophrenia. *PloS one* 2009; 4 (9): e6875.
 34. Choi KH, Zepp ME, Higgs BW, Weickert CS, Webster MJ. Expression profiles of schizophrenia susceptibility genes during human prefrontal cortical development. *Journal of psychiatry & neuroscience: JPN* 2009; 34 (6): 450-458.
 35. Ganda C, Schwab SG, Amir N, Heriani H, Irmansyah I, Kusumawardhani A, Nasrun M, Widyawati I, Maier W, Wildenauer DB. A family-based association study of DNA sequence variants in GRM7 with schizophrenia in an Indonesian population. *International Journal of Neuropsychopharmacology* 2009; 12 (9): 1283-1289.
 36. Shibata H, Tani A, Chikuhara T, Kikuta R, Sakai M, Ninomiya H, Tashiro N, Iwata N, Ozaki N, Fukumaki Y. Association study of polymorphisms in the group III metabotropic glutamate receptor genes, GRM4 and GRM7, with schizophrenia. *Psychiatry research* 2009; 167 (1): 88-96.
 37. Ji W, Li T, Pan Y, Tao H, Ju K, Wen Z, Fu Y, An Z, Zhao Q, Wang T. CNTNAP2 is significantly associated with schizophrenia and major depression in the Han Chinese population. *Psychiatry research* 2013; 207 (3): 225-228.
 38. Gregor A, Albrecht B, Bader I, Bijlsma EK, Ekici AB, Engels H, Hackmann K, Horn D,

- Hoyer J, Klapecki J, Expanding the clinical spectrum associated with defects in CNTNAP2 and NRXN1. *BMC medical genetics* 2011; 12 (1): 106.
39. Friedman J, Vrijenhoek T, Markx S, Janssen I, Van Der Vliet W, Faas B, Knoers N, Cahn W, Kahn R, Edelmann L. CNTNAP2 gene dosage variation is associated with schizophrenia and epilepsy. *Molecular psychiatry* 2008; 13 (3): 261-266.
 40. Chiesa A, Crisafulli C, Porcelli S, Han C, Patkar AA, Lee SJ, Park MH, Jun TY, Serretti A, Pae CU. Influence of GRIA1, GRIA2 and GRIA4 polymorphisms on diagnosis and response to treatment in patients with major depressive disorder. *European archives of psychiatry and clinical neuroscience* 2012; 262 (4): 305-311.
 41. Magri C, Gardella R, Valsecchi P, Barlati SD, Guizzetti L, Imperadori L, Bonvicini C, Tura GB. Study on GRIA2, GRIA3 and GRIA4 genes highlights a positive association between schizophrenia and GRIA3 in female patients. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2008; 147 (6): 745-753.
 42. Ota VK, Gadelha A, Assuncao IB, Santoro ML, Christofolini DM, Bellucco FT, Santos-Filho AF, Ottoni GL, Lara DR, Mari JJ. ZDHHC8 gene may play a role in cortical volumes of patients with schizophrenia. *Schizophrenia research* 2013; 145 (1): 33-35.
 43. Xu M, Clair DS, He L. Testing for genetic association between the ZDHHC8 gene locus and susceptibility to schizophrenia: an integrated analysis of multiple datasets. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics* 2010; 153 (7): 1266-1275.
 44. Chen WY, Shi YY, Zheng YL, Zhao XZ, Zhang GJ, Chen SQ, Yang PD, He L. Case-control study and transmission disequilibrium test provide consistent evidence for association between schizophrenia and genetic variation in the 22q11 gene ZDHHC8. *Human molecular genetics* 2004; 13 (23): 2991-2995.
 45. Yang D, Yang W, Zhang Q, Hu Y, Bao L, Damirin A. Migration of gastric cancer cells in response to lysophosphatidic acid is mediated by LPA receptor 2. *Oncology letters* 2013; 5 (3): 1048-1052.
 46. Popnikolov NK, Dalwadi BH, Thomas JD, Johannes GJ, Imagawa WT. Association of autotaxin and lysophosphatidic acid receptor 3 with aggressiveness of human breast carcinoma. *Tumor Biology* 2012; 33 (6): 2237-2243.
 47. Mackintosh C, Ordonez J, Garcia-Dominguez D, Sevillano V, Llombart-Bosch A, Suzhai K, Scotlandi K, Alberghini M, Sciot R, Sinnaeve F. 1q gain and CDT2 overexpression underlie an aggressive and highly proliferative form of Ewing sarcoma. *Oncogene* 2012; 31 (10): 1287-1298.
 48. Baraniskin A, Birkenkamp-Demtroder K, Maghnouj A, Zöllner H, Munding J, Klein-Scory S, Reinacher-Schick A, Schwarte-Waldhoff I, Schmiegel W, Hahn SA. MiR-30a-5p suppresses tumor growth in colon carcinoma by targeting DTL. *Carcinogenesis* 2012; 33 (4): 732-739.
 49. Su N, Qiu H, Chen Y, Yang T, Yan Q, Wan X. miR-205 promotes tumor proliferation and invasion through targeting ESRRG in endometrial carcinoma. *Oncology reports* 2013; 29 (6): 2297-2302.
 50. Yamamoto T, Mori T, Sawada M, Kuroboshi H, Tatsumi H, Yoshioka T, Matsushima H, Iwasaku K, Kitawaki J. Estrogen-related receptor- γ regulates estrogen receptor- α responsiveness in uterine endometrial cancer. *International Journal of Gynecological Cancer* 2012; 22 (9): 1509-1516.
 51. Chen HB, Pan K, Tang MK, Chui YL, Chen L, Su ZJ, Shen ZY, Li EM, Xie W, Lee KK. Comparative proteomic analysis reveals differentially expressed proteins regulated by a potential tumor promoter, BRE, in human esophageal carcinoma cells. *Biochemistry and Cell Biology* 2008; 86 (4): 302-311.
 52. Chan BC, Li Q, Chow SK, Ching AK, Liew CT, Lim PL, Lee KK, Chan JY, Chui YL. BRE enhances in vivo growth of tumor cells. *Biochemical and biophysical research communications* 2005; 326 (2): 268-273.
 53. Chui YL, Ching AK, Chen S, Yip FP, Rowlands DK, James AE, Lee KK, Chan JY. BRE overexpression promotes growth of hepatocellular carcinoma. *Biochemical and biophysical research communications* 2010; 391 (3): 1522-1525.
 54. Dong X, Lin D, Low C, Vucic EA, English JC, Yee J, Murray N, Lam WL, Ling V, Lam S. Elevated expression of BIRC6 protein in non-small-cell lung cancers is associated with cancer recurrence and chemoresistance. *Journal of Thoracic Oncology* 2013; 8 (2): 161-170.
 55. Lee M, Waser B, Reubi JC, Pellegata NS. Secretin receptor promotes the proliferation of endocrine tumor cells via the PI3K/AKT pathway. *Molecular endocrinology* 2012; 26 (8): 1394-1405.

56. Matin RN, Chikh A, Chong SL, Mesher D, Graf M, Sanza P, Senatore V, Scatolini M, Moretti F, Leigh IM. p63 is an alternative p53 repressor in melanoma that confers chemoresistance and a poor prognosis. *Journal of Experimental Medicine* 2013; 210 (3): 581-603.
57. Montariello D, Troiano A, Malanga M, Calabrò V, Quesada P. p63 involvement in poly (ADP-ribose) polymerase 1 signaling of topoisomerase I-dependent DNA damage in carcinoma cells. *Biochemical pharmacology* 2013; 85 (7): 999-1006.
58. Vainio P, Mpindi JP, Kohonen P, Fey V, Mirtti T, Alanen KA, Perälä M, Kallioniemi O, Iljin K. High-throughput transcriptomic and RNAi analysis identifies AIM1, ERGIC1, TMED3 and TPX2 as potential drug targets in prostate cancer. *PloS one* 2012; 7 (6): e39801.
59. Lochhead P, Kuchiba A, Imamura Y, Liao X, Yamauchi M, Nishihara R, Qian ZR, Morikawa T, Shen J, Meyerhardt JA. Microsatellite instability and BRAF mutation testing in colorectal cancer prognostication. *Journal of the National Cancer Institute* 2013; 105 (15): 1151-1156.
60. Reddi DM, Puri PK. Expression of focal TTF-1 expression in a case of CK7/CK20-positive Merkel cell carcinoma. *Journal of cutaneous pathology* 2013; 40 (4): 431-433.
61. Sullivan PS, Maresh EL, Seligson DB, Habeeb O, Wadehra M, Goodglick L, Dorig O. Expression of thyroid transcription factor-1 in normal endometrium is associated with risk of endometrial cancer development. *Modern pathology* 2012; 25 (8): 1140-1148.
62. Zeng T, Gao H, Yu P, He H, Ouyang X, Deng L, Zhang Y. Up-regulation of kin17 is essential for proliferation of breast cancer. *PLoS One* 2011; 6 (9): e25343.
63. Goldie SJ, Mulder KW, Tan DW, Lyons SK, Sims AH, Watt FM. FRMD4A upregulation in human squamous cell carcinoma promotes tumor growth and metastasis and is associated with poor prognosis. *Cancer research* 2012; 72 (13): 3424-3436.
64. Yoshida J, Iwabuchi K, Matsui T, Ishibashi T, Masuoka T, Nishio M. Knockdown of stromal interaction molecule 1 (STIM1) suppresses store-operated calcium entry, cell proliferation and tumorigenicity in human epidermoid carcinoma A431 cells. *Biochemical pharmacology* 2012; 84 (12): 1592-1603.
65. Motiani RK, Hyzinski-García MC, Zhang X, Henkel MM, Abdullaev IF, Kuo YH, Matrougui K, Mongin AA, Trebak M. STIM1 and Orail mediate CRAC channel activity and are essential for human glioblastoma invasion. *Pflügers Archiv-European Journal of Physiology* 2013; 465 (9): 1249-1260.
66. Chigita S, Sugiura T, Abe M, Kobayashi Y, Shimoda M, Onoda M, Shirasuna K. CD82 inhibits canonical Wnt signalling by controlling the cellular distribution of β -catenin in carcinoma cells. *International journal of oncology* 2012; 41 (6): 2021-2028.
67. Lee HA, Park I, Byun HJ, Jeoung D, Kim YM, Lee H. Metastasis suppressor KAI1/CD82 attenuates the matrix adhesion of human prostate cancer cells by suppressing fibronectin expression and β 1 integrin activation. *Cellular Physiology and Biochemistry* 2011; 27 (5): 575-586.
68. Liu Y, Sanders AJ, Zhang L, Jiang WG. EPLIN- α expression in human oesophageal cancer and its impact on cellular aggressiveness and clinical outcome. *Anticancer research* 2012; 32 (4): 1283-1289.
69. Zhang S, Wang X, Osunkoya AO, Iqbal S, Chen Z, Müller S, Chen Z, Jossion S, Coleman IM, Nelson PS. EPLIN downregulation promotes epithelial-mesenchymal transition in prostate cancer cells and correlates with clinical lymph node metastasis. *Oncogene* 2011; 30 (50): 4941-4952.
70. Yuan Y, Leszczynska M, Konstantinovskiy S, Tropé CG, Reich R, Davidson B. Netrin-4 is upregulated in breast carcinoma effusions compared to corresponding solid tumors. *Diagnostic cytopathology* 2011; 39 (8): 562-566.
71. Nacht M, Martin TB, Byrne A, Klinger KW, Teicher BA, Madden SL, Jiang Y. Netrin-4 regulates angiogenic responses and tumor cell growth. *Experimental cell research* 2009; 315 (5): 784-794.
72. Nakamura Y, Migita T, Hosoda F, Okada N, Gotoh M, Arai Y, Fukushima M, Ohki M, Miyata S, Takeuchi K. Krüppel-like factor 12 plays a significant role in poorly differentiated gastric cancer progression. *International journal of cancer* 2009; 125 (8): 1859-1867.
73. Lee JM, Kim IS, Kim H, Lee JS, Kim K, Yim HY, Jeong J, Kim JH, Kim JY, Lee H. ROR α attenuates Wnt/ β -catenin signaling by PKC α -dependent phosphorylation in colon cancer. *Molecular cell* 2010; 37 (2): 183-195.
74. Tahara T, Maegawa S, Chung W, Garriga J, Jelinek J, Estécio MR, Shibata T, Hirata I, Arisawa T, Issa JP. Examination of whole blood DNA methylation as a potential risk marker for

- gastric cancer. *Cancer Prevention Research* 2013; 6 (10): 1093-1100.
75. Mercier I, Vuolo M, Jasmin JF, Medina CM, Williams M, Mariadason JM, Qian H, Xue X, Pestell RG, Lisanti MP. ARC (apoptosis repressor with caspase recruitment domain) is a novel marker of human colon cancer. *Cell Cycle* 2008; 7 (11): 1640-1647.
 76. Gu J, Li K, Li M, Wu X, Zhang L, Ding Q, Wu W, Yang J, Mu J, Wen H. A role for p21-activated kinase 7 in the development of gastric cancer. *The FEBS journal* 2013; 280 (1): 46-55.
 77. Gong W, An Z, Wang Y, Pan X, Fang W, Jiang B, Zhang H. P21-activated kinase 5 is overexpressed during colorectal cancer progression and regulates colorectal carcinoma cell adhesion and migration. *International journal of cancer* 2009; 125 (3): 548-555.
 78. Duman-Scheel M. Deleted in colorectal cancer (DCC) pathfinding: axon guidance gene finally turned tumor suppressor. *Current drug targets* 2012; 13 (11): 1445-1453.
 79. Grant A, Fathalli F, Rouleau G, Joobor R, Flores C. Association between schizophrenia and genetic variation in DCC: a case-control study. *Schizophrenia research* 2012; 137 (1): 26-31.
 80. Saito M, Yamaguchi A, Goi T, Tsuchiyama T, Nakagawara G, Urano T, Shiku H, Furukawa K. Expression of DCC protein in colorectal tumors and its relationship to tumor progression and metastasis. *Oncology* 1999; 56 (2): 134-141.
 81. Kalathas D, THEOCHARIS DA, Bounias D, Kyriakopoulou D, Papageorgakopoulou N, Stavropoulos MS, Vynios DH. Chondroitin synthases I, II, III and chondroitin sulfate glucuronyltransferase expression in colorectal cancer. *Molecular medicine reports* 2011; 4 (2): 363-368.
 82. Fathallah RM, Dajani R. Comparison of population based cancer incidence rates among Circassians, Chechans and Arabs in Jordan (1996-2005). *Asian Pacific journal of cancer prevention* 2013; 14 (10): 6035-6040.

الجينات التي لها علاقة في مرض السرطان وانفصام الشخصية ومرض السكري في المجتمع الشركسي والشيشاني في الأردن

رنا الدجاني¹، طارق صلاح¹، صبا شبيبات¹، زي وي²، هاكون هاكونارسون³

- 1- قسم العلوم الحياتية والتكنولوجيا الحياتية، الجامعة الهاشمية، الزرقاء، الأردن.
- 2- معهد نيو جرزي للتكنولوجيا، نيوجرزي، الولايات المتحدة الأمريكية.
- 3- قسم طب الأطفال، كلية الطب، جامعة بنسلفانيا، الولايات المتحدة الأمريكية.

الملخص

الغرض: يصيب مرض السكري 16% من سكان الأردن في الأعمار فوق 18 وهو خامس سبب للوفاة في الأردن. لقد بحثنا في منظومة المعلومات في المركز الوطني للمعلومات البيوتكنولوجية الأمريكي عن جميع الجينات التي لها علاقة في قائمة SNPs من منظومة GWAS التي اخذت من 34 حالة سكري و110 حالة ضابطة من المجتمع الشيشاني و3 حالات سكري و106 حالات ضابطة من المجتمع الشركسي. أظهرت نتائج البحث أنّ 20 جيناً له علاقة بمرض السكري السرطان و6 جينات لها علاقة بمرض انفصام الشخصية في المجتمع الشركسي وجينان لهما علاقة بمرض السرطان و7 جينات لهما علاقة بمرض انفصام الشخصية في المجتمع الشيشاني. مما يشير إلى ان هذه الجينات يمكن أن يكون لها علاقة باثنولوجية مع مرض السكري. ان نتائج البحث من هذه الدراسة المبدئية تبين أن عدداً كبيراً من الجينات التي لها علاقة بمرض السكري لها علاقة بمرض السرطان ومرض انفصام الشخصية في المجتمع الشركسي والشيشاني في الأردن.

الكلمات الدالة: الجينات، السرطان، مرض السكري، الشيشان.