DEVELOPMENT OF DATABASE OF BIOMARKER FOR THYROID CANCER AND DISORDERS

BY

ANKUSH BANSAL (091508)

Under the supervision of

Dr. JAYASHREE RAMANA

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WAKNAGHAT

TABLE OF CONTENTS

2.3.2 Follicular

2.3.3 Medullary

2.3.4 Anaplastic

2.4 Diagnosis

2.4.1 Physical Exam

2.4.2 Blood Tests

2.4.3 Ultrasound

2.4.4 Thyroid Scan

2.4.5 Biopsy

2.4.5.1 with a Thin Needle

2.4.5.2 with Surgery

2.5 Staging

2.5.1 Ultrasound

2.5.2 CT Scan

2.5.3 MRI

2.5.4 Chest X-Ray

2.5.5 Whole Body Scan

2.6 Treatment

2.6.1 Endocrinologist

2.6.2 Thyroidologist

2.6.3 Surgeon

2.6.4 Nuclear Medicine Doctor

2.6.5 Medical Oncologist

2.6.6 Radiation Oncologist

2.7 Surgery

2.7.1 Removing the Entire Thyroid

2.7.2 Removing a Lobe

CERTIFICATE

This is to certify that the project titled "**Development of database of biomarkers for thyroid cancer and disorders**" submitted by "**Ankush Bansal"** to Jaypee University of Information Technology, Waknaghat, in partial fulfillment of the requirements for the award of Degree in **Bachelor of Technology (Bioinformatics)** is a record of bonafide work carried out by him. He has worked under my guidance and supervision. The matter embodied in this project has not been submitted in part or in full to any other university or institute for the award of any degree or diploma to the best of my knowledge.

I wish him best of luck for all his future endeavors.

Signature of Supervisor ..... Ramana

Name of Supervisor Dr. Jayashree Ramana

Designation Senior Lecturer,

Department of Biotechnology and Bioinformatics

Jaypee University of Information Technology

Waknaghat, Solan, India

Date 27/05/2013

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Signature of the student Ankush .....

Name of Student Ankush Bansal

Date 27/05/2013

ABSTRACT

Any cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids are considered as biomarkers. Nowadays, biomarkers are used for early detection of cancer. Thyroid carcinoma accounts for about 90% of malignancies of the entire endocrine system. About 56,460 new cases and 1,780 deaths from thyroid cancer were estimated by American Cancer Society in US (2012). According to projection from various studies on thyroid diseases, it has been estimated that 4.2 crore Indians suffer from thyroid cancer and disorders (2011). But, there is no such source available which integrates all the information of biomarkers scattered in literature. So, we have done exhaustive research from published research articles and collected genes, proteins and miRNA which can serve as a novel biomarker for diagnosis of thyroid cancer and disorders. We have linked this data with other public databases and also included the list of miRNA which are involved in other cancers. This list will help in prioritizing and systematic testing of candidate biomarkers. After generating this list of molecules, specific searches were carried out to identify the presence of miRNA in body fluids. We have constructed an integrated database with user friendly interface named as Thyroid Cancer and disorder Gene DataBase (TCGDB). In addition, database provides various browse and search options for user to extract information of his interest. We have also developed a sequence similarity search tool that will enable the exploration of relevant information for all experimentally determined genes and proteins present in the database.

LIST OF FIGURES AND TABLES

FIGURES

Chapter: 2

Chapter: 3

TABLES

Chapter: 3

CHAPTER 1

Introduction

Any cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids are considered as biomarkers. Now-a-days, biomarkers are used for early detection of cancer [1]. Thyroid carcinoma accounts for about 90% of malignancies of the entire endocrine system [2]. About 56,460 new cases and 1,780 deaths from thyroid cancer were estimated by American Cancer Society in US (2012) [3]. According to projection from various studies on thyroid diseases, it has been estimated that 4.2 crore Indians suffer from thyroid cancer and disorders (2011) [4]. But, there is no such source available which integrates all the information of biomarkers scattered in literature. So, we have done exhaustive research from published research articles and collected genes, proteins and miRNA which can serve as novel biomarker for diagnosis of thyroid cancer and disorders [5, 6]. We have linked this data with other public databases and also included the list of miRNA which are involved in other cancers. This list will help in prioritizing and systematic testing of candidate biomarkers [6]. After generating this list of molecules, specific searches were carried out to identify the presence of miRNA in body fluids [6]. We have constructed an integrated database with user friendly interface named as Thyroid Cancer and Disorder Gene DataBase (TCGDB). In addition, database provides various browse and search options for user to extract information of his interest. We have also incorporated the BLAST to enable the user to perform sequence similarity search in the database against his input/query sequences.

The major goals of this project will be separated into five main parts:

1.1 Data Collection

The first part of this project is to collect data for database development. For collection of genes playing key role in causation of thyroid cancer we have extensively searched PubMed database and collected the relevant literature manually. After we obtained the literature using keywords like thyroid cancer, thyroid carcinoma, thyroid hormone disorder, etc. we read through the full text of each article to identify one or more genes involved in disease process. Thereafter, information regarding the type of molecular and genetic events responsible for occurrence of

thyroid cancer as documented in the references was recorded along with the tracking number i.e. PubMed ID (PMID). Also, we have collected information about the location from which sample was collected by their respective authors to conduct the study. This information has been introduced in the reference table. Once a non-redundant list of genes was extracted from the literature further information regarding the gene was derived and has been integrated into other tables.

1.2 Database Development

Overall, TCGDB is divided into four different tables:

1.2.1 Gene Data

Table provides annotated information about genes involved in thyroid cancer. It includes gene symbol, gene id, protein name, protein length, chromosome number, chromosome location, cellular location, 3D method, gene family description, gene family tag, PMID.

1.2.2 miRNA Data

It includes information of miRNA which can be used as a potential biomarker for thyroid cancer and disorders. This table contains miRNA symbol, mechanism, location, chromosome number, other alternate names, gene ID, miRBase ID, sequence, mature 1 accession number, mature 1 ID, mature1 sequence, mature 2 accession number, mature 2 ID, mature 1 sequence, (miRNAs with nearly identical sequences except for one or two nucleotides are annotated with an additional lower case letter. For example, miR-123a would be closely related to miR-123b. Pre-miRNAs that lead to 100% identical mature miRNAs but that are located at different places in the genome are indicated with an additional dash-number suffix. For example, the pre-miRNAs hsa-mir-194-1 and hsa-mir-194-2 lead to an identical mature miRNA (hsa-miR-194) but are located in different regions of the genome. Species of origin is designated with a three-letter prefix, e.g., hsa-miR-123 is a human (*Homo sapiens*) miRNA and oar-miR-123 is a sheep (*Ovis aries*) miRNA) miRTarBase ID, target gene symbol, target gene ID, experiments, PMID.

1.2.3 miRNA Present In Body Fluid

Table contains information about miRNA present in different body fluids like bile, serum, blood platelets, blood cells, urine, semen, lymph, saliva, plasma and pancreatic juice.

1.2.4 miRNA Involved In Other Cancers And Diseases

Table contains information about miRNA which involved in other cancers with type of cancer and disease, mechanism, experiment and PMID. This list will help in prioritizing and systematic testing of candidate biomarkers.

1.3 Web Interface Development

To make the data accessible for user, we developed a user friendly web interface. By using a browser the web server can be accessed by an appropriate web address. The server creates and returns HTML pages which contain the requested information for the user.

1.4 Data Retrieve from Database

After compiling all the information, we imported the data in MYSQL, an object-relational Database Management System (RDBMS), which works at the backend and the web interface was built in PHP. By providing different options to user, we fetch data from database using PHP.

1.5 Linking Data with Other Public Databases

We also linked this data with other public databases using different IDs like HPRD ID, OMIM ID, HGNC ID, CCDS ID, UCDC ID, Uniprot ID, RefSeq ID, Entrez ID, Emsemble ID and PMID. This enables the user to find every information in same database and need not to browse other database separately.

CHAPTER 2

Background

Cancer, known medically as a malignant neoplasm, is a broad group of various diseases, all involving unregulated cell growth. In cancer, cells divide and grow uncontrollably, forming malignant tumors, and invade nearby parts of the body. The cancer may also spread to more distant parts of the body through the lymphatic system or bloodstream. Not all tumors are cancerous. Benign tumors do not grow uncontrollably, do not invade neighboring tissues, and do not spread throughout the body. There are over 200 different known cancers that afflict humans [7].

Determining what causes cancer is complex. Many things are known to increase the risk of cancer, including tobacco use, certain infections, radiation, lack of physical activity, obesity, and environmental pollutants [8]. These can directly damage genes or combine with existing genetic faults within cells to cause the disease [9]. Approximately five to ten percent of cancers are entirely hereditary.

Cancer can be detected in a number of ways, including the presence of certain signs and symptoms, screening tests, or medical imaging. Once a possible cancer is detected it is diagnosed by microscopic examination of a tissue sample. Cancer is usually treated with chemotherapy, radiation therapy and surgery. The chances of surviving the disease vary greatly by the type and location of the cancer and the extent of disease at the start of treatment. While cancer can affect people of all ages, and a few types of cancer are more common in children, the risk of developing cancer generally increases with age. In 2007, cancer caused about 13% of all human deaths worldwide (7.9 million). Rates are rising as more people live to an old age and as mass lifestyle changes occur in the developing world. [10]

2.1 Thyroid Cancer

The thyroid is a gland at the front of your neck beneath your voice box (larynx). A healthy thyroid is a little larger than a quarter. It usually can't be felt through the skin.

The thyroid has two parts (lobes). A thin piece of tissue (the isthmus) connects the two lobes.

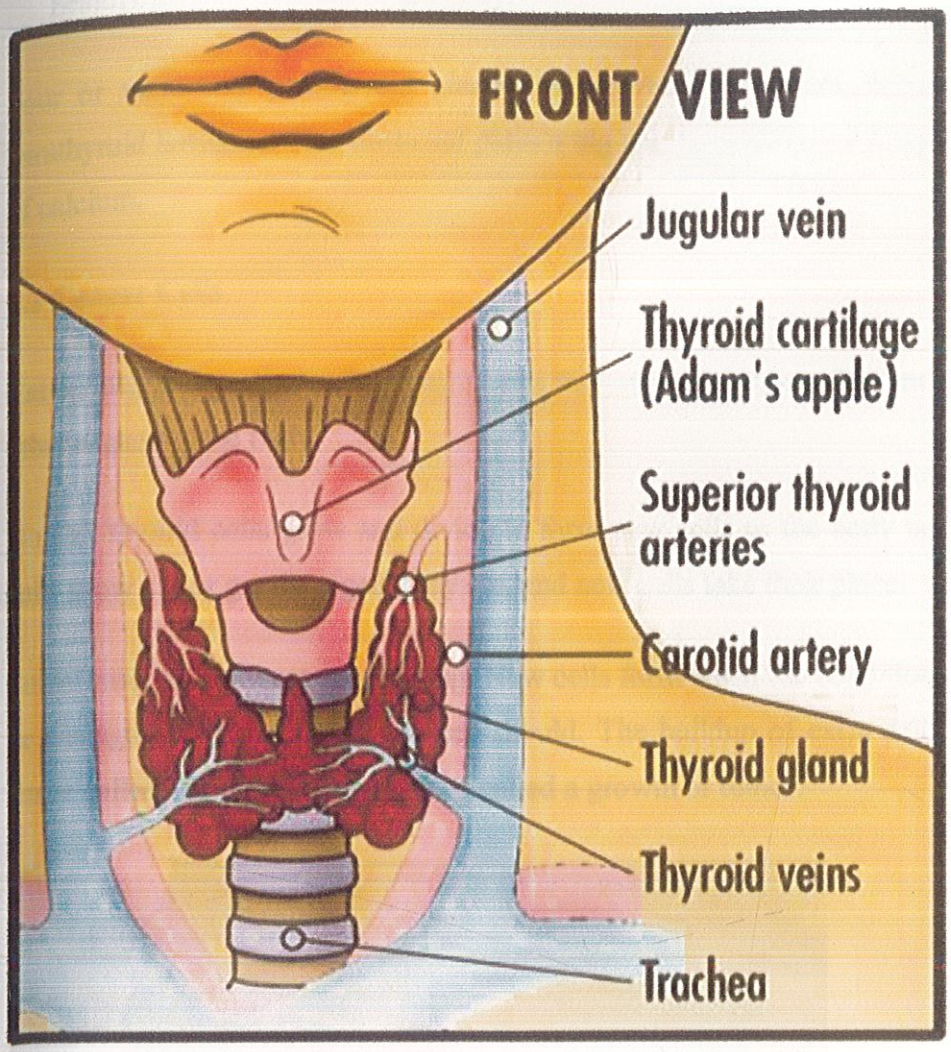


Figure 2.1: Thyroid Gland

The thyroid makes hormones:

2.1.1 Thyroid hormone

The thyroid follicular cells make thyroid hormone. This hormone affects heart rate, blood pressure, body temperature, and weight. For example, too much thyroid hormone makes your heart race, and too little makes you feel very tired.

2.1.2 Calcitonin

The C cells in the thyroid make calcitonin. This hormone plays a small role in keeping a healthy level of calcium in the body.

Four or more tiny parathyroid glands are on the back of the thyroid. These glands make parathyroid hormone. This hormone plays a big role in helping the body maintain a healthy level of calcium.

2.2 Cancer Cells

Cancer begins in cells, the building blocks that make up tissues. Tissues make up the thyroid and other organs of the body.

Normal thyroid cells grow and divide to form new cells as the body needs them. When normal cells grow old or get damaged, they die, and new cells take their place.

Sometimes, this process goes wrong. New cells form when the body does not need them, and old or damaged cells do not die as they should. The buildup of extra cells often forms a mass of tissue called a nodule. It may also be called a growth or tumor.

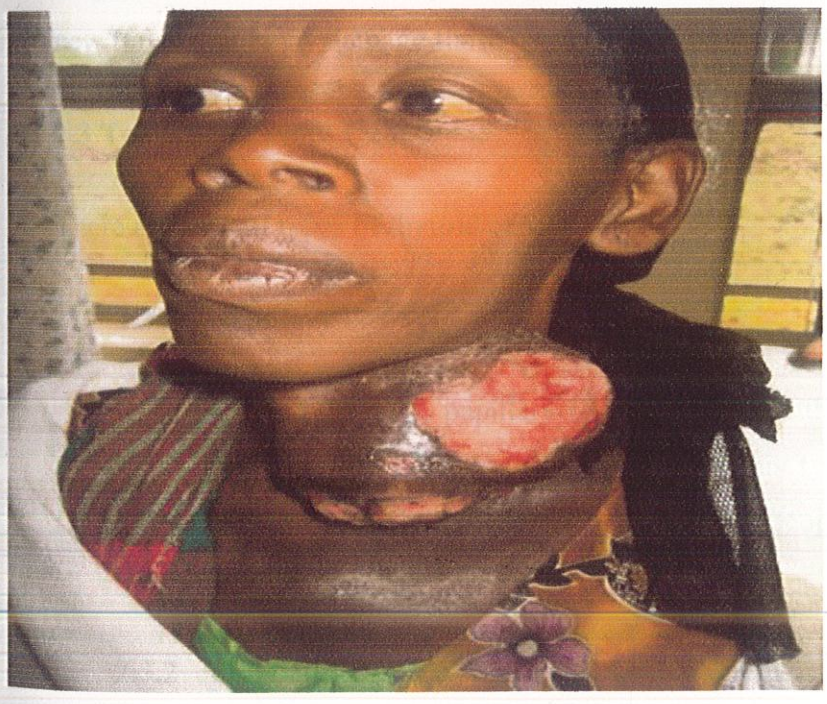


Figure 2.2: Thyroid Cancer

Most thyroid nodules are benign. Benign nodules are not cancer (malignant):

2.2.1 Benign nodules:

- Are usually not harmful
- Don't invade the tissues around them
- Don't spread to other parts of the body
- Usually don't need to be removed

2.2.2 Malignant nodules (thyroid cancer):

- May sometimes be a threat to life
- Can invade nearby tissues and organs
- Can spread to other parts of the body
- Often can be removed or destroyed, but sometimes thyroid cancer returns

Thyroid cancer cells can spread by breaking away from the thyroid tumor. They can travel through lymph vessels to nearby lymph nodes. They can also spread through blood vessels to the lungs, liver, or bones. After spreading, cancer cells may attach to other tissues and grow to form new tumors that may damage those tissues.

2.3 Types of Thyroid Cancer

There are several types of thyroid cancer:

2.3.1 Papillary

In the United States, papillary thyroid cancer is the most common type. About 86 of every 100 people with thyroid cancer have this type. It begins in follicular cells and usually grows slowly. If diagnosed early, most people with papillary thyroid cancer can be cured.

2.3.2 Follicular

The second most common type is follicular thyroid cancer. A little more than 9 of every 100 people with thyroid cancer have this type. It begins in follicular cells and usually grows slowly. If diagnosed early, most people with follicular thyroid cancer can be treated successfully.

2.3.3 Medullary

Medullary thyroid cancer is not common. About 2 of every 100 people with thyroid cancer have this type. It begins in C cells and can make abnormally high levels of calcitonin. Medullary thyroid cancer tends to grow slowly. It can be easier to control if it's found and treated before it spreads to other parts of the body.

Medullary Thyroid Cancer Sometimes Runs in Families

A change in a gene called RET can be passed from parent to child. Nearly everyone with a changed RET gene develops medullary thyroid cancer. The disease occurs alone, as familial medullary thyroid cancer, or with other cancers, as multiple endocrine neoplasia (MEN) syndrome.

A blood test can usually detect a changed RET gene. If it's found in a person with medullary thyroid cancer, the doctor may suggest that family members also be tested. For those who have a changed gene, the doctor may recommend frequent lab tests or surgery to remove the thyroid before cancer develops.

2.3.4 Anaplastic

The least common type is anaplastic thyroid cancer. About 1 of every 100 people with thyroid cancer has this type. Most people with anaplastic thyroid cancer are older than 60. The cancer begins in follicular cells of the thyroid. The cancer cells tend to grow and spread very quickly. Anaplastic thyroid cancer is very hard to control.

2.4 Diagnosis

If your doctor thinks that you may have thyroid cancer, you'll have one or more of the following tests:

2.4.1 Physical exam

Your doctor feels your thyroid for lumps (nodules). Your doctor also checks your neck and nearby lymph nodes for growths or swelling.

2.4.2 Blood tests

Your doctor may check for abnormal levels of thyroid-stimulating hormone (TSH) in the blood. Too much or too little TSH means the thyroid is not working well. If your doctor thinks that you may have medullary thyroid cancer, you'll be checked for a high level of calcitonin and have other blood tests.

2.4.3 Ultrasound

An ultrasound device uses sound waves that can't be heard by humans. The sound waves make a pattern of echoes as they bounce off organs inside your neck. The echoes create a picture of your thyroid and nearby tissues. The picture can show thyroid nodules that are too small to be felt. Your doctor uses the picture to learn the size and shape of each nodule and whether the nodules are solid or filled with fluid. Nodules that are filled with fluid are usually not cancer. Nodules that are solid may be cancer.

2.4.4 Thyroid scan

Your doctor may order a scan of your thyroid. You swallow a small amount of a radioactive substance (such as radioactive iodine), and it travels through the bloodstream. Thyroid cells that absorb the radioactive substance can be seen on a scan. Nodules that take up more of the substance than the thyroid tissue around them are called "hot" nodules. Hot nodules are usually not cancer. Nodules that take up less substance than the thyroid tissue around them are called "cold" nodules. Cold nodules may be cancer.

2.4.5 Biopsy

A biopsy is the only sure way to diagnose thyroid cancer. A pathologist checks a sample of thyroid tissue for cancer cells using a microscope.

Your doctor may take tissue for a biopsy in one of two ways:

2.4.5.1 with a thin needle

Your doctor removes a sample of tissue from a thyroid nodule with a thin needle. An ultrasound device can help your doctor see where to place the needle. Most people have this type of biopsy.

2.4.5.2 with surgery

If a diagnosis can't be made from tissue removed with a needle, a surgeon removes a lobe or the entire thyroid. For example, if the doctor suspects follicular thyroid cancer, the lobe that contains the nodule may be removed for diagnosis.

2.5 Staging

If the biopsy shows that you have cancer, your doctor will need to learn the extent (stage) of the disease to help you choose the best treatment.

The stage is based on the size of the nodule and whether the cancer has invaded nearby tissues or spread to other parts of the body. Thyroid cancer spreads most often to nearby tissues in the neck or to lymph nodes. It may also spread to the lungs and bones.

When cancer spreads from its original place to another part of the body, the new tumor has the same kind of cancer cells and the same name as the original tumor. For example, if thyroid cancer spreads to the lungs, the cancer cells in the lungs are actually thyroid cancer cells. The disease is metastatic thyroid cancer, not lung cancer. It's treated as thyroid cancer, not as lung cancer. Doctors sometimes call the new tumor in the lung "distant" disease.

Staging may involve one or more of these tests:

2.5.1 Ultrasound

An ultrasound exam of your neck may show whether cancer has spread to lymph nodes or other tissues near your thyroid.

2.5.2 CT scan

An x-ray machine linked to a computer takes a series of detailed pictures of your neck and chest area. A CT scan may show whether cancer has spread to lymph nodes, other areas in your neck, or your chest.

2.5.3 MRI

MRI uses a powerful magnet linked to a computer. It makes detailed pictures of your neck and chest area. MRI may show whether cancer has spread to lymph nodes or other areas.

2.5.4 Chest x-ray

An x-ray of the chest can often show whether cancer has spread to the lungs.

2.5.5 Whole body scan

You may have a whole body scan to see if cancer has spread from the thyroid to other parts of the body. You get a small amount of a radioactive substance (such as radioactive iodine). The substance travels through the bloodstream. Thyroid cancer cells in other organs or the bones take up the substance. Thyroid cancer that has spread may show up on a whole body scan.

2.6 Treatment

Treatment options for people with thyroid cancer are:

- Surgery
- Thyroid hormone treatment
- Radioactive iodine therapy
- External radiation therapy
- Chemotherapy

You'll probably receive more than one type of treatment. For example, the usual treatment for papillary thyroid cancer is surgery, thyroid hormone treatment, and radioactive iodine therapy. External radiation therapy and chemotherapy are not often used for people with papillary thyroid cancer.

The treatment that's right for you depends mainly on the type of thyroid cancer (papillary, follicular, medullary, or anaplastic). It also depends on the size of the nodule, your age, and whether the cancer has spread. You and your doctor can work together to develop a treatment plan that meets your needs.

Your doctor may refer you to a specialist who has experience treating thyroid cancer, or you may ask for a referral. You may have a team of specialists:

2.6.1 Endocrinologist

An endocrinologist is a doctor who specializes in treating people who have hormone disorders.

2.6.2 Thyroidologist

A thyroidologist is an endocrinologist who specializes in treating diseases of the thyroid.

2.6.3 Surgeon

This type of doctor can perform surgery.

2.6.4 Nuclear medicine doctor

A nuclear medicine doctor specializes in using radioactive substances to diagnose and treat cancer and other diseases.

2.6.5 Medical oncologist

A medical oncologist is a doctor who specializes in treating cancer with drugs.

2.6.6 Radiation oncologist

A radiation oncologist is a doctor who specializes in treating cancer with radiation therapy.

At any stage of the disease, supportive care is available to control pain and other symptoms, to relieve the side effects of treatment, and to ease emotional concerns.

2.7 Surgery

Most people with thyroid cancer have surgery. The surgeon removes all or part of the thyroid.

You and your surgeon can talk about the types of surgery and which may be right for you:

2.7.1 Removing the Entire Thyroid

This surgery can be used for all types of thyroid cancer. The surgeon removes the thyroid through an incision in the neck. If some of the thyroid tissue can't be removed, it can be destroyed later by radioactive iodine therapy. See the Radioactive Iodine Therapy section.

The surgeon may also remove nearby lymph nodes. If cancer has invaded tissue within the neck, the surgeon may remove as much of that tissue as possible. If cancer has spread outside the neck, treatment of those areas may involve surgery, radioactive iodine therapy, and external radiation therapy.

2.7.2 Removing a Lobe

Some people with follicular or papillary thyroid cancer may have a small tumor removed from only part of the thyroid. The surgeon will remove one lobe and the isthmus. See The Thyroid for a picture of the thyroid lobes and isthmus.

Some people who have a lobe removed have a second surgery later on to remove the rest of the thyroid. Less often, the remaining thyroid tissue is destroyed by radioactive iodine therapy.

It's common to feel tired or weak for a while after surgery for thyroid cancer. The time it takes to heal is different for each person.

You may have pain or discomfort for the first few days. Medicine can help control your pain. Before surgery, you should discuss the plan for pain relief with your health care team. After surgery, they can adjust the plan if you need more pain control.

Surgery for thyroid cancer removes the cells that make thyroid hormone. After surgery, most people need to take pills to replace the natural thyroid hormone. You'll probably need to take thyroid hormone pills for the rest of your life. See the Thyroid Hormone Treatment section.

If the surgeon removes the parathyroid glands, you may need to take calcium and vitamin D pills for the rest of your life.

2.8 Thyroid Hormone Treatment

After surgery to remove part or the entire thyroid, most people need to take pills to replace the natural thyroid hormone. However, thyroid hormone pills are also used as part of the treatment for papillary or follicular thyroid cancer. Thyroid hormone slows the growth of thyroid cancer cells left in the body after surgery.

Although thyroid hormone pills seldom cause side effects, too much thyroid hormone may cause you to lose weight and to feel hot and sweaty. Too much thyroid hormone may also cause a fast heart rate, chest pain, cramps, and diarrhea. Too little thyroid hormone may cause you to gain weight, feel cold and tired, and have dry skin and hair. If you have side effects, tell your doctor. Your doctor can give you a blood test to make sure you're getting the right dose of thyroid hormone.

2.9 Radioactive Iodine Therapy

Radioactive iodine therapy with I-131 is a treatment for papillary or follicular thyroid cancer. It kills thyroid cancer cells and normal thyroid cells that remain in the body after surgery.

People with medullary or anaplastic thyroid cancer usually do not receive I-131 therapy. These types of thyroid cancer rarely respond to I-131 therapy.

For one or two weeks before treatment, you will need to be on a special diet. Avoid fish (especially shellfish), seaweed, iodized salt, milk, yogurt, ice cream, bacon, ham, and other foods with iodine. Do not take vitamin pills or drugs that have iodine.

Because some imaging tests (such as CT scans) use iodine in the contrast material, tell your doctor if you had a CT scan or other imaging test in the past 6 months.

For the treatment, you will swallow one or more capsules or a liquid that contains I-131. Even people who are allergic to iodine can take I-131 therapy safely. I-131 goes into the bloodstream and travels to thyroid cancer cells throughout the body. When thyroid cancer cells take in enough I-131, they die.

Many people get I-131 therapy in a clinic or in the outpatient area of a hospital and can go home afterward. Other people have to stay in the hospital for one day or longer.

Most radiation from I-131 is gone in about one week. Within three weeks, only traces of radiation remain in the body.

During treatment, you can help protect your bladder and other healthy tissues by drinking a lot of fluids. Drinking fluids helps I-131 pass out of the body faster.

Some people have mild nausea the first day of I-131 therapy. A few people have swelling and pain in the neck where thyroid cells remain. If thyroid cancer cells have spread outside the neck, those areas may be painful too.

You may have a dry mouth or lose your sense of taste or smell for a short time after I-131 therapy. Gum or hard candy may help.

A rare side effect in men who receive a high dose of I-131 is loss of fertility. In women, I-131 may not cause loss of fertility, but some doctors advise women to avoid getting pregnant for one year after a high dose of I-131.

Researchers have reported that a very small number of patients may develop a second cancer years after treatment with a high dose of I-131. See the Follow-up Care section for information about checkups after treatment.

Because a high dose of I-131 also kills normal thyroid cells, you'll need to take thyroid hormone pills after this treatment to replace the natural hormone.

2.10 External Radiation Therapy

External radiation therapy is a treatment for any type of thyroid cancer that can't be treated with surgery or I-131 therapy. It's also sometimes used for cancer that returns after treatment or to relieve bone pain from cancer that has spread.

External radiation therapy uses high-energy rays to kill cancer cells. A large machine directs radiation at the neck or other tissues where cancer has spread.

The treatment usually is given in a hospital or clinic. You may receive external radiation therapy 5 days a week for several weeks. Each treatment takes only a few minutes.

Although radiation therapy is painless, it may cause side effects. The side effects depend mainly on how much radiation is given and which part of your body is treated. Radiation to the neck may cause a sore throat and trouble swallowing. Also, the skin on your neck may become red, dry, and tender.

You are likely to become tired during radiation therapy, especially in the later weeks of treatment. Resting is important, but doctors usually advise patients to try to stay as active as they can.

Although the side effects of radiation therapy can be upsetting, they can usually be treated or controlled. Talk with your doctor or nurse about ways to relieve discomfort. Most side effects go away when treatment ends.

2.11 Chemotherapy

Chemotherapy is a treatment for medullary and anaplastic thyroid cancer. It's sometimes used to relieve symptoms of other thyroid cancers.

Chemotherapy uses drugs to kill cancer cells. Most drugs for thyroid cancer are given directly into a vein (intravenously) through a thin needle, but a new drug for medullary thyroid cancer can be taken by mouth.

You may receive chemotherapy in a clinic, at the doctor's office, or at home. Some people need to stay in the hospital during treatment.

The side effects depend mainly on which drugs are given and how much. For drugs given directly into a vein, the most common side effects include mouth sores, nausea, vomiting, loss of appetite, and hair loss. For the drug given by mouth, side effects include diarrhea, high blood pressure, coughing, and a rash.

Your health care team can suggest ways to control many of these problems. Most go away when treatment ends.

Thyroid cancer may come back after treatment. Your doctor will check for the return of cancer.

Checkups may include blood tests and imaging tests, such as neck ultrasound. The tests depend on what type of thyroid cancer you have:

2.11.1 Papillary or Follicular

After treatment for papillary or follicular thyroid cancer, people have an ultrasound exam of the neck, a whole body scan, or blood tests to check the levels of TSH and thyroglobulin. If the whole thyroid was removed, very little or no thyroglobulin should be

in the blood. A high level of thyroglobulin may mean that thyroid cancer has returned. Before a thyroglobulin test or whole body scan, you'll need to get a shot of TSH or stop taking your thyroid hormone pill for about six weeks.

2.11.2 Medullary

After treatment for medullary thyroid cancer, people have blood tests to check the level of calcitonin and other substances. Checkups may also include an ultrasound exam of the neck, a CT scan, an MRI, or another imaging test.

2.11.3 Anaplastic

After treatment for anaplastic thyroid cancer, people may have imaging tests, such as a chest x-ray or CT scan.

2.12 Biomarker

Biological markers (biomarkers) have been defined by Hulka and colleagues [6] as "cellular, biochemical or molecular alterations that are measurable in biological media such as human tissues, cells, or fluids." More recently, the definition has been broadened to include biological characteristics that can be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention [7]. In practice, biomarkers include tools and technologies that can aid in understanding the prediction, cause, diagnosis, progression, regression, or outcome of treatment of disease. For the nervous system there is a wide range of techniques used to gain information about the brain in both the healthy and diseased state. These may involve measurements directly on biological media (e.g., blood or cerebrospinal fluid) or measurements such as brain imaging which do not involve direct sampling of biological media but measure changes in the composition or function of the nervous system.

Biomarkers provide a dynamic and powerful approach to understanding the spectrum of neurological disease with applications in observational and analytic epidemiology, randomized clinical trials, screening and diagnosis and prognosis. Defined as alterations in the constituents of

tissues or body fluids, these markers offer the means for homogeneous classification of a disease and risk factors, and the can extend our base information about the underlying pathogenesis of disease. Biomarkers can also reflect the entire spectrum of disease from the earliest manifestations to the terminal stages. This brief review describes the major uses of biomarkers in clinical investigation. Careful assessment of the validity of biomarkers is required with respect to the stage of disease. Causes of variability in the measurement of biomarkers range from the individual to the laboratory. Issues that affect the analysis of biomarkers are discussed along with recommendations on how to deal with bias and confounding.

There are number of databases like Renal Cancer Gene Database (RCDB), Cervical Cancer Database (CCDB), Human Lung Cancer Database (HLungDB) but there is no database which provides information of genes or miRNA involved in thyroid cancer and disorders. Therefore, We developed TCGDB.

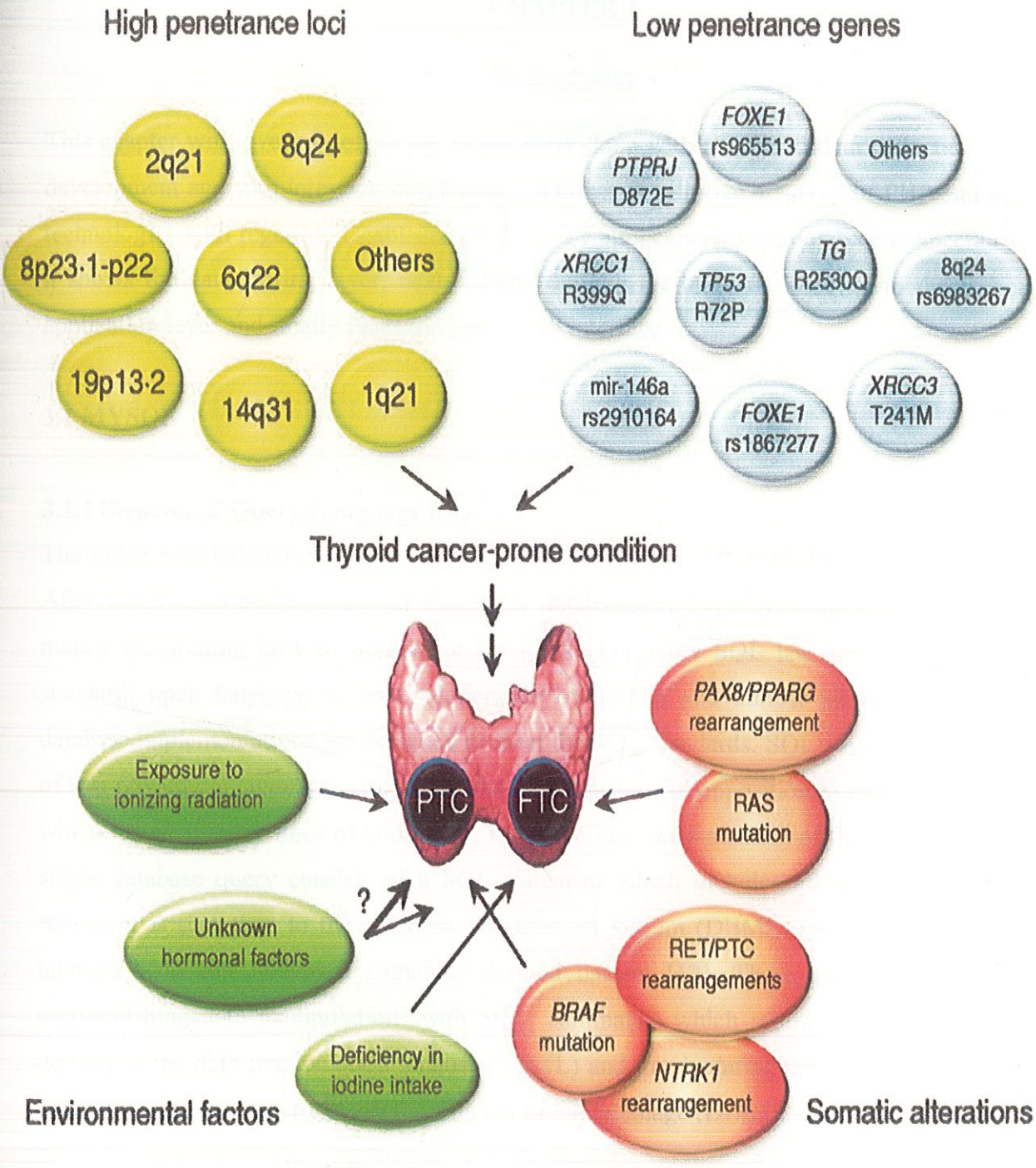


Figure 2.3: Factors Responsible for Thyroid Cancer

CHAPTER 3

Methodology

This chapter will give a brief survey of the work done with respect to data collection, database development and web interface development. Further it will give a survey of PHP and MYSQL technologies with regard to establishing server side applications with database connections. First it shows the data storing layer, next it leads through the business logic up to the web server application layer and finally faces the user's web interface.

3.1 MYSQL

3.1.1 Structured Query Language (SQL)

The father of relational databases, and thus SQL, is Dr. E.F. 'Ted' Codd who worked for IBM. After Codd described a relational model for databases in 1970, IBM spent a lot of time and money researching how to implement his ideas [11]. Now SQL has already evolved into a standard, open language without cooperative ownership and almost all nowadays available database implementations are designed to meet the SQL standards. SQL pertains to the category of non procedural languages called declarative languages. In opposition to procedural languages which result in many lines of code, SQL results in just one statement of the desired demand. A single database query consists of a SQL statement which includes all desired requests. This statement is sent then to the database management system (DBMS) which executes a hidden internal code and returns a somehow defined dataset [12]. There are two possibilities in accomplishing data manipulations with SQL: commands which return demanded datasets are defined in the data manipulation language (DML) and manipulating commands which alter the database's internal structures use the data definition language (DDL).

3.1.1.1 Data Definition Language (DDL)

The DDL is a sub section of SQL allowing the creation and deletion of tables in the database as well as the definition of indexes (keys) and links between tables. It is also possible to enable

constraints among different tables, defined by foreign keys [13]. Some of the most important DDL commands are listed below:

- **CREATE TABLE** - creates a new database table
- **ALTER TABLE** - alters (changes) a database table
- **DROP TABLE** - deletes a database table
- **CREATE INDEX** - creates an index (search key)
- **DROP INDEX** - deletes an index

3.1.1.2 Data Manipulation Language (DML)

The DML defines the second part of SQL commands. It includes the syntax for complex queries as well as for updates, insertions and deletions of data records [14]. The four basic manipulation commands are outlined below:

- **SELECT** - extracts data from a database table
- **UPDATE** - updates data in a database table
- **DELETE** - deletes data from a database table
- **INSERT INTO** - inserts new data into a database table

The basic body of almost all query statements is given in the following example:

- The **SELECT** statement creates a record set from existing tables according to the parameters that follow the statement.

- The **FROM** command apprises the database engine to return all the fields in the selected tables. The fields specified in the SQL statement become the columns in the new record set.

- The **WHERE** condition restricts the rows returned to only rows containing the data specified in the SQL statement.

- The **ORDER BY** command notifies the database engine to sort the records before returning them.

  Example: SELECT address FROM patients WHERE (name = '...')

3.2 PHP

PHP is a server-side scripting language designed for web development but also used as a general-purpose programming language. PHP is now installed on more than 244 million websites and 2.1 million web servers.[15]

3.3 Approach for Data Collection

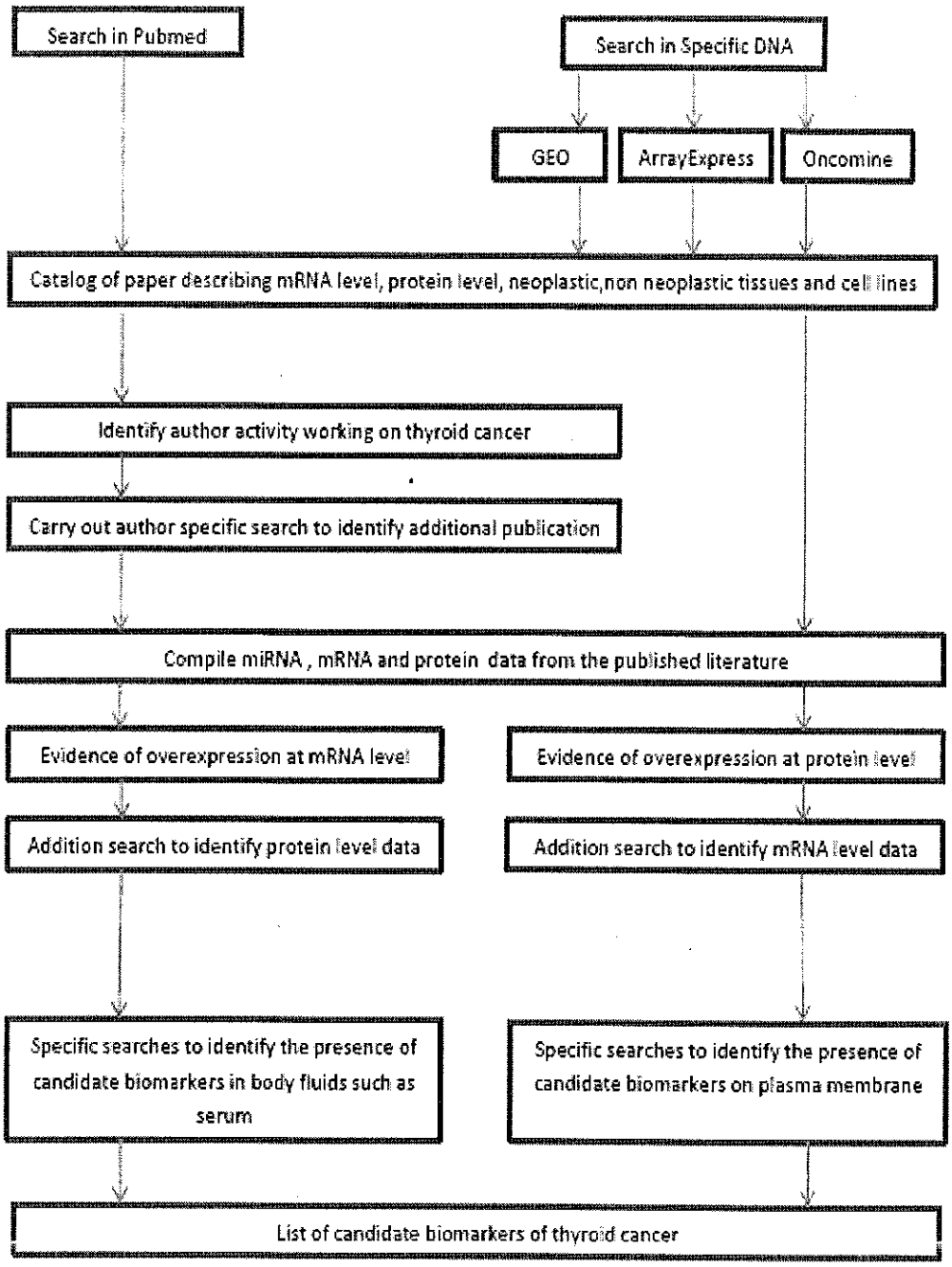


Figure 3.1: Approach for Data Collection

3.4 Data Model

Table 1: Table describes all the information of annotated genes which are thought to be involved in Thyroid cancer and disorders.

S. No	Gene Data
1	Gene Symbol
2	Gene ID (by using gene id user can access all possible information of gene involved in thyroid cancer)
3	Accession Number
4	Thyroid Cancer or Disorder Type (column contains information whether cancer is PTC, MTC, FTC, ATC or any other disorder)
5	Protein Name
6	Length of Protein (in amino acid)
7	Chromosome Number
8	Chromosomal Location (exact location of gene on chromosome)
9	3D Experimental Method (methods like X-ray crystallography, NMR spectroscopy)
10	Cellular Location (whether gene present in nucleus or mitochondrial DNA)
11	Comments (any other information which need to be mentioned)
12	Nucleotide (this column provide sequence and other information of nucleotide)
13	Protein (this column provide sequence and other information of nucleotide)
14	Description (any other description of protein which is not mentioned in other columns and seems important w.r.t. particular type of cancer)
15	Gene Family Description

16	Gene Family Tag
17	HPRD ID (column links gene with human protein reference database)
18	OMIM ID (OMIM id links gene involved in cancer to OMIM database of NCBI)
19	UNIPROT ID (to explore more information about protein)
20	HGNC ID (links gene to HUGO Nomenclature Committee database)
21	ENTREZ ID (links gene to Entrez database of NCBI)
22	ENSEMLE ID
23	REFSEQ ID (for nucleotide sequence information)
24	CCDS ID (The CCDS database identifies a core set of human protein coding regions that are consistently annotated by multiple public resources and pass quality tests.)
25	UCDC ID
26	PMID (research paper for reference, so that user can understand why we included gene in database)

Table 2: Table describes all the information of annotated miRNA which are thought to be involved in Thyroid cancer and disorders.

S. No	miRNA Data
1	miRNA
2	Mechanism (upregulation or downregulation)
3	Location (exact location on chromosome)
4	Chromosome Number
5	Other Names
6	Gene ID (provides all the information related to gene)
7	miRBase Accession Number (links with miRBase Database)
8	Sequence of miRNA
9	Mature 1 Accession Number*
10	Mature 1 ID*
11	Mature 1 Sequence*
12	Mature 2 Accession Number*
13	Mature 2 ID*
14	Mature 2 Sequence*
15	miRTarBase ID (link with miRTarBase Database)
16	Target Gene Symbol
17	Target Gene ID (to access more information of target gene)
18	Experiments (like microarray, immunohistochemistry, etc)
19	PMID (to provide reference of research paper from where miRNA is included in database)

*miRNAs with nearly identical sequences except for one or two nucleotides are annotated with an additional lower case letter. For example, miR-123a would be closely related to miR-123b. Pre-miRNAs that lead to 100% identical mature miRNAs but that are located at different places

in the genome are indicated with an additional dash-number suffix. For example, the pre-miRNAs hsa-mir-194-1 and hsa-mir-194-2 lead to an identical mature miRNA (hsa-miR-194) but are located in different regions of the genome. Species of origin is designated with a three-letter prefix, e.g., hsa-miR-123 is a human (*Homo sapiens*).

Table 3: Table describes the miRNA information which are present in body fluid.

S.No	**Fluid Data**
1	miRNA
2	Body Fluid (saliva, urine, blood, plasma, bile, lymph, serum)
3	Chromosome (chromosome number where miRNA is located)
4	Pubmed ID (reference of research paper from where data is extracted)

Table 4: Tables describes the information of miRNA which are also present in other cancers.

S.No	Other Cancer and Diseases
1	miRNA
2	Other Cancer or Disorder Type
3	Mechanism (upregulated or downregulated)
4	Experiments (microarray, immunohistochemistry, etc)
5	Pubmed ID (research paper for reference from where data is extracted)

Table 5: Table describes the information of diseases and different cancer types which share common miRNA with thyroid cancer and disorders.

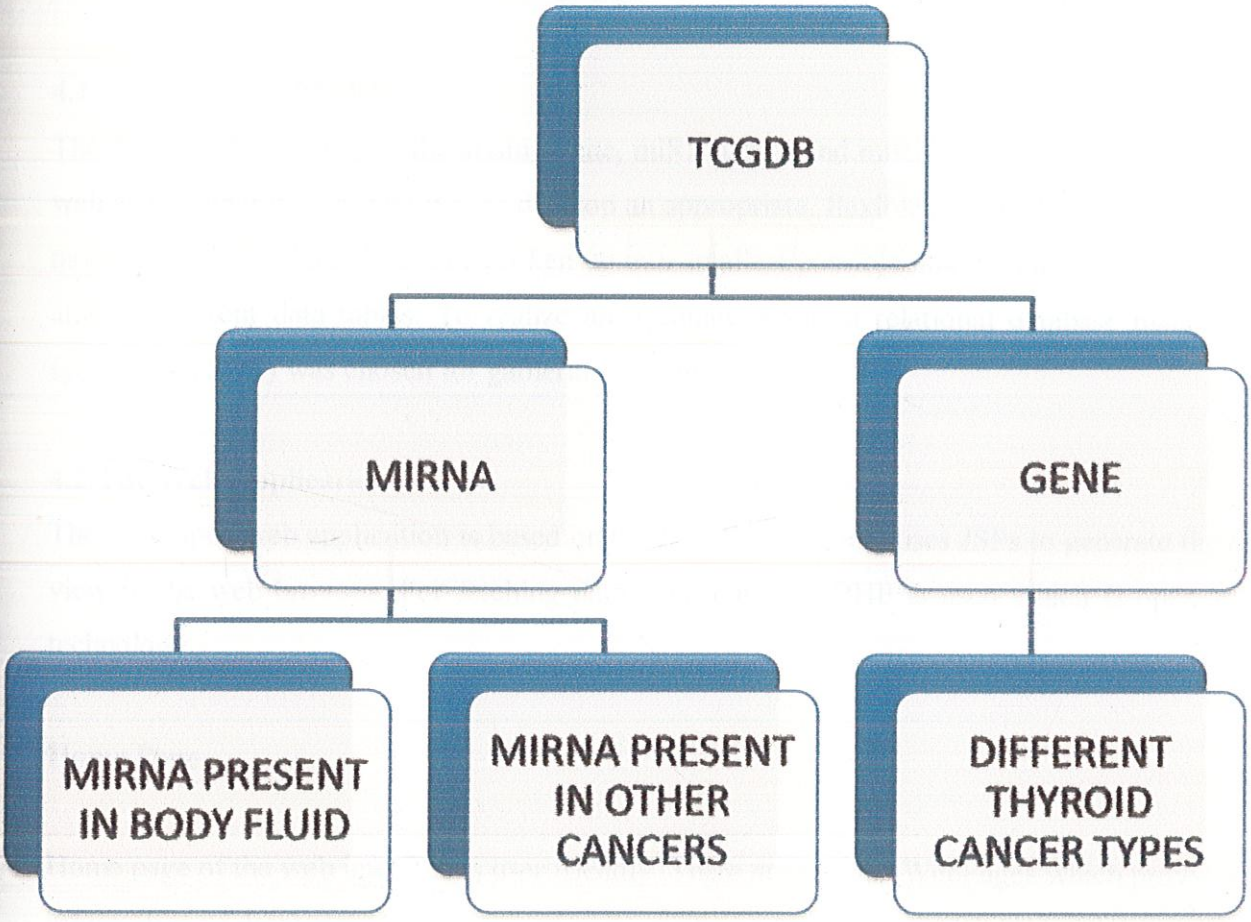
S.No	Name of Other Cancer and diseases
1	Non-Alcoholic Fatty Liver Disease (NAFLD)
2	Acute Promyelocytic Leukemia (APL)
3	Lung Cancer
4	Ovarian Cancer (OC)
5	Breast Cancer
6	Epithelial Ovarian Cancer (EOC)
7	Hepatocellular Carcinoma (HCC)
8	Malignant Melanoma
9	Oral Squamous Cell Carcinoma (OSCC)
10	Pancreatic Cancer
11	Prostate Cancer
12	Cardiac Hypertrophy
13	Kidney Cancer

14	Non-Small Cell Lung Cancer (NSCLC)
15	Colorectal Cancer
16	Head And Neck Squamous Cell Carcinoma (HNSCC)
17	Myocardial Infarction
18	Nasopharyngeal Carcinoma (NPC)
19	Bladder Cancer
20	Diffuse Large B-Cell Lymphoma (DLBCL)
21	Psoriasis
22	Uterine Leiomyoma (ULM)
23	B-Cell Chronic Lymphocytic Leukemia
24	Chronic Pancreatitis
25	Glioblastoma
26	Serous Ovarian Cancer
27	Cardiomyopathy
28	Gastric Cancer (Stomach Cancer)
29	HCV Infection
30	Metabolic Disease
31	Acute Lymphoblastic Leukemia (ALL)
32	Acute Myeloid Leukemia (AML)
33	Neuroblastoma (NB)
34	Vascular Disease
35	Type 2 Diabetes
36	Multiple Myeloma (MM)
37	Alzheimer's Disease
38	Cerebellar Neurodegeneration
39	Heart Failure
40	Asthma
41	Intrahepatic Cholangiocarcinoma (ICC)
42	Limb-Girdle Muscular Dystrophies Types 2A (LGMD2A)
43	Miyoshi Myopathy (MM)

44	Nemaline Myopathy (NM)
45	Polymyositis (PM)
46	Glioma
47	Pancreatic Ductal Adenocarcinoma (PDAC)
48	Tongue Squamous Cell Carcinoma
49	Glioblastoma Multiforme (GBM)
50	Primary Biliary Cirrhosis (PBC)
51	Retinitis Pigmentosa (RP)
52	Parkinson's Disease
53	Testicular Germ Cell Tumor
54	Multiple Sclerosis
55	Autism Spectrum Disorder (ASD)
56	Primary Myelofibrosis
57	Becker Muscular Dystrophy (BMD)
58	Dermatomyositis (DM)
59	Duchenne Muscular Dystrophy (DMD)
60	Hodgkin's Lymphoma
61	Chronic Lymphocytic Leukemia (CLL)
62	Mantle Cell Lymphoma (MCL)
63	Pituitary Adenoma
64	Polycystic Kidney Disease
65	MYC-Rearranged Lymphoma
66	Malignant Lymphoma
67	Oral Carcinoma
68	Cowden Syndrome
69	T-Cell Leukemia
70	Cholangiocarcinoma
71	Esophageal Cancer
72	Insulinoma
73	Rhabdomyosarcoma

74	Cervical Cancer
75	Cholesteatoma
76	Acute Myelogeneous Leukemia (AML)
77	Schizophrenia
78	Medulloblastoma
79	Recurrent Ovarian Cancer

This data was compiled published research articles and imported in MYSQL. PHP was used to connect the database and dynamically generate user-friendly HTML front-end queries, using IIS web server.



CHAPTER 4

Result

This chapter will present the developed data model for the Thyroid Cancer and Disorder Gene database (TCGDB) for storing the gene and miRNA data, which was obtained from different published articles in Pubmed using keyword search. Further the functionality of the developed web application will be shown by giving some maintaining and querying examples.

4.1 The Database Model

The first part for storing all the arising gene, miRNA data and miRNA present in other cancer as well as the other cancer data was to develop an appropriate, flexible and easily maintainable data model. The data tables should be broken up into smallest possible units to ensure best flexibility among different data tables. To realize an adequate model a relational database management system (MYSQL) was chosen for gathering the data.

4.2 The Web Application

The developed web application is based on the HTML, CSS, and uses JSPs to generate the users view in the web browser. For fetching data from database PHP is used which is open source technology.

Home Page

Home page of the web interface is user friendly .There are various WebPages which provides information of database:

- **Browse**

  Browse gene and miRNA in different categories.

- **Search**

Search gene and miRNA data using particular gene ID, gene symbol, miRNA symbol, accession number.

- **Other Databases**

  This page provides link of other databases containing information of genes and miRNA involved in different types of cancer. These links will help user to explore data on the basis of specific type of cancer.
- **Blast**

  For sequence similarity search with data present in database.
- **Contact**

  Contact page is designed to send any query and contact to admin.

Home page also provides options for:

- **Database Search**

  User can perform database search by clicking "Database Search" Button.

- **Frequently Asked Questions**

  FAQ page is designed to answer general questions about TCGDB.

- **Statistics**

  To show how many genes and miRNA involved in what type of cancer.

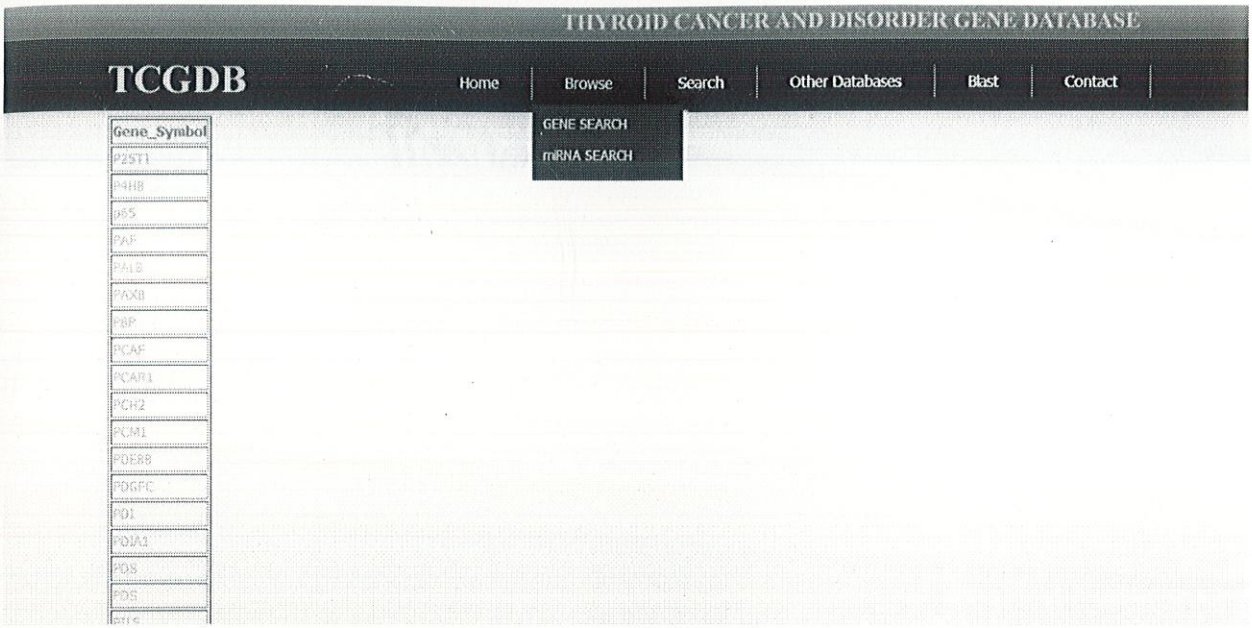
- **Submit Data**

  If user has any doubt about data or he want to include any information about data present in database, he can use this option.

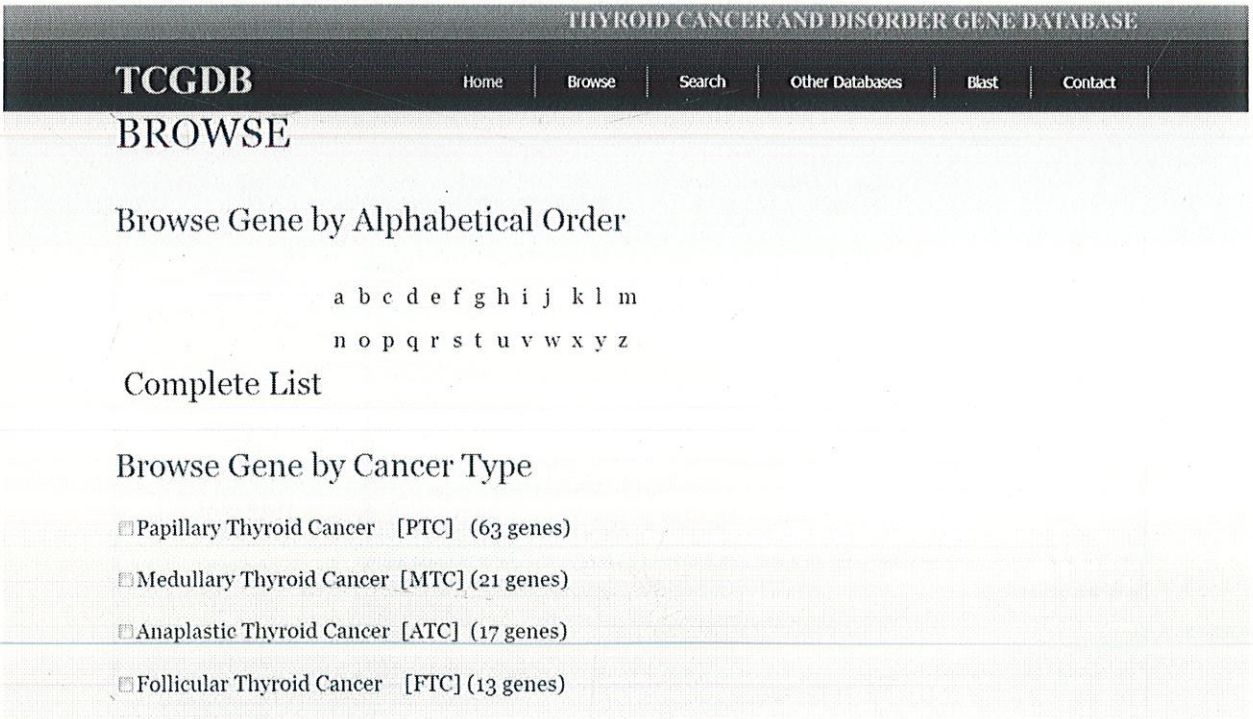
- **Help**

  Help page is designed to provide support for user to understand about database structure and use.

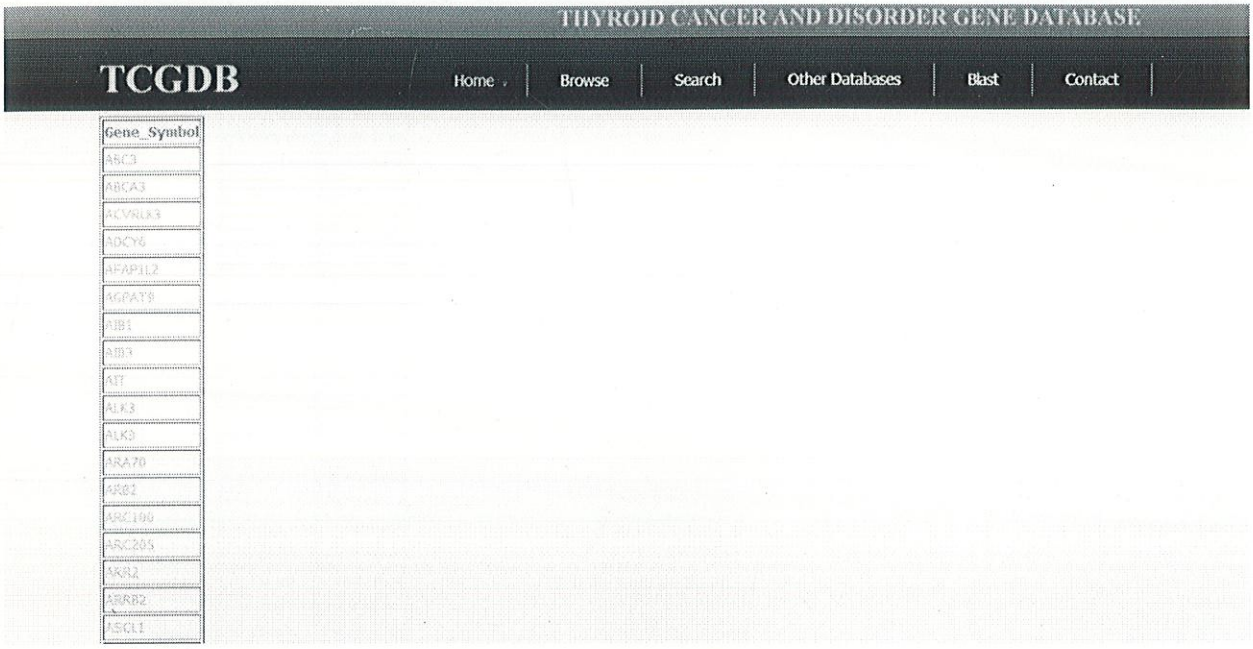
- User can come to "Gene Search" and "miRNA Search" by using dropdown menu from "Browse".



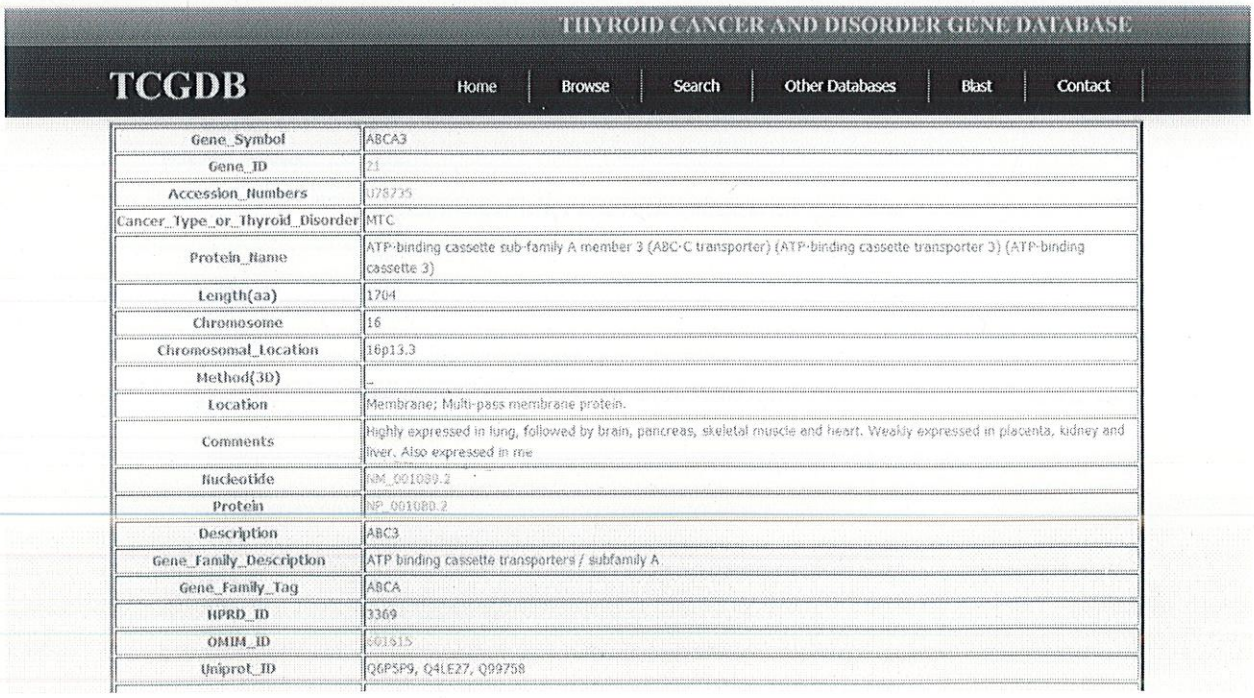
- Gene data can be browsed using given categories.



- If user wants to search alphabetically, user can click on any alphabet and find genes. Example given below: A

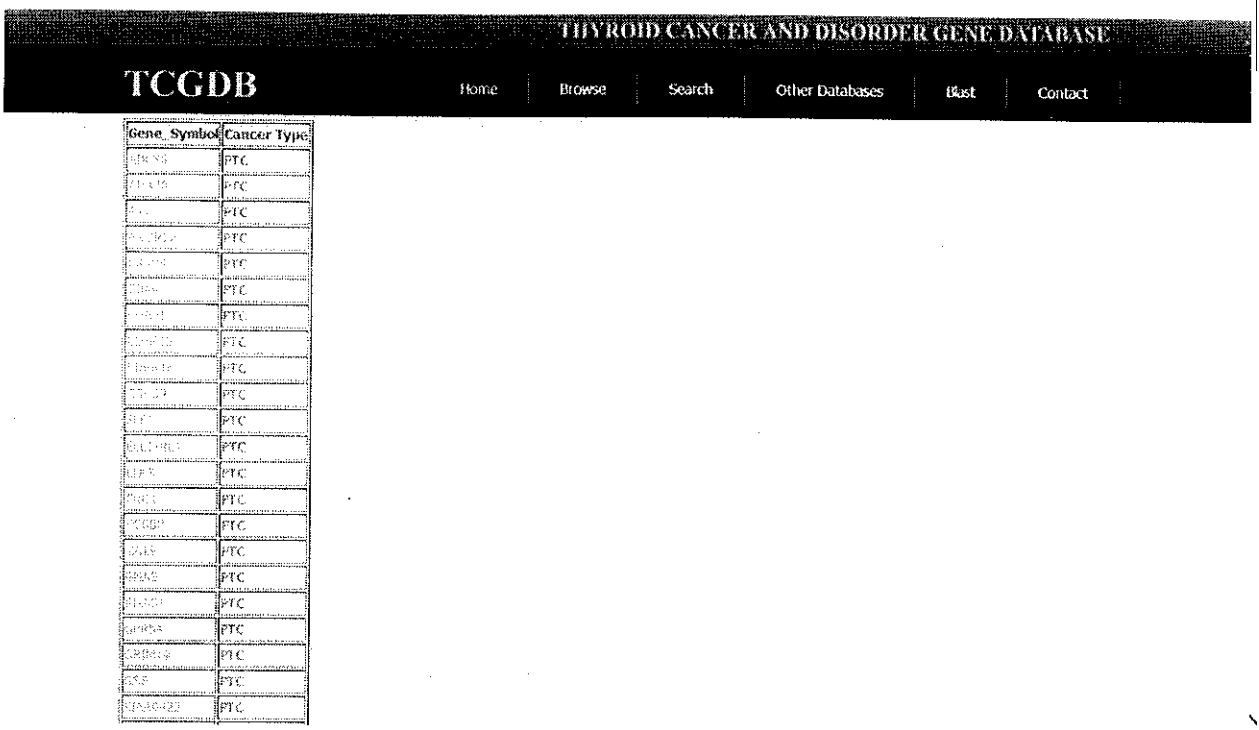


- By clicking on genes, user can find all information of gene and find further information with other databases by clicking on links.



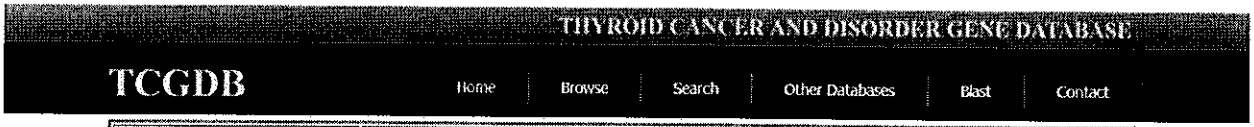
Gene_Symbol	ABCA3
Gene_ID	21
Accession_Numbers	U78735
Cancer_Type_or_Thyroid_Disorder	MTC
Protein_Name	ATP-binding cassette sub-family A member 3 (ABC-C transporter) (ATP-binding cassette transporter 3) (ATP-binding cassette 3)
Length(aa)	1704
Chromosome	16
Chromosomal_Location	16p13.3
Method(3D)	-
Location	Membrane; Multi-pass membrane protein.
Comments	Highly expressed in lung, followed by brain, pancreas, skeletal muscle and heart. Weakly expressed in placenta, kidney and liver. Also expressed in me
Nucleotide	NM_001089.2
Protein	NP_001080.2
Description	ABC3
Gene_Family_Description	ATP binding cassette transporters / subfamily A
Gene_Family_Tag	ABCA
HPRD_ID	3369
OMIM_ID	601615
Uniprot_ID	Q6PSP9, Q4LE27, Q99758

- User can find information of particular type of thyroid cancer like Papillary Thyroid Cancer



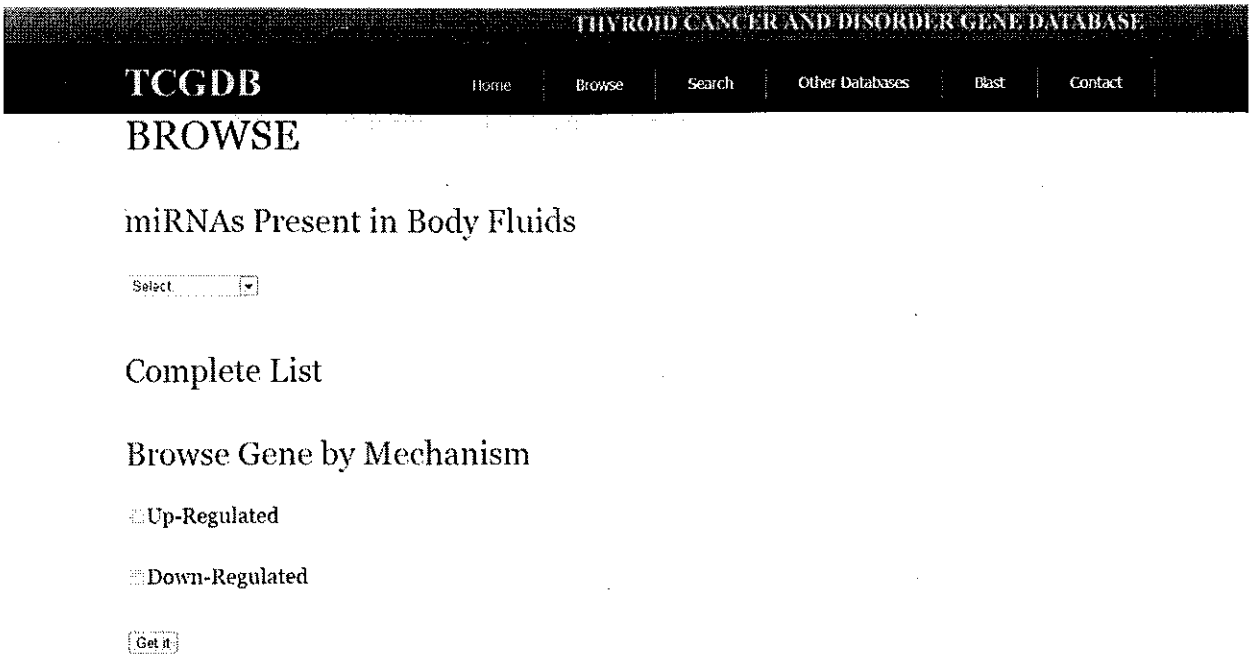
Gene_Symbol	Cancer Type
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC
[illegible]	PTC

- Clicking on genes, fetch all information of gene.

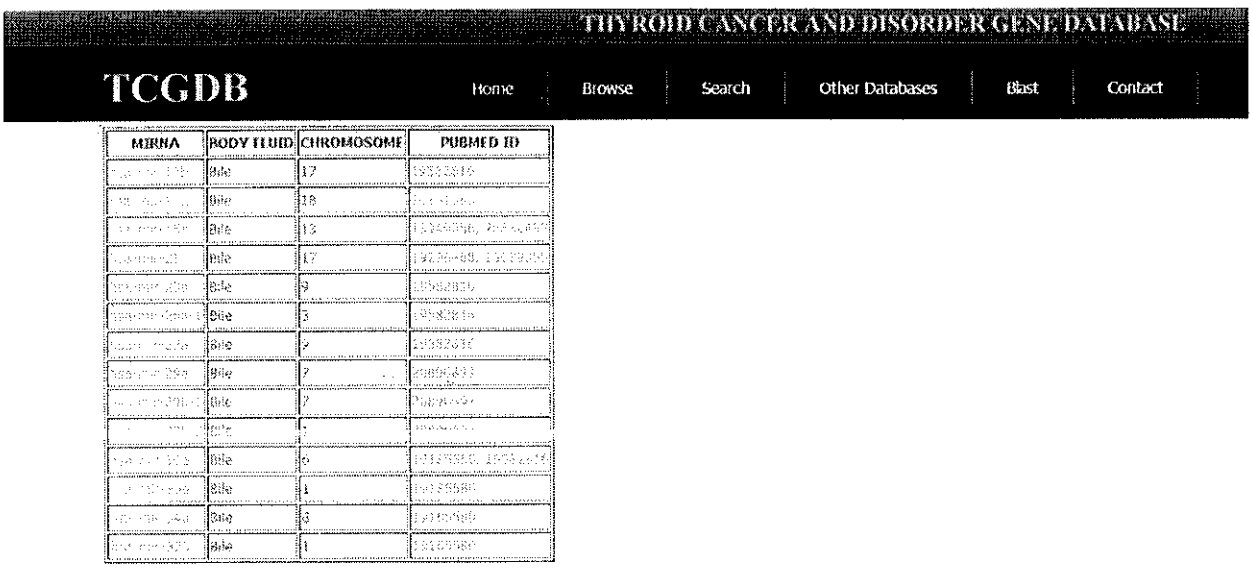


Gene_Symbol	ABCA3
Gene_ID	21
Accession_Numbers	[illegible]
Cancer_Type_or_Thyroid_Disorder	MTC
Protein_Name	ATP-binding cassette sub-family A member 3 (ABC-C transporter) (ATP-binding cassette transporter 3) (ATP-binding cassette 3)
Length(aa)	1704
Chromosome	16
Chromosomal_Location	16p13.3
Method(3D)	-
Location	Membrane; Multi-pass membrane protein
Comments	Highly expressed in lung, followed by brain, pancreas, skeletal muscle and heart. Weakly expressed in placenta, kidney and liver. Also expressed in me
Nucleotide	[illegible]
Protein	[illegible]
Description	ABC3
Gene_Family_Description	ATP binding cassette transporters / subfamily A
Gene_Family_Tag	ABCA
HPRD_ID	3369
OMIM_ID	[illegible]
Uniprot_ID	Q8IPS9, Q4LE27, Q99758

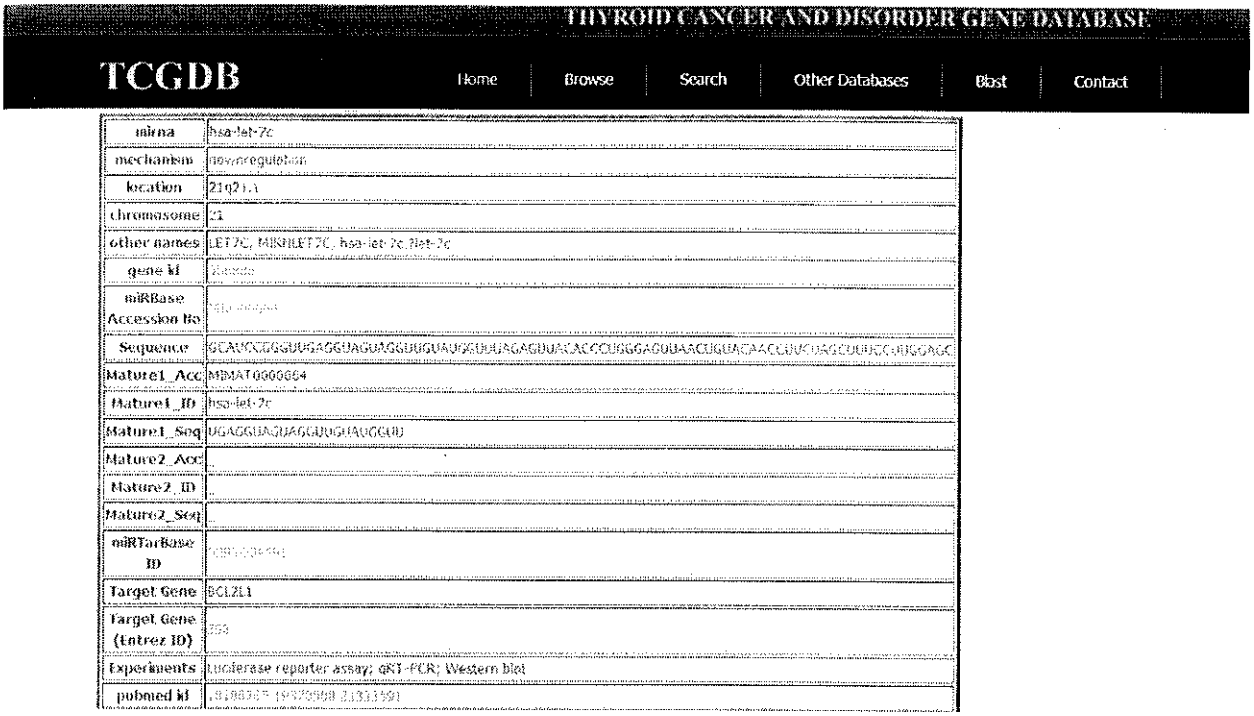
- miRNA browse page has given options by which user can extract data of his interest.



- miRNA present in body fluid can selected from drop down list and user find respective results
- Result for user body fluid selection "Bile"



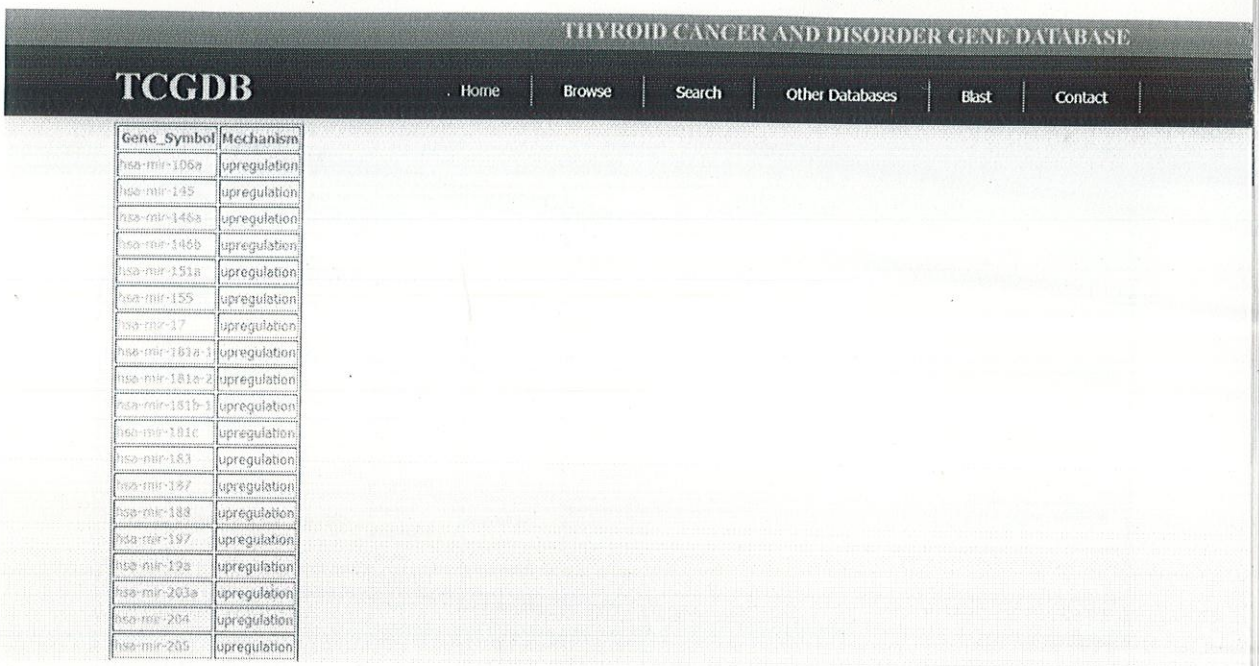
- Further information about specific miRNA can also be obtained by just clicking on miRNA.



mirna	hsa-let-7c
mechanism	downregulation
location	21q21.1
chromosome	21
other names	LET7C, MIRNLET7C, hsa-let-7c,Let-7c
gene id	406935
miRBase Accession No	MI0000064
Sequence	GCAUCUGGGUUGAGGUAGGUAGGUUGUAUGGUUAGAGUUACACCCUGGGAGUUAACUGUACAACCUUCUAGCUUUCCUUGGAGC
Mature1_Acc	MIMAT0000064
Mature1_ID	hsa-let-7c
Mature1_Seq	UGAGGUAGUAGGUUGUAUGGUU
Mature2_Acc	
Mature2_ID	
Mature2_Seq	
miRTarBase ID	MIRT036440
Target Gene	BCL2L1
Target Gene (Entrez ID)	598
Experiments	Luciferase reporter assay; qRT-PCR; Western blot
pubmed id	18188367,19372588,21331360

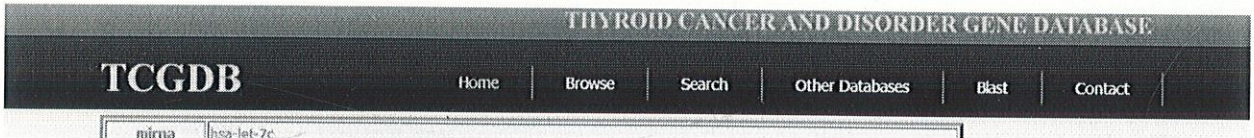
- Complete List of miRNA can be browse by user by just clicking on "Complete List"

- Search by Mechanism can be performed as follows: Result for upregulation



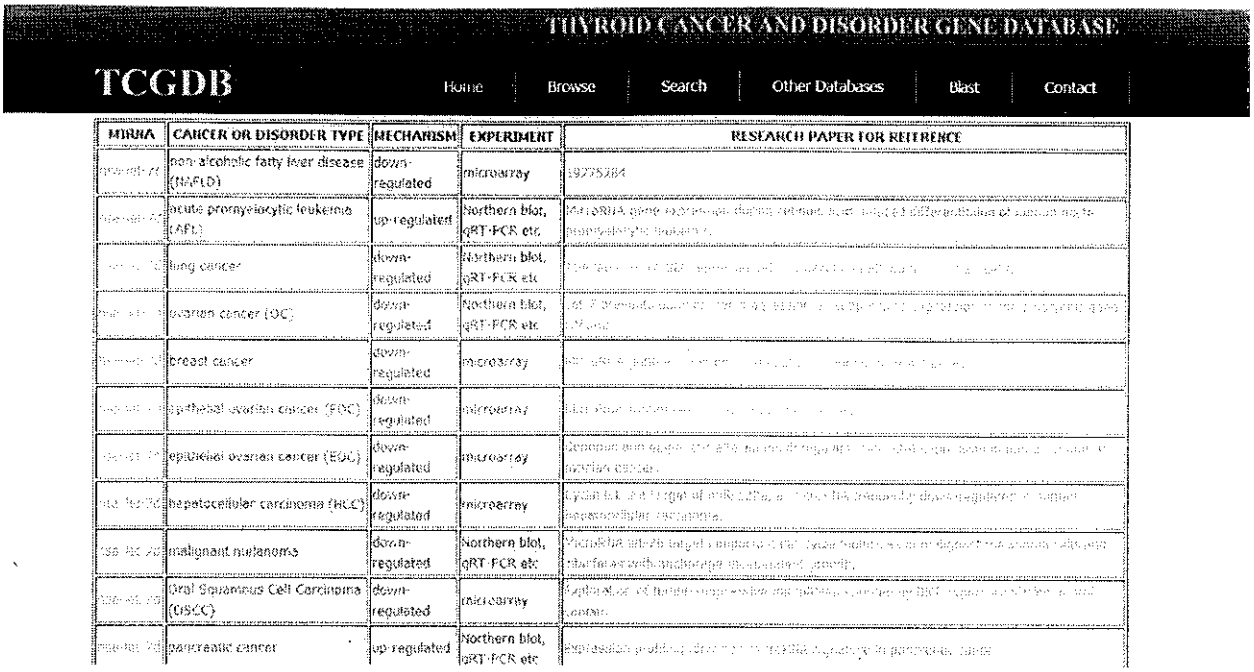
Gene_Symbol	Mechanism
hsa-mir-106a	upregulation
hsa-mir-145	upregulation
hsa-mir-146a	upregulation
hsa-mir-146b	upregulation
hsa-mir-151a	upregulation
hsa-mir-155	upregulation
hsa-mir-17	upregulation
hsa-mir-181a-1	upregulation
hsa-mir-181a-2	upregulation
hsa-mir-181b-1	upregulation
hsa-mir-181c	upregulation
hsa-mir-183	upregulation
hsa-mir-187	upregulation
hsa-mir-188	upregulation
hsa-mir-197	upregulation
hsa-mir-19a	upregulation
hsa-mir-203a	upregulation
hsa-mir-204	upregulation
hsa-mir-205	upregulation

- Further details of upregulated, downregulated and all miRNA can be browsed by clicking on links.



mirna	hsa-let-7c
mechanism	downregulation
location	21q21.1
chromosome	21
other names	LET7C, MIRNLET7C, hsa-let-7c,?let-7c
gene id	406883
miRBase Accession No	MI0000064
Sequence	GCAUCCGGGUUGAGGUAGUAGGUUGUAUGGUUUAGAGUUACACCCUGGGAGUUAACUGUACAACCUUCUAGCUUUCCUUGGAGC
Mature1_Acc	MIMAT0000064
Mature1_ID	hsa-let-7c
Mature1_Seq	UGAGGUAGUAGGUUGUAUGGUU
Mature2_Acc	_
Mature2_ID	_
Mature2_Seq	_
miRTarBase ID	MIRT004491
Target Gene	BCL2L1
Target Gene (Entrez ID)	598
Experiments	Luciferase reporter assay; qRT-PCR; Western blot
pubmed id	18188765 19370508 21322593

- miRNA involved in other cancers and diseases with reference



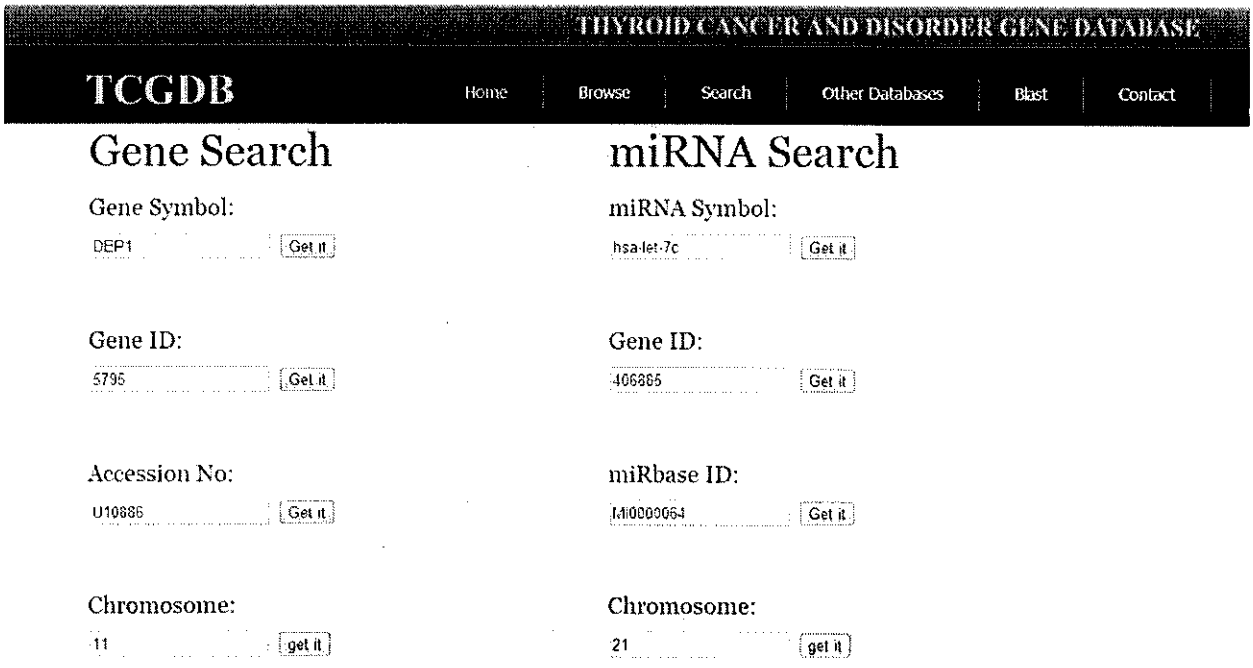
THYROID CANCER AND DISORDER GENE DATABASE

TCGDB

Home | Browse | Search | Other Databases | Blast | Contact

MIRNA	CANCER OR DISORDER TYPE	MECHANISM	EXPERIMENT	RESEARCH PAPER FOR REFERENCE
[illegible]	non-alcoholic fatty liver disease (NAFLD)	down-regulated	microarray	19775384
[illegible]	acute promyelocytic leukemia (APL)	up-regulated	Northern blot, qRT-PCR etc	MicroRNA gene expression during retinoic acid-induced differentiation of human acute promyelocytic leukemia.
[illegible]	lung cancer	down-regulated	Northern blot, qRT-PCR etc	[illegible]
[illegible]	ovarian cancer (OC)	down-regulated	Northern blot, qRT-PCR etc	[illegible]
[illegible]	breast cancer	down-regulated	microarray	[illegible]
[illegible]	epithelial ovarian cancer (EOC)	down-regulated	microarray	[illegible]
[illegible]	epithelial ovarian cancer (EOC)	down-regulated	microarray	[illegible]
[illegible]	hepatocellular carcinoma (HCC)	down-regulated	microarray	[illegible]
[illegible]	malignant melanoma	down-regulated	Northern blot, qRT-PCR etc	[illegible]
[illegible]	Oral Squamous Cell Carcinoma (OSCC)	down-regulated	microarray	[illegible]
[illegible]	pancreatic cancer	up-regulated	Northern blot, qRT-PCR etc	[illegible]

- Search Page: user can search according to his requirement.



THYROID CANCER AND DISORDER GENE DATABASE

TCGDB

Home | Browse | Search | Other Databases | Blast | Contact

Gene Search

Gene Symbol: DEP1 Get it

Gene ID: 5795 Get it

Accession No: U10886 Get it

Chromosome: 11 get it

miRNA Search

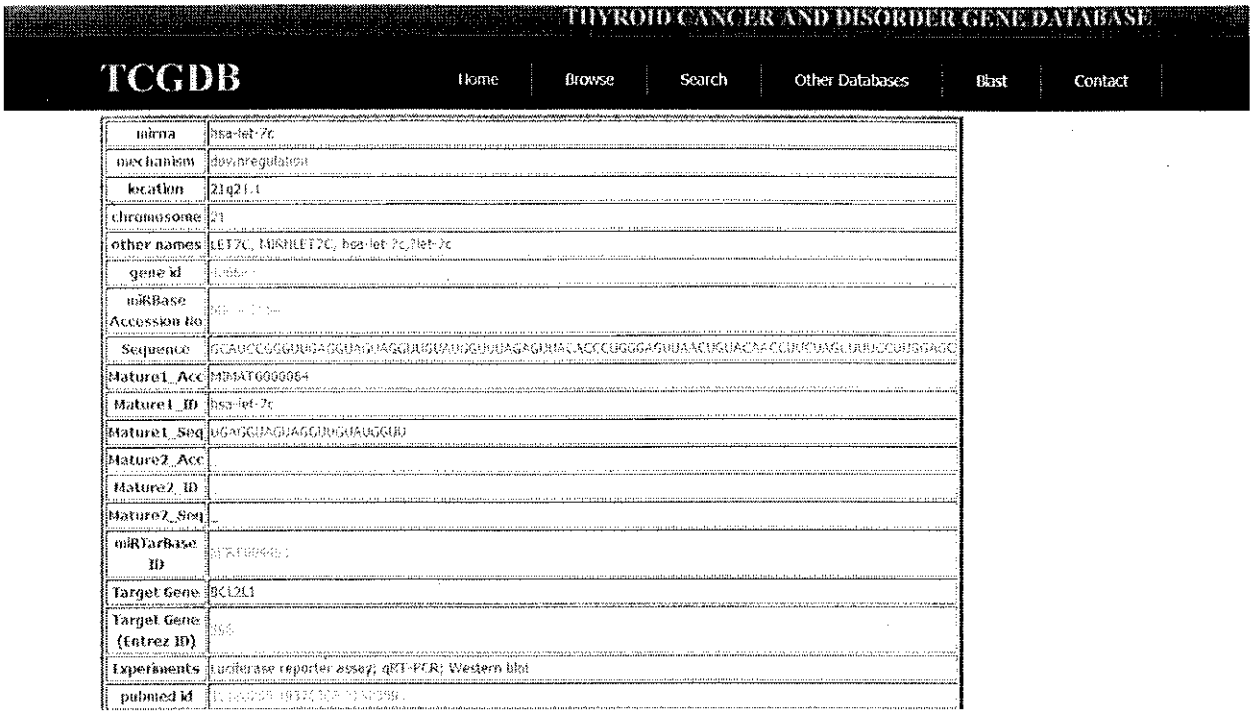
miRNA Symbol: hsa-let-7c Get it

Gene ID: 406885 Get it

miRbase ID: MI0000064 Get it

Chromosome: 21 get it

- Result of Search for genes
- Results for search of miRNA



CHAPTER 5

Conclusion

We have developed a database named Thyroid Cancer and Disorder Gene Database (TCGDB) which will allow the users to search for different types of thyroid cancers and disorders available in the database. It provides all the experimentally known genes involved in any thyroid cancer type or disorder. It will also include other information related to that gene like its function etc. Apart from the above mentioned information, database will also include corresponding literature for reference through PubMed.

Researchers have found that one of the causes of the thyroid cancer and disorders is lack of iodine in diet and smoking. They are investigating the proteins or miRNA which may work as a potential biomarker for early diagnosis of thyroid cancer and disorders. As the required information is scattered in the literature, so there is a need to refer to databases that could provide such information in an organized manner. Though there are several databases available today but none of them provide all the information about thyroid cancer. Every database lacks something or other. Hence for this purpose and to add consistency, we have developed a database which provides a handful of information on different thyroid cancers and disorders. It will help students, researchers and medical professionals to obtain the desired information with different types of queries. They can search for a specific gene and can obtain all the information relevant to that gene. They can also search a particular disorder and can look for all the genes involved in that disorder and the mutations related to it. They can find miRNA which are also present in body fluids. They can further look for genes shared by different types of cancers and diseases.

Database is available for research and academic use at: http://www.juit.ac.in/attachments/tcgdb/

(VI)

REFERENCE

1 Richard Mayeux, et al. Biomarkers: Potential Uses and Limitations.

2 D H Shah, et al. Epidemiological Observations of Thyroid Cancer.

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(VII)

BRIEF BIO DATA OF STUDENT

Project Title	: Development of database of thyroid cancer and disorder.
Project Guide	: Dr. Jayashree Ramana
Name of Student	: Ankush Bansal
Enrollment No.	: 091508
Batch	: H2 Batch
Branch	: B.Tech in Bioinformatics
Field of Interest	: Datawarehousing, Drug Designing, Machine Learning.
Language	: C, PERL, HTML, PHP, CSS, Javascript
Email ID	: bansal.ankush13@gmail.com
Mobile No	: +91-8091119750