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In silico Characterization of Esophageal Cancer Predominant Genes

Gizem KOPRULULU KUCUK *1

Abstract

Cancer is an important health problem nowadays. One of these problems is esophageal cancer (EC). The 7th most common cancer is EC worldwide. Rhomboid-related biomarkers play an important role in EC. Analysis of such biomarkers can yield important insights into the role of rhomboid 5 Homolog 2 (RHBDF2) in cancer pathology. The characterization of genes was made in silico tools such as STRING, SWISS-MODEL, UCSF Chimera ver 1.15, ProtParam, and GeneCards. The protein interactions string of the rhomboid 5 homologs 2 (RHBDF2) gene was obtained from STRING. Epidermal growth factor (EGF), and ADAM Metallopeptidase Domain 17 (ADAM17) genes were detected as related genes. Amino acid sequences of these genes were obtained from NCBI. Homology models, and Ramachandran graphic of RHBDF2, ADAM17, and EGF genes were created by the SWISS-MODEL database and UCSF Chimera ver 1.15 program. Physicochemical properties of RHBDF2, ADAM17, and EGF genes were calculated by the ProtParam database. Subcellular localizations were detected by the GeneCards server. As a result of this study, genomic and subcellular localization of RHBDF2, ADAM17, and EGF genes were obtained. Amino acid sequences, 3D-protein structures, and physicochemical properties were detected.

Keywords: Eusopagheal cancer, homology model, RHBDF2, EGF, ADAM17

1. INTRODUCTION

The esophagus is a muscular and tubular organ. It connects the pharynx and stomach. Esophagus cancer (EC) is the 7th most common cancer worldwide. Because of this situation, it is a most important health problem [1-3]. EC is one of the most common diseases in low- and middle-income countries [1].EC has a bad prognosis due to its late diagnosis [4]. EC has two main subtypes as histological. They are squamous cell cancer (ESCC) and adeno cancer (EAD) [5]. Smoking, alcohol, genetic factors, obesity, and irregular diet affect the development of EC. It was detected that it was stated that the risk of ESCC increased three to seven times in smokers [6]. It has been stated that when cigarettes and alcohol are taken together, the risk of ESCC increases 10-25 times compared to smokers who do not drink alcohol [7]. Some dietary factors have been identified that have been associated with EAD. While some foods with high saturated fat and cholesterol ratios increase the risk of EAD, it has been stated that plant foods (vitamin C, b-carotene, and folate) reduce the risk [8]. Obesity causes

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the risk of EAD to increase approximately two-three times in individuals [9].

Environmental and genetic factors play a role in the formation of esophageal cancer. The mechanisms of action of these factors are usually directly or indirectly related to DNA damage [10].

The rhomboid 5 Homolog 2 (RHBDF2) gene was identified in Drosophila first [11]. RHBDF2 belongs to a rhomboids family which is a seven transmembrane-spanning proteins family. It was detected that RHBDF2 is a serine intramembrane protease linked with the epidermal growth factor receptor (EGFR) signal and mitochondrial remodeling [12]. In vitro studies were shown that RHBDF2 interacts with Tumor Growth Factor a by EGFR signal pathway and arranges the epithelial cancer cell growth and survival [13, 14].

ADAM family is a disintegrin and metalloproteinase and plays a role in cell adhesion, cell migration, cell proliferation, and cell proteolysis. ADAM molecules trigger tumor growth and metastasis [15, 16]. ADAM17 is a key role in malignity. The ADAM17 is located on chromosome 2. ADAM17 is a Tumor necrosis factor α (TNFα) cleaving enzyme. The molecular weight of ADAM17 is 70 kDa [15]. In the arrangement of the ADAM17 process, the first step is the intracellular activation of transmembrane protein by fibroblast growth factor (FGF) or dopamine receptors (R). The second step is the shedding of cell surface proteins by activation of ADAM17 and as a result of this situation, it provides cytokine releases for EGF-R ligands. The third step is the activation of the intracellular signaling pathways. EGF-R binds cleaved ligand and causes this pathway activation [17].

The epithelial growth factor (EGF) is located on chromosome 4. Epidermal growth factor (EGF) is a 6 kDa polypeptide growth factor [18]. EGF is a growth factor and plays a role in cell growth, proliferation, and differentiation. It shows its effects by binding to its own receptor EGFR. EGF has receptors in the kidney, thyroid, gland, duodenum, ovary, stomach, uterus, lung, smooth muscle cells, lens, glial cells, and astrocytes [19-21].

In this study, the characterization of esophageal cancer's predominant genes was made. Genes associated with the RHBDF2 gene associated with EC were identified in the STRING database [22]. The genes associated with RHBDF2 were identified as ADAM17 and EGF. The amino acid sequence of the RHBDF2, ADAM17, and EGF genes were obtained from the National Center for Biotechnology (NCBI)-protein and UniProt databases [23, 24]. Protein templates were obtained from the SWISS-MODEL database using amino acid sequences [25].

Ideal models were selected on the SWISS-MODEL according to Qualitative Model Energy Analysis (QMEAN) values. These model files obtained as documents with .pdb extension were viewed using the UCSF Chimera ver 1.15 program [26]. The amino acid number, molecular weight, theoretical pI value, the percent composition of amino acids, and the total amino acid content of RHBDF2, ADAM17, and EGF proteins were calculated via ProtParam [27].

2. MATERIAL AND METHODS

In this study National Center for Biotechnology (NCBI) [23], UniProt [24], SWISS-MODEL [25], Expasy Protparam [27], and GeneCards [28] databases and UCSF Chimera ver 1.15 program [26] were used in silico analysis. There is no need for ethics committee approval. The genomic location of the RHBDF2 gene was obtained from the GeneCard database in Figure 1 [28].

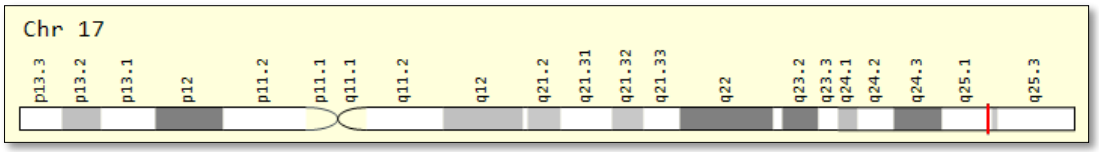


Figure 1 The genomic location of the RHBDF2 gene on the long arm (q) of chromosome number 17 at position (17q25.1) [28]

2.1. Determination of Genes Interacting With Rhomboid 5 Homolog 2 Genes (RHBDF2) in Esophageal Cancer

STRING is a database that shows known and predicted protein-protein interactions. These interactions include physical and functional associations. This database makes use of computational analysis, information transfer between organisms, and interactions collected from other databases. Genes interacting with the RHBDF2 gene were obtained by the STRING database [22].

2.2. Detection of RHBDF2, ADAM17, and EGF Genes Amino acid Sequence

The amino acid sequences of RHBDF2, ADAM17, and EGF genes were obtained by the National Center for Biotechnology (NCBI) protein database and Uniprot [23, 24]. The FASTA format of RHBDF2, ADAM17, and EGF genes was obtained and used to create homology models.

2.3. Obtaining Homology Models of RHBDF2, ADAM17, and EGF Genes

SWISS-MODEL is a protein modeling server. This program serves 3D structures of proteins. When the user enters the amino acid sequence of protein on this server, SWISS-MODEL gives different templates for the target protein. In this study, the protein structures of RHBDF2, ADAM17, and EGF genes were obtained by the SWISS-MODEL server [25]. Ideal templates of RHBDF2, ADAM17, and EGF genes were imaged by the UCSF Chimera ver 1.15 program [26].

2.4. The Obtaining Subcellular Localization of the RHBDF2, ADAM17, and EGF Genes

Subcellular localization determines the environments of operated proteins. For this reason, subcellular localization affects protein function [29-31]. GeneCards is a database that provides information on genomic, proteomic, transcriptomic, genetic, and functional about known and predicted human genes. The subcellular localizations of RHBDF2, ADAM17, and EGF genes were obtained in the GeneCards database [28].

2.5. Detection of the Physicochemical Properties of RHBDF2, ADAM17, and EGF Genes

Expasy is a bioinformatic portal. It provides information on genomic, proteomic, and structural biology, evolution, system biology, and medical chemistry [27].

ProtParam calculates the physicochemical properties of a protein sequence. This server uses an access number from Swiss-Prot/TrEMBL and makes an analysis. Molecular weight, theoretical pI, amino acid composition, the total number of atoms, instability index, hydropathic average (GRAVY), aliphatic index, atomic composition, the total number of negatively charged residues, and the total number of positively charged residues are calculated by ProtParam server [27].

3. CONCLUSIONS AND DISCUSSION

The amino acid sequence of Rhomboid 5 homolog 2 (RHBDF2) was obtained by the NCBI protein and UniProt database [23, 24].

The rhomboid protein 2 isoform 2 (RHBDF2) amino acid sequence is shown in Table 1.

The protein interactions string of the rhomboid 5 homologs 2 (RHBDF2) gene was shown in Figure 2. Disco-interacting protein 2 homolog A (DIP2A), Ubiquitin Conjugating Enzyme E2 O (UBE2O), Rhomboid Domain Containing 1 (RHBDD1), Presenilin Associated Rhomboid Like (PARL), Rhomboid Domain Containing 3 (RHBDD3), Cytoglobin (CYGB), Signal Sequence Receptor Subunit 2 (SSR2), Epidermal growth factor (EGF), ADAM Metallopeptidase Domain 17 (ADAM17), Rhomboid Like 1 (RHBDL1) genes were detected as interact genes with RHBDF2.

Table 1 Rhomboid protein 2 isoform 2 (RHBDF2) amino acid sequence [23, 24]

MASADKNGGSVSSVSSSRLQSRKPPNLSITIPP PEKETQAPGEQDSMLPERKNPAYLKSVSLQE PRSRWQ
ESSEKRPGFRRQASLSQSIRKGAAQWFGVSG DWEGQRQQWQRRSLHHCSMRYGRLKASCQ RDLELPSQEAPSFQGTESPKPCKMPKIVDPLA RGRAFRHPEEMDRPHAPHPPLTPGVLSLTSFT SVRSGYSHLPRRKRMSVAHMSLQAAAALLK GRSVLDATGQRCRVVKRSFAFPSFLEEDVVD GADTFDSSFFSKEEMSSMPDDVFESPPLSASY FRGIPHSASPVSPDGVQIPLKEYGRAPVPGPR RGKRIASKVKHFAFDRKKRHYGLGVVGNWL NRSYRRSISSTVQRQLESFDSHRPYFTYWLTF VHVIITLLVICTYGIAPVGFAQHVTTQLVLRN KGVYESVKYIQQENFWVGPSSIDLIHLGAKFS PCIRKDGQIEQLVLRERDLERDSGCCVQNDH SGCIQTQRKDCSETLATFVKWQDDTGPPMD KSDLGQKRTSGAVCHQDPRTCEEPASSGAHI WPDDITKWPICTEQARSNHTGFLHMDCEIKG RPCCIGTKGSCEITTREYCEFMHGYFHEEATL CSQVHCLDKVCGLLPFLNPEVPDQFYRLWLS LFLHAGVVHCLVSVVFQMTILRDLEKLAGW HRIAIIFILSGITGNLASAIFLPYRAEVGPAGSQ FGLLACLFVELFQSWPLLERPWKAFLNLSAIV LFLFICGLLPWIDNIAHIFGFLSGLLLAFAFLPY ITFGTSDKYRKRALILVSLLAFAGLFAALVLW LYIYPINWPWIEHLTCFPFTSRFCEKYELDQV LH

In this study, it was detected that three genes (RHBDF2, ADAM17, and EGF) play a crucial role in Esophagus cancer. The information on these genes was obtained in NCBI, Uniprot, and GeneCards databases [23, 24, 28]. The genomic location of the ADAM17 and EGF genes was obtained from the GeneCard database in Figure 3 [28]. The genomic localization of the ADAM17 gene is 2p25.1 and the genomic localization of the EGF gene is 4q2.

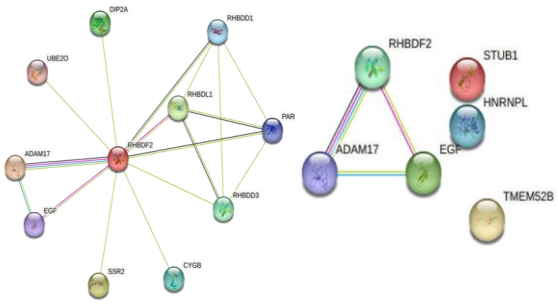


Figure 2 The protein interactions string of rhomboid 5 homologs 2 (RHBDF2) [22]

The amino acid sequence of ADAM Metallopeptidase Domain 17 (ADAM17) and Epidermal growth factor (EGF) were obtained by the NCBI protein and UniProt database [23, 24]. The ADAM Metallopeptidase Domain 17 (ADAM17) and Epidermal growth factor (EGF) amino acid sequences were shown in Table 2.

The RHBDF2, ADAM17, and EGF protein templates were obtained in the SWISS-MODEL database [25]. QMEAN and QMEANDisco values were evaluated and the ideal model was selected on the SWISS-MODEL database [25]. The RHBDF2, ADAM17, and EGF homology models were imaged by the UCSF Chimera ver 1.15 program [26]. The Ramachandran plot for RHBDF2, ADAM17, and EGF proteins amino acid residues, QMEAN and QMEANDisco values, and homology models were shown in Table 3.

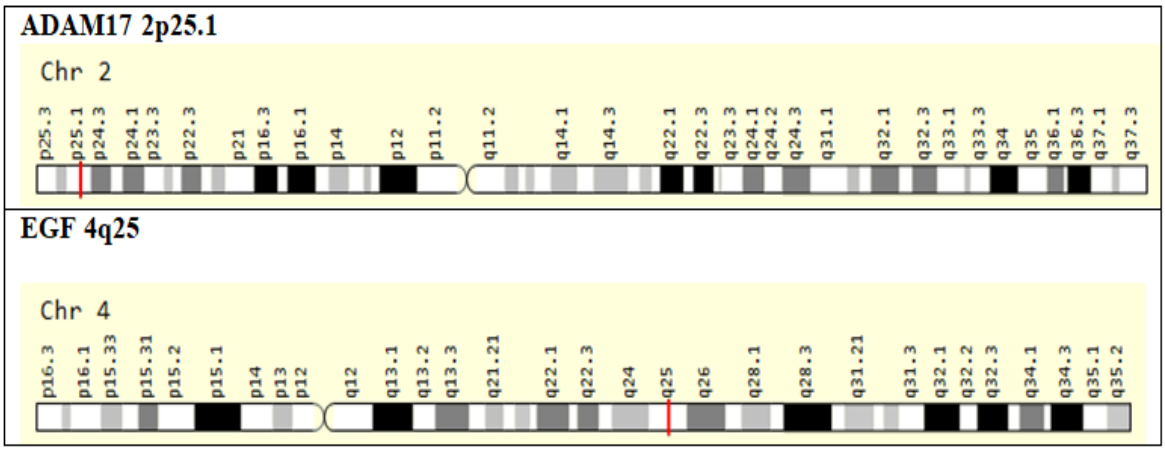


Figure 3 The genomic location of the ADAM17 and EGF genes [28]

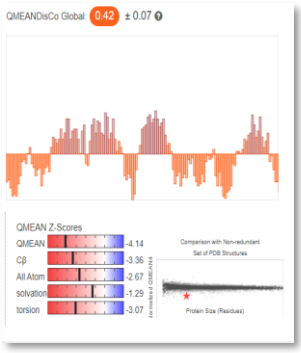
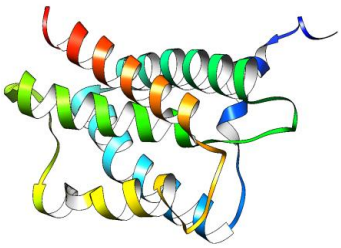
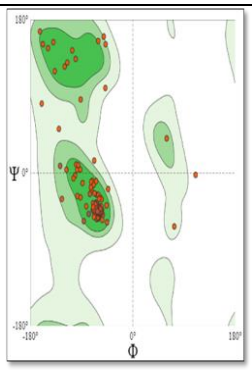
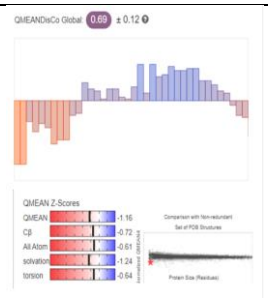
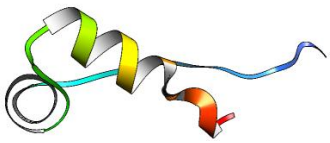
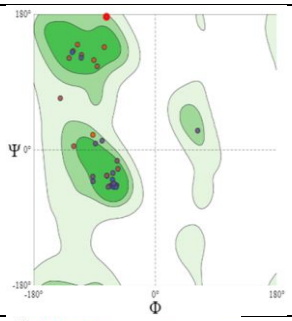
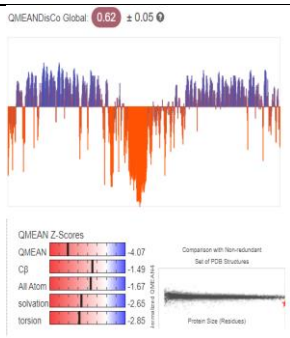
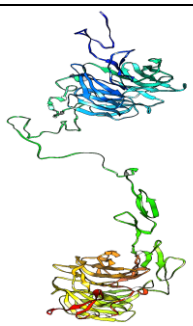
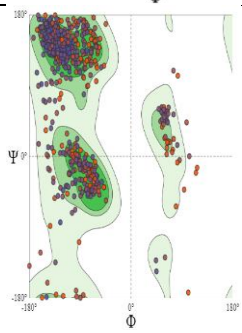
Table 2 ADAM Metallopeptidase Domain 17 (ADAM17) and Epidermal growth factor (EGF) amino acid sequences [23, 24]

ADAM Metallopeptidase Domain 17 (ADAM17)
MRQSLLFLTSVVPFVLAPRPPDDPGFGPHQRLEKLDSLLSDYDILSLSNIQQHSVRKRDLQTSTHVETL LTFSALKRHFKLYLTSSTERFSQNFKVVVVDGKNESEYTVKWQDFFTGHVVGEPDSRVLAHIRDDDV IIRINTDGAEYNIEPLWRFVNDTKDKRMLVYKSEDIKNVSRLQSPKVCGYLKVDNEELLPKGLVDREP PEELVHRVKRRADPDPMKNTCKLLVVADHRFYRYMGRGEESTTTNYLIHTDRAN
Epidermal growth factor (EGF)
MLLTLIILLPVVSKFSFVSLSAPQHWSCPEGTLAGNGNSTCVGPAPFLIFSHGNSIFRIDTEGTNYEQLV VDAGVSVIMDFHYNEKRIYWVDLERQLLQRVFLNGSRQERVCNIEKNVSGMAINWINEEVIWSNQQ EGIITVTDMKGNNSHILLSALKYPANVAVDPVERFIFWSSEVAGSLYRADLDGVGVKALLETSEKITA VSLDVLDKRLFWIQYNREGSNSLICSCDYDGGSVHISKHPTQHNLFAMSLFGDRIFYSTWKMKTIWIA NKHTGKDMVRINLHSSFVPLGELKVVHP LAQPKAEDDTWEPEQKLCKLRKGNCSSTVCGQDLQSHLCMCAEGYALSRDRKYCEDVNECAFWNH GCTLGCKNTPGSYYCTCPVGFVLLPDGKRCHQLVSCPRNVSECSHDCVLTSEGPLCFCPEGSVLERD GKTCSGCSSPDNGGCSQLCVPLSPVSWECDCFPGYDLQLDEKSCAASGPQPFLLFANSQDIRHMHFD GTDYGTLLSQQMGMVYALDHDPVENKIYFAHTALKWIERANMDG SQRERLIEEGVDVPEGLAVDWIGRRFYWTDRGKSLIGRSDLNGKRSKIITKENISQP RGIAVHPMAKRLFWTDTGINPRIESSSLQGLGRLVIASSDLIWPSGITIDFLTDKLYWCDAKQSVIEMA NLDGSKRRRLTQNDVGHPFAVAVFEDYVWFSDWAMPSVMRVNKRTGKDRVRLQGSMLKPSSLVV VHPLAKPGADPCLYQNGGCEHICKKRLGTAWCSCREGFMKASDGKTCLALDGHQLLAGGEVDLKN QVTPLDILSKTRVSEDNITESQHMLVAEIMVSDQDDCAPVGCSMYARCISEGEDATCQCLKGFAGDG KLCSDIDECEMGVPVCPPASSKCINTEGGYVCRCS EGYQGDGIHCLDIDECQLGEHSCGENASCTNTEGGYTCMCAGRLSEPGLICPDSTPPPHLREDDHHYS VRNSDSECPLSHDGYCLHDGVCMYIEALDKYACNCVVGYIGERCQYRDLKWWELRHAGHGQQQK VIVVAVCVVVLVMLLLLSLWGAHYYRTQKLLSKNPKNPYEESSRDVRSRRPADTEDGMSSCPQPWF VVIKEHQDLKNGGQPVAGEDGQAADGSMQPTSWRQEPQLCGMGTEQGCWIPVSSDKGSCPQVMER SFHMPSYGTQTLEGGVEKPHSLLSANPLWQQRALDPP HQMELTQ

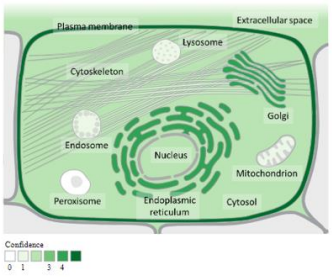
Ramachandran plots use the amino acid information to predict the secondary structures of protein. Each amino acid has rotatable two backbone bonds. They set the dihedral angles (φ and ψ). This plot takes the values of φ on X- the axis and values of ψ on Y- the axis.

The subcellular localization of the RHBDF2, ADAM17, and EGF genes were shown in Figure 4 [28]. It was detected that the RHBDF gene is localized in the plasma membrane, the ADAM17 gene is localized in the cytosol and plasma membrane, and the EGF gene is localized in the lysosome, extracellular, and plasma membrane [28]. The light green color presented low confidence and, dark green presented high confidence on the confidence scale.

Table 3 The homology models of RHBDF2, ADAM17, and EGF proteins [25, 26]

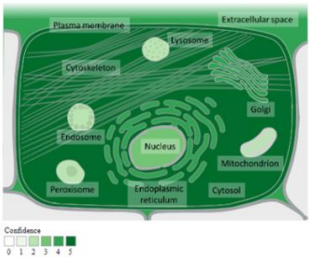
	QMEAN Values	Homology Models	Ramachandran Plots
RHBDF2			
ADAM17			
EGF			

RHBDF2



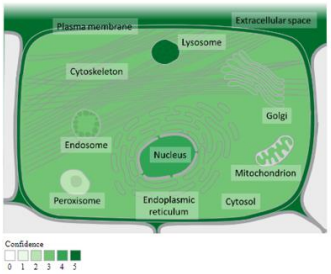
Compartment	Confidence
plasma membrane	5
golgi apparatus	4
endoplasmic reticulum	4
cytosol	2
nucleus	2
extracellular	2
lysosome	1
endosome	1
mitochondrion	1
cytoskeleton	1
peroxisome	0

ADAM17



Compartment	Confidence
cytosol	5
plasma membrane	5
golgi apparatus	4
endoplasmic reticulum	4
cytoskeleton	4
extracellular	4
nucleus	3
lysosome	2
endosome	2
peroxisome	2
mitochondrion	2

EGF



Compartment	Confidence
lysosome	5
extracellular	5
plasma membrane	5
nucleus	4
golgi apparatus	3
cytosol	3
endosome	3
endoplasmic reticulum	3
mitochondrion	3
cytoskeleton	3
peroxisome	2

Figure 4 The subcellular localization of the RHBDF2, ADAM17, and EGF genes [28]

Table 4 Physical properties of RHBDF2, ADAM17, and EGF [27]

RHBDF2	**ADAM17**	**EGF**
Number of amino acids: 827 **Molecular weight:** 93379.31 **Theoretical pI:** 8.91 **Amino acid composition** Ala (A) 52 6.3% Arg (R) 58 7.0% Asn (N) 14 1.7% Asp (D) 36 4.4% Cys (C) 26 3.1% Gln (Q) 39 4.7% Glu (E) 43 5.2% Gly (G) 54 6.5% His (H) 28 3.4% Ile (I) 41 5.0% Leu (L) 82 9.9% Lys (K) 38 4.6% Met (M) 13 1.6% Phe (F) 47 5.7% Pro (P) 57 6.9% Ser (S) 78 9.4% Thr (T) 34 4.1% Trp (W) 18 2.2% Tyr (Y) 21 2.5% Val (V) 48 5.8% Pyl (O) 0 0.0% Sec (U) 0 0.0% (B) 0 0.0% (Z) 0 0.0% (X) 0 0.0% **Total number of negatively charged residues (Asp + Glu):** 79 **Total number of positively charged residues (Arg+ Lys):** 96 **Atomic composition:** Carbon C 4204 Hydrogen H 6500 Nitrogen N 1166 Oxygen O 1172 Sulfur S 39 **Formula:** C4204H6500N1166O1172S39 **Total number of atoms:** 13081 **Instability index:** The instability index (II) is computed to be 54.18 This classifies the protein as unstable. **Aliphatic index:** 81.12 **Grand average of hydropathicity (GRAVY):** -0.231	**Number of amino acids:** 258 **Molecular weight**: 29959.04 **Theoretical pI:** 7.14 **Amino acid composition** Ala (A) 7 2.7% Arg (R) 21 8.1% Asn (N) 11 4.3% Asp (D) 22 8.5% Cys (C) 2 0.8% Gln (Q) 8 3.1% Glu (E) 16 6.2% Gly (G) 10 3.9% His (H) 9 3.5% Ile (I) 9 3.5% Leu (L) 28 10.9% Lys (K) 17 6.6% Met (M) 4 1.6% Phe (F) 11 4.3% Pro (P) 14 5.4% Ser (S) 18 7.0% Thr (T) 16 6.2% Trp (W) 2 0.8% Tyr (Y) 9 3.5% Val (V) 24 9.3% Pyl (O) 0 0.0% Sec (U) 0 0.0% (B) 0 0.0% (Z) 0 0.0% (X) 0 0.0% **Total number of negatively charged residues (Asp + Glu):** 38 **Total number of positively charged residues (Arg + Lys):** 38 **Atomic composition:** Carbon C 1333 Hydrogen H 2107 Nitrogen N 377 Oxygen O 397 Sulfur S 6 **Formula:** C1333H2107N377O397S6 **Total number of atoms:** 4220 **Instability index:** The instability index (II) is computed to be 44.46 This classifies the protein as unstable. **Aliphatic index:** 85.62 **Grand average of hydropathicity (GRAVY):** -0.585	**Number of amino acids:** 1207 **Molecular weight:** 133994.17 **Theoretical pI:** 5.53 **Amino acid composition** Ala (A) 60 5.0% Arg (R) 57 4.7% Asn (N) 46 3.8% Asp (D) 78 6.5% Cys (C) 65 5.4% Gln (Q) 53 4.4% Glu (E) 71 5.9% Gly (G) 101 8.4% His (H) 38 3.1% Ile (I) 55 4.6% Leu (L) 107 8.9% Lys (K) 56 4.6% Met (M) 31 2.6% Phe (F) 32 2.7% Pro (P) 62 5.1% Ser (S) 102 8.5% Thr (T) 49 4.1% Trp (W) 27 2.2% Tyr (Y) 34 2.8% Val (V) 83 6.9% Pyl (O) 0 0.0% Sec (U) 0 0.0% (B) 0 0.0% (Z) 0 0.0% (X) 0 0.0% **Total number of negatively charged residues (Asp + Glu):** 149 **Total number of positively charged residues (Arg + Lys):** 113 **Atomic composition:** Carbon C 5844 Hydrogen H 9098 Nitrogen N 1636 Oxygen O 1790 Sulfur S 96 **Formula:** 5844H9098N1636O1790S96 **Total number of atoms:** 18464 **Instability index:** The instability index (II) is computed to be 48.69**.** This classifies the protein as unstable. **Aliphatic index:** 77.26 **Grand average of hydropathicity (GRAVY):** -0.304

The general average of the Hydrophatiy (GRAVY) index shows the solubility of proteins. The positive charge means hydrophilic and the negative charge means hydrophilic [32].

The physical properties of RHBDF2, ADAM17, and EGF genes were shown in Table 4. RHBDF2 is more hydrophilic than ADAM17 and EGF genes.

4. CONCLUSION

The socioeconomic situation, smoking, alcohol, and irregular diet are responsible for the development of EC. Besides these factors, genetic factors are also responsible for EC. RHBDF2 has a main role in the development of EC. Scope of this study, The protein interaction string was made for the RHBDF2 gene and associated genes with RHBDF2 were detected. ADAM17 and EGF genes

were detected as related genes. It investigated the role of these genes in the development of EC. Homology models, Ramachandran plots, subcellular localization, and physicochemical properties of RHBDF2, ADAM17, and EGF genes were detected and the characterization study was completed *in silico.* As a result of this
study, It is thought that ADAM17 and EGF genes play an active role in the development of esophageal cancer.

Genetic characterization studies are important in terms of determining the causes and formation mechanism of diseases, providing control, and developing treatment approaches. It contributes to the literature by identifying new genes that may be associated with the disease. In the future, these studies will be pioneering in the treatment of diseases by contributing to pharmacogenetic analysis, drug development, and analysis related to drug resistance.

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The Declaration of Research and Publication Ethics
The author of the paper declares that I comply with the scientific, ethical, and quotation rules of SAUJS in all processes of the paper and that I do not make any falsification on the data collected. In addition, I declare that Sakarya University Journal of Science and its editorial board have no responsibility for any ethical violations that may be encountered and that this study has not been evaluated in any academic publication environment other than Sakarya University Journal of Science.

The Declaration of Conflict of Interest/ Common Interest
No conflict f interest or common interest has been declared by the author.

The Declaration of Ethics Committee Approval
This study does not require ethics committee permission or any special permission.

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