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Editorial

Mitochondrial tRNA$^{leu(UUR)}$ gene A3245G Mutation in Type 2 Diabetes

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Editorial

A dwarfish thief today, diabetes, is a hazard that troubles the society, thriving every single moment. The time is not far away when it arises as a wicked giant, seizing the world in the deadly grasps and becoming a severe challenge for physicians everywhere. Diabetes Mellitus (DM), a commonly occurring, multifactorial disorder, has affected around 10% of the population in Western countries and Japan. The pandemic frequency of DM is continuously cropping up. Increased prevalence of DM has been observed in Asian region. As per one report published in 2013, 36 % of diabetic population is from Asian countries.

This increased occurrence in Asian population can be attributed to increasing incidence of more body weight, sedentary life style, genetic or other environmental factors including poverty. In such countries death rate is higher in diabetics due to overwhelming diabetic complications like infections and cardiovascular pathologies. In past few decades, clinical features of the diabetic patients were analyzed and a new trend of lower body mass index and early onset of Type 2 diabetes mellitus (T2D)was observed. The involvement of molecular element in the development of T2D in younger age group remains focus of research for many years and is yet to be explored fully [1].

Previous studies carried out in Indian population residing in South Africa have stated a higher prevalence ofT2Din younger age group. Similarly a study done in United Kingdom reported the increased incidence of T2Din Indian children and young adults settled in UK, as compared to white local diabetics. Some studies have stated that total number of diabetics of more than twenty years age worldwide is expected to rise in a generation, from 171,228 in 2000 to 366,212 by 2030, especially T2D.

In the last 20 – 30 years, due to extensive research and advancement, concepts regarding the mechanism of development of T2D have now been updated and modified, but the progressis facing multiple hurdles making the scenario as complicated as "untying the Gordian knot of mythology". Apart from hormonal and metabolic defects, underlying molecular proceedings leading to the disease have been researched methodically during last few decades but despite painstaking hard work, a lot of exploration is still required. Research work of T Surozzes et al (1998) in Japanhas stated that the individuals carryingpro-diabetic genetic mutations show decrease in response to insulin and impairment of glucose handling before the onset of DM. Recent studies have suggested the role of mitochondrial DNA mutations in the pathogenesis of T2D. Ubiquitous organelles, mitochondria, in the cells play important role in many metabolic pathways of energy production by the cell. Mitochondrial oxidative phosphorylation (OXPHOS) is the process playing a crucial role in the synthesis and release of insulin from cells of pancreas [2].

Hence mtDNA mutations maylead to alteration in the *OXPHOS* and subsequently the development of disorders. mtDNAmutations areassociatedwith various diseases which rangefrom rarely seen muscular syndromes tosome commonly found diseases like diabetes mellitus. Facts and figures related to pathogenic mtDNA mutations have been gathered at a heart stirring pace since the first pathogenic mtDNA mutation was discovered. Illustration of the entire human mtDNA sequence and cognition of its pathogenic mutations has made it easy and simple to appreciate the clinical implications of mtDNA mutations.

Any kind of disruption in the production of ATP can upset the normal hearing power of patients suffering from mtT2D, leading to development of "Sensory-neural deafness" along with the diabetes. Therefore, owing to combination of these defects, the aforementioned disease acquired its name of MIDD, "Maternally Inherited Diabetes and Deafness". Till now, approximately 978,000

carriers of mtDNA A3243G mutations are present globally. Almost twenty mtDNA mutations have been identified to be linked with maternally inherited diabetes such as homoplasmic mutations i.e*G1888A*, *A*4917*G*, *T4216G*,and*T14709C*.

Out of the twenty mutations, *A3242G* mutation is continually recognized in 0.1-1.5% of the diabetics. Diabetogenicheteroplasmic*A*3243*G* gene mutation is present on the *MTTL1* gene encoding the $tRNA^{(Leu)\ (UUR)}$. It is a major reason of maternally inherited disease accompanied by sensorineural hearing defect – "Maternally Inherited Diabetes and Deafness (MIDD)". *A3243G* point mutation in the $tRNA^{Leu(UUR)}$ gene is considered to be a very strongly linked mutation with pathogenesis of MIDD. This mutation leads to impairment in mtDNA transcription, in spite of precise progression of translation as well as insulin secretion induced by glucose [3].

It has been seen that in mitochondrial $tRNA^{Leu(UUR)}$ gene mutation, there is impaired synthesis of $tRNA^{(UUR)Leu}$ and defective translation process at UUR codons of the mitochondrial mRNA. The level of $tRNA^{Leu(UUR)}$ is decreased in the patients with *A*3243*G* gene mutation indicating enhanced degradation of $tRNA^{Leu(UUR}$ due to its decreased affinity towards Leucyl– tRNA synthetase. It's not easy to draw any conclusion at this stage as the situation is complicated. Coordinated action of two genetic sources has been involved in the biogenesis of all functional mitochondria i.e. the nuclear and mitochondrial genome. So defect in any of these genetic sources may be the contributing factor in the pathogenesis of diseases which are mitochondrial in origin. This would suggest that mutations in nuclear genome, inherited from the father or the mother, may be a high risk factor for T2D in Asian population showing no mtDNA*A*3243*G* mutation. The situation is hard to understand due to the reality that every cell possesses a large number of mitochondria and a single mitochondrion has multiple copies of the mtDNA. Hence, the level of heteroplasmy also fluctuates among the different tissues and is highest in post-mitotic tissues like brain, pancreas and skeletal muscles, and at the lowest level in the cells that divide rapidly, such as leukocyte – being the commonest source of mtDNA isolation.

It should not be excluded that differences which involve genes other than these can also contribute a lot in the causation of mitochondrial diabetes. Whole of the mitochondrial genome is susceptible to display of pathogenic mutations. Hence comprehensive and systematic detection of mutation in mitochondrial DNA requires proper sequencing of the entire mtDNA molecule. Individual susceptibility to develop mitochondrial diseases depends on the identification of genes and probing into the basic molecular events implicated in the development of T2D. This will help the doctors dealing with diabetics to develop more sensitive and accurate preventive as well as therapeutic tools.

Unfortunately, the mutation's heteroplasmy is lowest in the leukocytes in the blood and at its highest in affected tissues. So, the chances of detecting this mutation become lesser in leukocytes which might hamper detection of such mutation. Moreover, a decline of ~0.7% in heteroplasmy levels of the leukocytes is seen every year. In this case, the pancreas becomes best source of tissues for the examination and detection of A3243G mutations in patients suffering from diabetes. Yet, biopsy of pancreas is not a desirable way of routine screening. Furthermore, it is virtually impossible.

As a matter of fact, reliable and accurate mitochondrial DNA mutations detection in T2D necessitates analysis of thousands of well-defined diabetics. Large cohort studies and samples are required to be analyzed to get exact data concerning the disease and to identify the suspected diabetogenic gene mutation. The recognition and isolation of such genes requires more precise clinical characterization of the patients. This characterization should include the information about the phenotype of deafness including age of onset, severity, audiometric study, dynamics and the familial phenotypic mutations.

In conclusion, though prior clinical observations and studies have proposed role of mitochondrial dysfunctions in the advancement of T2D, the A3243G mutation in the mitochondrial $tRNA^{Leu(UUR)}$ gene could not be labeled as a chief contributing causative factor of T2D in Asian population. The clinical hallmarks observed in diabetes might be the be the consequence of a combination of numerous other mechanism or factors involved in the pathogenesis of T2D. Furthermore, larger study group screening is required to fully determine the exact prevelance of such mutation in Asian population.

Moreover, β-cell auto antibodies analysis should also be performed in all people presenting with early onset of maternally inherited T2D atages 30–45 years. Phenotypically defined subjects need to be targeted by Genetic investigations. The finding of a possible explicitetiology will allow effective and proper management of the disease and can provide patients with valuable information about the condition.

Direct sequencing of isolated mitochondrial proteins should also be done to identify alteration in the proteins primary structures and also their possible participation in diabetes inherited maternally. Studying families having non-syndromic monogenic hearing loss should lead to the improved comprehension of furthur association of hearing loss with diabetes inherited maternally.

More specific techniques should be developed to recognize novel mutations as well to investigate post mitotic tissues. This will be of great value because post mitotic tissues show highest level of heteroplasmy and make the situation more reliable and fruitful for the researcher. By this effort it would be easy to screen all those

patients who are strongly suspected to carry mitochondrial DNA mutation. Moreover, specialized centers with such techniques can be used to carry out extensive investigation for other mtDNA defects. The entire mtDNA molecule should be sequenced to rule out the occurrence of known and novel mutations. Finally, the association of maternally inherited diabetes with*A3243G*mutation needs to be confirmed by scrutinizing larger sample of Asian diabetics with phenotype of mitochondrial T2D.(51)The fundamental mechanism by which this happens is still an important issue to be investigated by the researchers.

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