Nephrogenic diabetes insipidus (ndi) causes

Introduction

During the past two decades, significant and advance scientific researches in molecular biology and genetics have set the stage for a revolution in medical science. Advance researches in gene cloning, gene mapping and mutation study have contributed to an explosion of new information regarding the fundamental biological and patho-physiological basis for hundreds of human diseases. After the completion of Human Genome Project, a new wave of bioinformatics has been launched and genomic informations are widely used in medical research (Schlesinger, 1980) of several applied genomics. Physiological genomics could be a new application and it tasks at formidable attaching function to genes within the human genome. Diabetes is one of them that could be a cluster of metabolic disorders.

Diabetes: An Overview

In accordance with medical science description, diseases are of different types; each has its own different cause, in which Diabetes is a big form of disease. Diabetes is a Greek word meaning “ siphon”; is derived from the verb diabainein, which means “ to stand with legs apart (as in urination) or to go through” (Chan, 2013). Consequently diabetes is a metabolic disorders marked by excessive discharge of urine. On the basis of pathology, Diabetes is divided into two following conditions –

- Diabetes Mellitus(DM)
- Diabetes Insipidus (DI)

Diabetes Mellitus–Diabetes Mellitus (DM) is the most common form of diabetes. It is a metabolic disorder in which there is an inability to oxidize

carbohydrates due to a disturbance in insulin production or function. In DM the β-cells no longer produces enough insulin or cells stop responding to the insulin that is produced, so that glucose in the blood cannot be retained into the cells of the body resulting in elevated glucose in the plasma, unnecessary release of urine and persistent thirst. On the basis of pathology Diabetes Mellitus is also divided into two following types –

- Insulin Dependent DM (Type 1)
- Non- Insulin Dependent DM (Type 2)

In Diabetes Type 1 the body is not producing insulin, while in Diabetes Type 2 the cells are not responding properly to the insulin (http://kidney. niddk. nih. gov/kudiseases/pubs/insipidus/#types).

Diabetes Insipidus –Diabetes Insipidus (DI) is a rare form of diabetes resulting from a deficiency of vasopressin (the pituitary hormone that regulates the kidneys); characterized by the chronic excretion of large amounts of pale dilute urine which results in dehydration and extreme thirst. It is a neuroendocrine disorder that has the highest prevalence. Diabetes Insipidus is classified into as follows-

- Central Diabetes Insipidus
- Dipsogenic Diabetes Insipidus
- Gestational Diabetes Insipidus
- Nephrogenic Diabetes Insipidus

In all the above types of the Diabetes Insipidus, Nephrogenic Diabetes Insipidus (NDI) is more common in children (Chan, 2013).

Nephrogenic Diabetes Insipidus:

Nephrogenic Diabetes Insipidus (NDI) results from inadequate response of the kidney to the antidiuretic hormone (ADH), arginine vasopressin, which is produced in hypothalamus, then put away and discharged from the pituitary gland. Nephrogenic Diabetes Insipidus (NDI) can result from the genetic or acquired causes. NDI may be acquired by iatrogenic (lithium or demeclocycline), hypokalemia, hypercalcaemia, various types of renal diseases and sickle cell disease etc. Genetic causes are less common however additional severe than acquired forms of NDI (Robert et al. 2012).

NDI is characterized by Lack of ability to concentrate the urine in the body, which results in extreme urine production (polyuria) and excessive thirst (polydipsia) (Knoers, 2012). The polyuria (urine output > 4 ml/kg/hr) and polydipsia (water intake > 2 L/m2/d) associated with genetic NDI usually presents within the first several week of life but may only become apparent after weaning or with longer periods of night time sleep. Many infants initially suffer with fever, vomiting and dehydration. Failure to thrive may be secondary to the ingestion of large amount of water, resulting in caloric malnutrition. Long standing ingestion and excretion of large volumes of water may lead to severity of the disease and produce complications in the patient, like non-obstructive hydronephrosis, hydroureter and megabladder etc. (Robert et al. 2012).

Genetic Involvement in NDI:

Genesare coding region of DNA (deoxyribonucleic acid) inside each of our cells that are responsible for the synthesis of particular proteins, which are necessary in the body for a particular function. DNA is the genetic “

blueprint” found in each cell. Genes have an effect on inherited traits passed on from parents to child. They also affect whether a person is likely to develop certain diseases, such as Diabetes Insipidus. In nephrology, a wide range of clinical phenotypes can now be explained at a molecular level. The greatest strides have been made in defining genes that are responsible for a variety of inherited syndromes like nephrogenic diabetes insipidus (Knoers, 2012). Genetically, mutations in two genes are known to cause NDI, these genes are –

- AVPR2 (Arginine Vasopressine Receptor 2: X-linked)
- AQP2 (Aquaporin 2: autosomal recessiveanddominant)

On the basis of inheritance mechanism, NDI has its three different types, which are –

- X-linked manner (~90% of individuals)
- Autosomal RecessiveManner (~9% of individuals)
- Autosomal DominantManner (~1% of individuals)

AVPR2is thegenein which mutations are known to cause X-linked nephrogenic diabetes insipidus, while AQP2is thegenein which mutations are known to causeautosomal recessiveandautosomal dominantnephrogenic diabetes insipidus. Around 90% of NDI patients were reported as male with X-linked recessive NDI and have mutations in the AVPR2 gene, where 10% of the NDI patients were reported as having autosomal mode of inheritance and is mainly due to mutations in the AQP2 gene. However it is reported that in some female who had classical features of the disease by the result of AVPR2 mutations, had excess of mutant cells because of skewed X

inactivation, the most severe had the greatest amount of skewing. The cellular mosaicism resulting from X inactivation in female patients is mostly protecting carriers of X-linked mutations from the severe clinical manifestations seen in males.

Need of present research work:

As described previously, NDI characterized by the chronic excretion of large amount of pale dilute urine, which outcomes in dehydration and extreme thirst, NDI can bring about human body to retain deficient water to function properly except with primary polydipsia. As a result of the lake of retained water in the body, the patient comes to be dehydrated. Dehydration can cause symptoms like Dry mouth, Muscle weakness, Hypotension, Hypernatremia, Sunken eyes, Fever, Headache, High heart rate, Weight loss, etc. Nephrogenic Diabetes Insipidus can also cause an electrolyte imbalance (http://www. mayoclinic. org/diseases-conditions/diabetes-insipidus/basics/causes/con-20026841). Electrolytes are minerals in blood such as sodium and potassium that maintain the balance of fluids in the body. Electrolyte imbalance can cause symptoms, such as Fatigue or Lethargy, Irritability, Nausea, Loss of appetite and Muscle pains etc.

Dehydrated people who have not been diagnosed to have NDI or who are incompetent to communicate their complaints, run the danger of being improperly treated with administration of usual saline, mainly in emergency conditions. This may exacerbate hypernatremia, Prolonged, unrecognized, or repeated episodes of hypernatremic dehydration may result in Seizures,

Permanent brain damage, Developmental delay, and Cognitive impairment. On the opposite hand, with primary diagnosis and appropriate management, intelligence and life span are generally normal (Knoers, 2012).

As we know, the diagnosis part is more important to treat the root cause of the disease. Through early diagnosis and proper management, intelligence and life span can manage to normal condition in many patients of NDI, while undiagnosed and untreated NDI can cause the death of the patient. In undiagnosed and untreated patients, long standing ingestion and excretion of large volumes of water may lead to severity of the disease and produce complications in the patient, which can cause danger to the life. Children who go untreated for NDI can fail to thrive. In severe cases, they may experiencemental retardationfrom the constant dehydration (Phadke et al. 2001). Thus, NDI can lead to death from dehydration in the absence of proper treatment. Prognosis is good for those who receive proper treatment and medication, which can keep health stable. Here, one thing also should be kept in the mind that the proper treatment is always based on the proper diagnosis. That’s why; present study is being designed to diagnose the root cause of the underlying disease.

Generally, most of the diseases are treated on the basis of diagnosis by the symptoms and some laboratory tests but in NDI the root cause may be genetic or acquired. Genetic causes are less common but more severe than acquired forms of NDI. In that situation, treatment will be based on symptoms or other tests. So there is need of a diagnostic tool which determines the actual root cause of the underlying disease and also determines the actual defect at the genetic level. Due to the lack of such

type of diagnostic tool to know the root cause of NDI at genome level; most of the patients become undiagnosed and specialists also faced difficulty to treat those patients. Present study is based on the study and pattern of genes or protein(s); which involved in the pathogenesis of Nephrogenic Diabetes Insipidus.

Bioinformatic Approach in study of NDI:

Bioinformatics is a blend of molecular science and computer sciences. It is the innovation in which computers are used to gather, store, analyze and integrate biological and genetic information. The necessity for Bioinformatics emerged when a project to determine the sequence of the whole human genome was initiated. Bioinformatics is more significant for the use of genomic information to understand human diseases and to classify new ways for gene-based drug discovery and development. Consequently, numerous universities, government institutions and pharmaceutical organization have approached to form bioinformatics clusters to do research related to computational biology so that better ways are utilized to make processes more efficient and less time consuming (http://www. biotechnologyforums. com/thread-40. html).

In health and medical fields, bioinformatics plays a remarkable role and enables advances in various areas, such as Drug discovery, Diagnostics, Disease management. In modern era, a healthy understanding of complex pathways and interactions at the molecular level has modified our approach to the analysis of proteomic information. In bioinformatics, large-scale proteomic profiling of organelles and sub-cellular large structures has yielded

valuable data about DNA, RNA and protein to identify regions of similarity that may be a consequence of functional, structural or evolutionary relationships between the sequences (Schlesinger, 1980). Aligned sequences of nucleotide or amino acid residues are usually denoted as rows within a matrix. Gaps are inserted between the residues in order that residues with identical or similar characters are aligned in successive columns. Complete and accurate profiling of the sub-cellular localization of proteins is critical for understanding their functions. However, organelle proteome characterization is challenging for numerous reasons. In addition, equivalent organelles in different tissues or cell types may have different profiles (Zhang-Zhi et al 2007).

Presently the scientist are concentrating for search for the ideal tool to diagnosed the root cause of NDI at genomic level, the present project/study was launched to undertake the development of sequence analysing tool; i. e. NDIDVT (Nephrogenic Diabetes Insipidus Diagnostic and Visualization tool) for evaluating it’s possible impact in the present context, with following main objectives-

- To study the patho-physiology of nephrogenic diabetes insipidus (NDI).
- To study of the protein(s)/gene involved in the pathogenesis of NDI.
- To study the comparative analysis between candidate genes & identified protein, using bioinformatic databases and tools.
- To study the structure prediction of candidate protein AQP2 and AVPR2.
- To develop the sequence analysis tool (NDIDVT) against the identical protein sequences.

In present study, this concept is being used that there are two genes (AVPR2 and AQP2), those contain high genetically relationship in the etio-pathogenesis of NDI. With the help of basics of bioinformatic the diagnostic tool was designed to know the genetic relationship between genes and this also reflects the usefulness of physiogenomic approach to detect the genes with physiogenomic correlation. Systemic approach on the pathophysiology and genomics may provide useful information to better understand the pathogenesis of NDI. In this study, physiological genomics analysis for NDI was performed with the help of bioinformatic databases and tools to obtain all the objectives.

The Diagnostic Tool – NDIDVT:

In this present research work, Patho-physiological study of candidate genes and protein(s) involved in the pathogenesis of NDI was analysed/ reviewed to know the biological relationship between all these proteins. For this purpose the candidate genes and mutant sequences were collected in FASTA format from KEGG and NCBI database respectively. On the other hand, to obtain the realistic alignment result & evolutionary changes in the aligned sequence, Multiple Sequence Alignment was also done between candidate gene & mutant sequence with the use of Clustal Omega.

The study of molecular weight, amino acid composition and other information of the candidate gene, study of Primary, Secondary & Three dimensional structures of candidate gene was done with the help of bioinformatic tools. Study of Primary Structure was done with the help of PROTPARAM, Secondary Structure study was done with the help of SOPMA

and the three dimensional (3-D) structure study of candidate gene was done with the help of Swiss Model & PSVS.

Methods of above database study will be detailed at appropriate place i. e. chapter Materials and Methods of this dissertation. Here it is assumed that, the method, multiple sequence alignment reflects the evolutionary changes in the aligned sequences and the more appropriate distribution of gaps between conserved domains, but it cannot give any result regarding unknown sequences, which are involved in evolution of NDI or not. That’s why this tool NDIDVT was designed to know the information about unknown sequences or query sequences; by these information can conclude that the sequences of the patient are diseased or not.

As a final outcome of this study, the toolNDIDVTis stand forNephrogenic Diabetes Insipidus Diagnostic & Visualization Tool, has to be developed. This tool performs analysis & visualization of the sequences involved in NDI with query sequences, collected from the patient. It finds regions of similarity between sequences. This tool compares query nucleotide sequences to sequence databases and calculates the statistical significance of matches. NDIDVT enables to align query sequence with previously known patients sequence as well as standard vasopressin sequence and gives the expected outcomes regarding diseased sequences.