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Computational Analysis of Mutations in Neonatal Diabetes (KCNJ11) Gene Reveals no Relation with Microsatellites

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Abstract

Gain-of-function mutations in the genes encoding the ATP-sensitive potassium (K (ATP)) channel subunit Kir6.2 (KCNJ11) is a common cause of neonatal diabetes mellitus.(de Wet H 2007 et al). Neonatal diabetes was defined as hyperglycemia that requires insulin treatment and occurs during the first month of life ,it is also known as monogenic diabetes of infancy, which includes both the permanent and the transient types (Barbetti F. Endocr Dev. 2007) and the mutations in KCNJ11 gene causes Neonatal diabetes(Mlynarski W 2007 et al). We tried to find out whether the presence of micro satellite or simple sequence repeats in the KCNJ11 gene has any significance in the generation of these mutations and checked whether these mutations are fallen in the regions of those microsatillites and if so is there any significance of these microsatillites in the functional domains of the each gene. Our analysis reveled that all the microsatellites (National diabetes information clearinghouse) of the KCNJ11 does not contain any mutations and these mutations also does not fall in the functional domains of the KCNJ11 thus indicating that here there is no role of microsatellites in the mutations of KCNJ11 gene.

Keywords: Microsatellites; Bioinformatics; Neonatal Diabetes

Introduction

Neonatal diabetes mellitus is a rare form of Insulin dependent diabetes mellitus that present Within the first month of life, lasting at least two weeks and requiring insulin therapy. Intrauterine growth restriction, failure to thrive, fever, dehydration, hyperglycemia and acidosis with or without ketonuria are the clinical features of the disease. Monogenic forms of diabetes account for about 1 to 5 percent of all cases of diabetes in young people. In most cases of monogenic diabetes, the gene mutation is inherited; in the remaining cases the gene mutation develops spontaneously. Most mutations in monogenic diabetes reduce the body's ability to produce insulin, a protein produced in the pancreas that helps the body use glucose for energy. Neonatal diabetes mellitus (NDM) and maturity-onset diabetes of the young (MODY) are the two main forms of monogenic diabetes. MODY is much more common than NDM. NDM first occurs in newborns and young infants; MODY usually first occurs in children or adolescents but may be mild and not detected until adulthood .

Micro satellites are known to be highly polymorphic due to the high rate of mutations in their tracts (Fan H , Chu, J.Y 2007). These mutations can be either in the form of increase / decrease of repeat units or in the form of single nucleotide substitutions/deletions/insertions and other events (Li, Y.C., Korol, A.B., Fahima, T. and Nevo, E. 2004) . Increase or decrease of repeat units of micro satellites in coding regions might lead to shift in reading frames there by causing changes in protein product (Martin P 2005)and in non-coding regions are known to effect the gene regulation(Sibly 2003 et al). Point mutations (Substitutions and Indels) are also found to occur at a higher rate in micro satellites than elsewhere (Stenson 2003 et al). Micro satellite mutations with in or near certain genes are known to be responsible

And the mutations of KCNJ11 gene are

Accession number	Codon change	Amino acid change	Codon number
CM970815	TACG-TAA	Tyr-Term	12
CM981121	cGAG-AAG	Glu-Lys	23
CM050649	CGC-CAC	Arg-His	34
CM042726	cTTT-GTT	Phe-Val	35
CM051548	cTGC-CGC	Cys-Arg	42
CMO50280	CGG-CCG	Arg-Pro	50
CMO40760	CAG-CGG	Gln-Arg	52
CMO50650	gGGC-AGC	Gly-Ser	53
CMO50651	gGGC-CGC	Gly-Arg	53
CMO40762	cGTG-ATG	Val-Mat	59
CMO40761	GTG-GGG	Val-Gly	59
CMO24598	AAGt-AAC	Lys-Asn	67
CM994423	gTGG-CGG	Trp-Arg	91
CMO51091	GCC-GAC	Ala-Asp	101
CMO51092	GGG-GCG	Gly-Ala	134
CMO51093	CGC-CTC	Arg-Leu	136
CM960894	CTG-CCG	Leu-Pro	147
CMO50281	AAG-AGG	Lys-Arg	170
CMO50282	AAGa-AAC	Lys-Asn	170

CMO50652	cATC-GTC	Arg-Cys	182
CMO40763	aCGT-TGT	Arg-Cys	201
CMO40764	CGT-CAT	Arg-His	201
CMO43296	CCG-CTG	Pro-Leu	254
CMO53288	CAT-CGT	His-Arg	259
CMO51094	CCA-CTA	Pro-Leu	266
CMO40765	cATC-CTC	Ile-eu	296
Cmo51095	CGC-CAC	Arg-His	301
CMO42727	gGAG-AAG	Glu-Lys	322
CMO42728	TAC-TGC	Tyr-Cys	330
CMO42729	gTTT-ATT	Phe-Ile	333

Table 1 : List of Mutations HGMD*Materials.*

for some human neurodegenerative diseases. So, we made a brief study to check whether the mutations in this KCNJ11 gene have any relation with these micro satellites repeats and the study revealed the following results.

Methods

All the 30 proved mutations except the mutations, which occur at codon numbers 12,23,34 and, 35 of the KCNJ11gene are falling inside the coding region and are eventually leading to phenotypic differences were collected from the Human Gene Mutation Database (HGMD)(Mudunuri S.B., Nagarajaram 2007). Micro satellites are obtained from the Imperfect Micro satellite Extractor (IMEX) (Letunic, I., 2004 et al)tool using intermediate mode with default values 10 for single 5 for di 3 tri 3 for tetra 2 for penta and 2 for hexa and obtained only 4 micro satellites in KCN1J1. Since micro satellites are drawn from the nucleotide sequence and HGMD mutations are given for protein sequence we have used DNA to Amino Acid translator. We compared the microsatellite regions with the mutations whether they have mutations in those regions and found that no mutations fall in the microsatellite regions. Now we analyzed whether these mutations have fallen in the functional domains of those genes by using Simple Modular Architecture Research Tool (SMART)(Endocr Dev 2007) and the results are as follows

Name of the domain	Begin	End
low complexity	25	34
Pfam:IRK	36	366

The microsatellites found in KCNJ11 gene

Consensus	iterations	from	to	Imperfection
CAC	3	639	648	10%
CAC	4	826	837	8%
ACCT	3	904	914	9%
GGCCAA	3	1125	1142	5%

Results and Discussion

The mutations in the KCNJ11 are causing the neonatal diabetes mellitus. These mutations result in reduced ATP sensitivity of the KATP channels compared with the wild types. The level of channel activity defect is responsible for different clinical features: the 'mild' form confers isolated permanent neonatal diabetes whereas the severe form combines diabetes and neurological symptoms such as epilepsy, developmental delay, muscle weakness and mild dysmorphic features.so to check whether is there any relationship is there between the microsatellites and the mutations. we analyzed and found that there are no mutations in the microsatellite regions and therefore can say that the microsatellites are not responsible for mutations in the KCNJ11 gene.

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