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Bioinformatics Analysis of Gestational Diabetes Mellitus using Functional Protein Sequences

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Abstract: Gestational diabetes mellitus [GDM] is a transient asymptomatic disorder in which glucose intolerance ofvariable severity with onset or first recognition during pregnancy. GDM is emerging as reliable risk predictor for the development of type II diabetes. GDM has also beenassociated with many adverse perinatal pediatric complications. It is crucial to pinpoint the key susceptible gene that is of great importance in the pathophysiology of gestational diabetes. In this regard, We evaluated the role of several genes/proteins that are believed to be involved in the evolution of Gestational diabetes by employing multiple sequence alignment using ClustalW tool and constructed a phylogram tree using functional protein sequences extracted from NCBI. Phylogram was constructed using Neighbor- Joining Algorithm in bioinformatics approach. Our bioiformatis anlysis yielded Glucokinase[MODY 2] gene as a key susceptible gene closely associated with Gestational diabetes mellitus. This is the first bioinformatics study to lend further support for the proximate association between Glucokinase[MODY 2] gene and Gestational diabetes mellitus. The identification of Glucokinase mutation in a patient with gestational diabetes is important for both the mother and the baby. It is suggested that early identification of Glucokinase[MODY2] gene mutations may help to preventthe evolution of gestational diabetes and subsequently type II diabetes that develops later in the life.

Keywords: Gestational Diabetes Mellitus (GDM), NCBI National Center for Biotechnology Information.

I. INTRODUCTION

Gestational diabetes mellitus [GDM] is a transient asymptomatic disorder in which glucose intolerance ofvariable severity with onset or first recognition during pregnancy. [1] GDM is a heterogeneous disorder associated with a high degree of maternal and fetal mortality. There is growing likelihood for the development of type 2 diabetes among women with previous history of GDM. [2].GDM patients are also at increased risk for perinatal morbidity and long term obesity and glucose intolerance in offspring. [3].The prevalence of GDM increased in developed countries from 2.9% to 8.8% over the past two decades. [4]. Previous experimental studies reported that the altered metabolic environment of the gestational diabetic women produces permanent aberrations in glucose homeostasis in the offspring that evolutes to diabetes later in life. [5]. GDM has beenassociated with many adverse perinatal pediatric outcomes. Macrosomia is the most common problem [6] and is referred as the infant birth weight over 4000 grams or over the 90th percentile of birth weight for gestational age. These largebabies are at increased risk of shoulder dystocia. Neonates of gestational diabetic mothers also have an increased risk of having hypoglycemia, respiratory distress and neonatal death

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[7]. The offspring also tend to have increased rates of Diabetes mellitus before the age of 18. [8]Moreover, diabetic pregnancy in rat models causes multiple perturbations in glucose homeostasis and insulin secretion in the fetus that leads to defective fetal growth. The high dosage of STZ produces growth retardation in rats while the lower dosage of STZ causes fetal macrosomia in rats[5].

The pathophisiology of GDM is believed to involve a combination of increased insulin resistance and beta cell dysfunction. [9] The majority of gestational diabetic women seem to have beta cell dysfunction that occurs on abackground of chronic insulin resistance. Pregnant womenwith GDM tend to have higher insulin resistance than normal pregnant women. [3] In normal pregnant women, insulin resistance resulted from increased maternal adiposity and insulin desensitizing effects of hormones released by placenta. Insulin resistance abates immediately after delivery suggests that insulin resistance developed during pregnancy may be majorly attributed to the placental hormones in normal pregnant women. [3] But in the case of diabetic pregnant patients, though glucose regulation usually reverts to normal following delivery, features of metabolic syndrome may persists and glucose tolerance often deteriorates with time. [10] Majority of epidemiological and experimental studies revealed that intrauterine diabetic milieu promotes the risk for hypertension, obesity and type 2 diabetes in adulthood. [11] Our Bioinformatics analysis aimed to pinpoint the key gene/protein that has proximate association with pathobiologyof GDM.

II MATERIAL METHODS

We collected 17 known Proteins that are believed to involve in the paythogenesis of Gestational diabetes mellitus. Thefunctional Protein sequences in FASTA format for these Proteins are collected from NCBI [National Center for BiotechnologyInformation [Ref:http\\www.ncbi. nih.nlm.gov]. These sequences are given to ClustalW [Ref:http\\www.ebi.ac.uk\ clustalw] for the Multiple Sequence Alignment. [It calculates the best match for the selected sequences, and lines them up so that the identities, similarities and differences can be seen]. Based on these results, the scores table and Phylogeetic tree shows the distance between the Protein sequencesIt is suggested that early identification of Glucokinase [MODY2] gene mutations may help to prevent the evolution of gestational diabetes and subsequently type II diabetes that develops later in the life.

III DISCUSSION

GDM is characterized by impaired insulin secretion andaction.[12]Women with GDM often have a history ofmaternal diabetes that suggests a genetic component for the disease. To date, several genetic studies have been carried out to identify susceptibility genes predisposing for thedevelopment of GDM. Associations have been reported between GDM and variants in the glucokinase[13],mitochondrial DNA [14,15], beta 3 adrenergic receptor [16], sulphonyl urea receptor 1 [SUR 1][17], Insulin receptor and Insulin like growth factor 2 [IGF2] genes [18]Increased frequencies of HLA risk antigens and high prevalence of islet cell antibodies, insulin associated antigen 2 and GADantibodies have also been reported in women with GDM. In addition, few studies reported the increased levels of leptin[19] and inflammatory markers of TNF-alpha [20] and C-reactive protein [21] and decreased levels of adiponectin[22,23] in women with GDM. Mutations that cause several subtypes of MODY have been found in women with GDM. These include mutations in genes encoding Glucokinase[MODY 2][24,25-27], Hepatocyte nuclear factor-alpha [MODY 3][24]. Glucokinase mutations cause maturity

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onset diabetes of young type II [MODY 2], In MODY 2 women, hyperglycemia persists through out pregnancy. [28] Altered fetal insulin secretion caused by fetal or maternal Glucokinase mutations affect birth weight. [28] Yet, genetic and environmental components are implicated in the pathophysiology of GDM.

In consonance with the several previous experimental reports, Our bioinformatics analysis revealed that genetic component, particularly Glucokinase gene, plays predominant role in history of evolution of Gestational diabetes. Glucokinase mutations were identified in 80% of the gestational diabetic patients selected on the basis of clinical phenotype. [29] In the large group of French MODY2 families, birth weight is declined in the presence of a fetal glucokinase mutation and increased by the presence of maternal glucokinase mutation. [28] It is imperative to identify these patients with Glucokinase mutations because they have a predictable clinical course and the autosomal dominant inheritance. [29] The identification of Glucokinase mutation in a patient with gestational diabetes is important for both the mother and the baby. [29] Patients with glucokinase mutations are frequently diagnosed during screening in pregnancy. In the series of European Whites, the prevalence of glucokinase mutations ranged from 0% to 6%. [29] The recognition of the subjects with glucokinase mutations is important because they have a different clinical course both within and outside pregnancy compared with most other subjects with gestational diabetes, Patients clinical characteristics can be used to detect those who are most likely to have a glucokinase mutation. Specific criteria favoring a diagnosis of a glucokinase mutation have been shown to be persistent fasting hyperglycemia [29].

TABLE I: Table Showing the Genes/Proteins That Have Been Studied In the Present Study, Which Are Believed To Be Involved In Gestational Diabetes Mellitus

S.no	Gene name	Accession number	Length	Tissue	References
1	ADIPOQ	AAH54496	244 aa	Peripheral Nervous System, sympathetic Trunk	
2	ADRB3	NP_000016	408 aa	NOT SPECIFIED	
3	CRP	AAH20766	91 aa	Liver	
4	GCK	AAA67542	14 aa	Blood	
5	GIP	AAH69746	153 aa	PCR rescued clones	
6	HFE	AAH74721	345 aa	Brain, PCR rescued clones	
7	HLA-DQA1	AAI25046	254 aa	PCR rescued clones	
8	HNF4A	CAC01303	474 aa		
9	HP	AAH70299	281 aa	Liver	
10	LEP	AAH69452	167 aa	PCR rescued clones	
11	PPARBP	AAH60758	556 aa	Testis	
12	PPARGC1A	NP_037393	798 aa	No	
13	PTPRN	AAH70053	950 aa	Brain, hypothalamus	
14	TNF	CAI18649	233 aa		
15	SHBG	AAH69597	401 aa	PCR rescued clones	
16	IGF2	AAH42127	113 aa	Muscle, rhabdomyosarcoma	
17	SUR5	AAM44124	665 aa		

Fetal growth in pregnant patients with MODY 2 has been shown to be dependent on whether the fetus has inherited the mutation from its mother.[30] Fetal insulin secretion is a key determinant of fetal growth, acting mainly during the third trimester when the weight of the

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fetus increased markedly. Macrosomic children born to mothers with diabetes in pregnancy have increased fetal insulin secretion in response to fetal pancreatic sensing of maternal hyperglycemia. Factors that alter fetal insulin secretion will therefore alter intrauterine growth by altering fetal insulin mediated growth. [31] A glucokinase mutation in a pregnant mother will result in maternal hyperglycemia, hence increasing fetal insulin secretion and fetal growth as shown in Fig.1. Inheritance of the mutation by the fetus will result in reduced sensing of the maternal glucose by the fetal pancreas and hence reduced fetal.

Bioinformatics Analysis of Gestational Diabetes Mellitus using Functional Protein Sequences insulin secretion and reduced intrauterine growth. [31] GDM provides an excellent model for studying early events in the natural history of type II diabetes and early identification of Glucokinase[MODY2] gene mutations may help to prevent the evolution of gestational diabetes and subsequently type 2 diabetes that develops in later in the life.

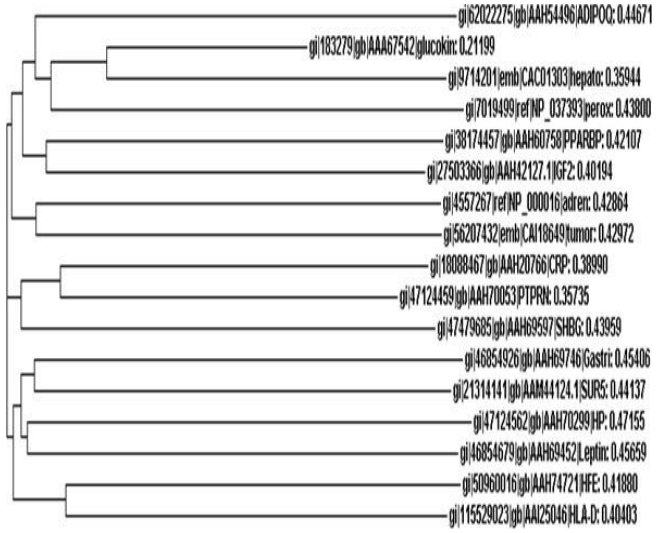

Fig.1. The phylogenetic tree that was constructed based on the alignment score of all the protein sequences involved in Gestational diabetes mellitus.

IV CONCLUSION

Gestational diabetes is great opportunity for studying early events in the development of type II diabetes. Our bioinformatics study support the dominant role of Glucokinase[MODY 2] gene in the evolution of gestational diabetes. The early identification of Glucokinase[MODY 2] gene mutations could produce promising results in the clinical practice.

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