ICMR CENTER FOR ADVANCED RESEARCH (CAR) IN GENOMICS OF DIABETES MADRAS DIABETES RESEARCH FOUNDATION, CHENNAI, INDIA

Background and scope

The genetics of type 2 diabetes can be considered under two broad groups: Genetics of Monogenic forms of diabetes, where a single gene is causal in the development of the disease and genetics of polygenic forms of diabetes where a number of genes are responsible for the susceptibility of the disease.
One of the important monogenic forms of diabetes, known as Maturity-Onset Diabetes of the Young (MODY), whose onset of diabetes is early and is a heterogeneous group of diabetes caused by single gene defects in at least 13 genes affecting pancreas development and beta-cell function.

MODY is often misdiagnosed as type 1 or type 2 diabetes (T2DM) as there is significant overlap in clinical features and hence the importance of genetic screening for MODY mutations. A genetic diagnosis of MODY helps in optimal treatment. Early identification and screening of family members can help to define the clinical course, and prevent the development of complications. Neonatal diabetes (NDM) is defined as diabetes, either isolated or with syndromic features, diagnosed within the first 6 months of life. NDM affects approximately 1:100,000 live births. In the case of neonatal and syndromic diabetes, the most striking clinical implication of a molecular diagnosis of mutations in certain genes is the radical change from life long insulin injections to an oral sulfonylurea (SU) drug to treat diabetes.

The earlier clinical studies reported on the high prevalence of MODY (4.8%) in Chennai (1,2). In India, genetic screening of monogenic diabetes gains importance as the common garden variety T2DM occurs a decade earlier than it does in other population. So delineation of the genetic defect at molecular level has tremendous clinical implications. However genetic testing for mutations is not available in many centers in India. With this background, the Indian Council of Medical Research (ICMR) Govt. of India funded this study, to screen patients for mutation in MODY genes and neonatal diabetes genes in order to offer clinical genetics screening services to patients in India. The study was executed at ICMR Centre for Advance Research on Genomics in Type 2 Diabetes Mellitus located at Madras Diabetes Research Foundation (MDRF), Chennai. As a continuation of the study and in order to keep the neonatal and MODY genetic screening and the training for capacity building amongst scientists going continuously, the project on “Genetic analysis of MODY and Neonatal Diabetes in India” was undertaken.

Study Methods

The Centre for Advanced Research (CAR) addressed two main components viz: research studies and training component. Under the research component, two projects were undertaken. The project entitled “Study of genes related to maturity onset diabetes of the young (MODY) and early onset diabetes” aimed at determining the prevalence of MODY in different regions of India and to screen the known MODY genes for mutation and to examine their association with the causation of the disease status in Indians. The criteria followed for MODY sample recruitment were as follows: age at onset of diabetes <25 years, absence of ketonuria at any time, family history of diabetes, negative for GAD- antibodies,

should have sufficient β-cell function and absence of acanthosis nigricans. Clinically suspected MODY patients were screened for the common MODY genes by using bi-directional Sanger sequencing method.

The second project entitled "Study of genes implicated in ion channel dysfunction in diabetes," aimed to screen the known Neonatal diabetic genes for mutations and to examine their association with the causation of the disease status in Indians. Neonatal diabetes patients with age at onset of diabetes within the first year of life were screened for the genes implicated in NDM.

Under the training component, the centre conducted Hands-on Workshops (under the aegis of ICMR – CAR) in basic and advanced genomics techniques for capacity building and transfer of technology of Scientists and Researchers of multiple centers from all over India. Approximately 150 researchers and young scientists have benefited through this program.

Key findings

Genes related to Maturity Onset Diabetes of the Young, Early Onset type 2 diabetes and neonatal diabetes were studied in this project and findings are as listed below:

1. MODY mutations were identified MODY1, 2, 3, 4, 5, 9, 11 and MODY12 genes (3-7).
2. The novel *HNF1A* gene mutation **Arg263His** was found to co-segregate with diabetes in a family. The mutant **R263H** showed complete lack of DNA binding activity which was revealed by functional studies conducted in MDRF. This therefore is a true novel MODY 3 mutation of South India, causing the disease (3).
3. Neonatal diabetes children with age at onset of diabetes less than a year were screened for *KCNJ11, ABCC8, INS GLUD1, EIF2AK3, SLC2A2, WFS1, INSR, AGPAT2, BSCL2* and *mtDNA c.3243A>G* genes. A total of 41 mutations were identified in *KCNJ11* (10), *ABCC8* (27) and *INS* genes (4) in patients with neonatal diabetes and hyperinsulinemia, which were collected from various hospitals in India. In addition, 9 mutations were identified in different genes (*AGPAT2*, *EIF2AK3, INSR*, *WFS1*, *SLC2A2*) implicated in various monogenic syndromes (8-15).
4. Patients with certain mutations in *KCNJ11* and *ABCC8* genes have been shown to respond very well to oral sulfonylurea. In this project, such mutations were identified in several patients. This genetic diagnosis has made it possible to switch these children from insulin treatment to oral sulfonylurea drugs, which is the most important translational aspect of this project (8).

Practice and Health Care Implications:

Change in treatment management in MODY patients:

Identification of an *HNF1A* or *HNF4A* gene mutation in patients with diabetes confirms a diagnosis of MODY and establishes the subtype. This information helps to predict the likely clinical course in MODY patients. Patients with MODY caused by mutations in *HNF1A* and *HNF4A* genes are sensitive to low-dose sulfonylureas and those with *GCK* mutations do not require pharmacological treatment.

Change in treatment management in NDM patients:

In the case of Neonatal and syndromic diabetes, the most striking clinical implication of molecular diagnosis of a KATP channel mutation is the radical change from insulin injections to an oral sulfonylurea (SU) drug to treat diabetes. Most of the patients carrying a *Kir6.2* or *SUR1* mutation retain sensitivity to SU but the effectiveness of oral SU treatment is determined by the nature of the mutations. These findings represent a remarkable example of successful genomic medicine, in that knowledge of the mutation can be translated from "Bench to bedside" and can definitively improve both patient care and the patient's long-term condition.

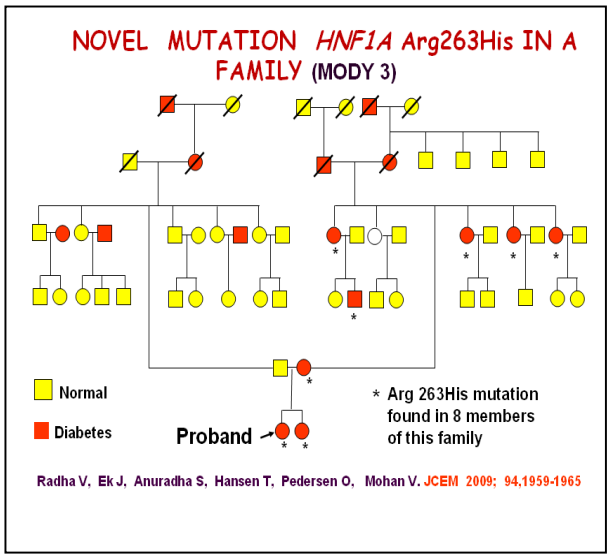
Creation of Monogenic Diabetes Registry

A website ***http://www.neonataldiabetes.in*** called "**Neonatal and Monogenic Diabetes Registry**" has been created, where the doctors can get a neonatal or a MODY case registered and also request the MODY and NDM genetic testing for their patients. The purpose of this registry is to follow these people over time to learn more about monogenic forms of diabetes.

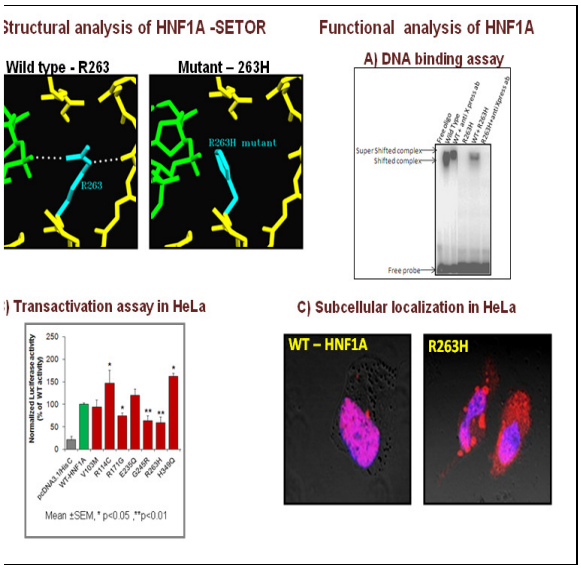
Next Steps:

- As a follow up of the research findings mentioned above under two phases of the ICMR funded projects, proposing to expand the screening of genetic abnormalities involved in the etiology of NDM, monogenic syndromes and HI and the all the subtypes of MODY for the patients referred to centre from all over India with a view to establish a national referral centre for genetic screening as this is much needed in India and which has direct translational application.

"Novel MODY 3 mutations in a South Indian family. The functional investigations proved this mutation to be a casual for MODY phenotype"



Successful transfer from insulin injection to oral sulphonylurea tablet in a child with neonatal diabetes identified to have KCNJ11 Gly334Val mutation. This validated the translational potential of genetic



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*[References marked with a * were directly under the research work done at the support of the Advanced Centre"]*

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