In order of importance, list of ten best papers of the candidate, highlighting the important discoveries/contributions described in them briefly

1. Kavitha B, Ranganathan S, Gopi S, Vetrivel U, Hemavathy N, Mohan V, **Radha V**. Molecular characterization and re-interpretation of HNF1A variants identified in Indian MODY subjects towards precision medicine. Front Endocrinol (Lausanne). 2023; 14:1177268.

This paper highlights the importance of functional investigations that offer substantial support for classifying a variant as pathogenic or otherwise and this helps in reporting the discovered variants as either clinically actionable or not.

To explain the context, this study was performed on a cohort of clinically proven Maturity Onset Diabetes of the young (MODY) subtype, the hepatocyte nuclear factor 1A (*HNF1A*) subtype, which is the most prevalent subtypes of monogenic forms of diabetes that results due to mutation in a single gene. There are about 10 subtypes of MODY caused by mutations in 10 different genes. The *HNF1A* gene, is an essential component of the transcription factor network that controls pancreatic β-cell differentiation, maintenance, and glucose stimulated insulin secretion (GSIS). Mutations in the genes that cause Maturity-Onset Diabetes of the Young (MODY) are clinically important because they help determine the best treatment and prognosis for patients. Functional investigations helps in classifying a variant as pathogenic(P),likely pathogenic (LP), Variants of Uncertain Significance (VUS), Likely Benign(LB) or Benign(B) and reporting the discovered variations as relevant in clinical diagnosis.Functional evaluation of the *HNF1A* variants is necessary to better predict the pathogenic effects and to improve the diagnostic interpretation and treatment.

With this in the background, the objective of the work was to determine the molecular basis for the variations in the *HNF1A* gene found in patients with monogenic diabetes in India.We used a suite of molecular biology techniques and structural biology and bioinformatic analyses. Patients harboring the pathogenic/likely pathogenic variants were able to successfully switch from insulin to sulfonylureas (SU) making these variants clinically actionable. As given in the table below, we were able to demonstrate that some of the variants had to be re interpreted, proving that functional evaluation can improve the bioinformatics interpretation of the pathogenicity of 14 *HNF1A.*

S.No	Amino acid change at protein level	Variant Interpretation_ ACMG guidelines 2015	Functional Study								Structural Prediction			Reinterpation Based on functional evidence	Clinical Actionability
			Transactivation Assay (% WT)		DNA Binding Activity (% WT)	Protein Expression (% WT)	Nuclear Localisation (% WT)	GSIS (Insulin Levels)			Sequence Based Prediction	Structure Based predic- tion	Molecular Dynamics		
			HeLa	Ins 1				Basal	Stimulated	On adding 100µM GBC					
1	p.K120N	VUS	47	90	92	76	81	5	4	15	Destabilization effect	Higher Destabilization effect	Defect	LP	Actionable
2	p.Q125H	VUS	53	52	103	67	77	9	4	32	Destabilization effect	Least Destabilization effect	–	LP	Actionable
3	p.N127del	VUS	23	58	21	66	57	7	5	19	–	–	–	P	Actionable
4	p.V134I	VUS	38	32	38	75	71	8	1	21	No defect	Least Destabilization effect	–	LP	Actionable
5	p.R200W	VUS	27	84	32	71	67	5	2	19	Destabilization effect	Higher Destabilization effect	No defect	P	Actionable
6	p.R272H	LP	26	59	31	91	84	7	4	19	Destabilization effect	Higher Destabilization effect	Defect	P	Actionable
7	p.G292fs*25	LP	18	55	23	58	98	9	4	31	–	–	–	P	Actionable
8	p.A301T	VUS	105	123	105	54	75	8	45	48	–	–	–	B	_
9	p.T354M	VUS	62	57	118	97	71	5	2	11	–	–	–	LP	Actionable
10	p.A367V	VUS	61	56	130	87	76	3	8	8	–	–	–	VUS	Unresolved
11	p.P379S	LP	42	75	125	80	65	15	5	37	–	–	–	LP	Actionable
12	p.D602N	VUS	51	72	115	68	95	3	11	11	–	–	–	VUS	Unresolved
13	p.L611P	VUS	45	137	112	76	71	5	7	25	–	–	–	LP	Actionable
14	p.E619K	VUS	97	90	97	81	60	6	16	11	–	–	–	VUS	Unresolved

In summary, this is the first large and detailed genetic and functional investigation of *HNF1A* variants in the Indian MODY population. A functional evaluation should henceforth be included in the diagnostic work-up of any *HNF1A* variant in medical genetic departments, and particularly for variants where the family history or clinical data are not available or inconclusive. This would aid clinicians in determining the correct treatment for patients, since having a genetic diagnosis and functional understanding leads to discontinuation of unnecessary treatment for some patients and switching from injectable insulin treatment to convenient oral tablet with excellent glycemic control in others. This therefore is a hallmark study in India in precision diabetes and precision treatment in India.

2. Gopi S, Kavitha B, Kanthimathi S, (…), Raghupathy P, Mohan V, **Radha V**. Genotype-phenotype correlation of KATPchannel gene defects causing permanent neonatal diabetes in Indian patients. Pediatr Diabetes. 2021;22 (1):82-92

This is the first, largest study describing the spectrum of mutations in KATP channel NDM in India. It has demonstrated the importance of KATP channel gene screening in PNDM and efficacy of sulfonylurea for Indian patients with KATP-PNDM.

ATP-sensitive potassium channels (K_{ATP} channels) regulate insulin secretion from pancreatic β-cells by closing in response to metabolically generated ATP.Gain of function mutations in the genes encoding either of the two types of K_{ATP} channel subunit (Kir6.2 and SUR1) result in neonatal diabetes mellitus, whereas loss-of-function mutations cause hyperinsulinaemic hypoglycaemia of infancy. Gain of function mutations of KATP channel genes namely *KCNJ11* and *ABCC8* are most predominant cause of permanent neonatal diabetes mellitus (PNDM). There are very few reports pertaining to Indian patients with neonatal diabetes mellitus (NDM).This paper describes our important work in identifying the genotype-phenotype correlation of KATP channel gene defects in a large series of (n = 181) Indian PNDM patients.Direct gene sequencing of all exons of KCNJ11 and ABCC8 genes in all 181 patients with PNDM were performed. Clinical and biochemical data were collected.Extensive pedigree data were collected and analysed.

We identified the molecular defects in 22% of the PNDM patients. The severity of the disease phenotype is known to reflect the channel dysfunction. All the *KCNJ11* mutations identified in this study were PNDM or DEND syndrome. A prominent feature among patients with *KCNJ11* mutations is that some of them manifest neurological dysfunction. In our series, three patients manifested DEND syndrome; two with V59M mutation and one with V64M mutation. The severity of

developmental delay and epileptic seizures were greater in the patient with V64M compared to V59M.

With regard to ABCC8 gene, we identified four novel mutations, all of them lying in regions of the gene that form critical site for potassium channel opener and is both physically and functionally important region. We have functionally characterized two of these mutations, namely. D212Y, R992C. Both these mutants were inhibited by the KATP channel inhibitors glibenclamide and carbamazepine which paved the way for us to transfer the patients with these mutations from Insulin injections to oral Sulphonylurea drugs.

This study is significant in many ways. This is the largest study describing the spectrum of mutations in KATP channel NDM in India. It has demonstrated the importance of KATP channel gene screening in PNDM and efficacy of sulfonylurea for Indian patients with KATP-PNDM. Further, the reported rate of KATP channel mutations is much lesser in proportion in Indians compared to Caucasian and Japanese populations. The unknown genetic aetiology in about 78 % of PNDM patients underscores the importance of investigating non KATP channel genes as well as the urgent need to search for novel genes and genetic aetiology of NDM in this population. This paper is a landmark paper as it truly describes and demonstrates the translation research from Bench to Bedside in clinical Practice.

3. Jahnavi S, Poovazhagi V, Mohan V, (…), Njolstad P, Unnikrishnan R, **Radha V**. Clinical and molecular characterization of neonatal diabetes and monogenic syndromic diabetes in Asian Indian children. Clinical Genetics, 2014: 83: 439–445.

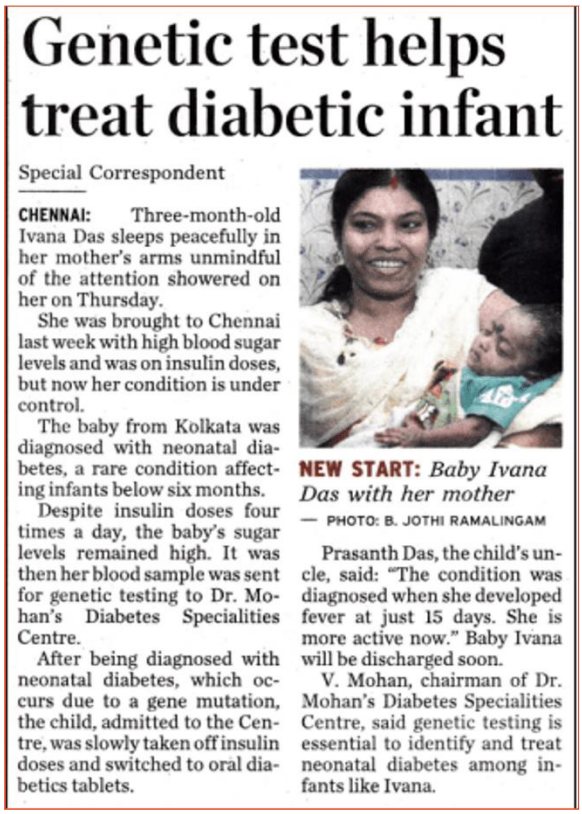
At a time when there were just four isolated case reports on neonatal diabetes from India, we presented the first large genetic screening study of neonatal diabetes through this paper. More significantly, we also shifted children with KCNJ11 and ABCC8 mutations from insulin injections to oral drugs.

This paper described the clinical presentation and molecular characterization of Asian Indian children with neonatal diabetes and monogenic syndromes of diabetes. Mutations in the pancreatic ATP sensitive K+ channel proteins [sulfonyluea receptor 1 (SUR1) and inward rectifier K+ channel Kir6.2 (Kir6.2), encoded by ATP-binding cassette transporter subfamily C member 8 (ABCC8) and potassium channel J11 (KCNJ11), respectively], are the most common cause of neonatal diabetes. We sequenced *KCNJ11*, *ABCC8* and *INS* genes in 33 unrelated Indian probands with onset of diabetes below one year of age. A total of 12 mutations were identified which included seven *ABCC8* mutations, three *KCNJ11* mutations and two *INS* mutations. The Asp212Tyr mutation in *ABCC8* was novel. We also detected two

novel mutations (Val67Met in *AGPAT2* and Leu19Arg in *SLC2A2*) in children with syndromic forms of diabetes like Berardinelli Seip syndrome and Fanconi Bickel syndrome respectively. We also successfully shifted the children with *KCNJ11* (Cys42Arg and Arg201Cys) and *ABCC8* (Val86Ala and Asp212Tyr) mutations from insulin therapy to sulfonylurea treatment using an inpatient-based short transfer protocol.

4. **Radha V,** Ramya B, Gopi S, (…), Unnikrishnan R, Mohan V, Gupta PK. Successful transition to sulphonylurea therapy from insulin in a child with permanent neonatal diabetes due to a KCNJ11 gene mutation. J. of Diabetology (2018) 9(2):65-67.

This was a case report on a 3-month old baby girl from Kolkata with neonatal diabetes (NDM) who was shifted from insulin to sulfonylurea, based on the genetic diagnosis made in our lab and this case attracted much of the media attention as well.



Genetic test helps treat diabetic infant

Special Correspondent

CHENNAI: Three-month-old Ivana Das sleeps peacefully in her mother's arms unmindful of the attention showered on her on Thursday.

She was brought to Chennai last week with high blood sugar levels and was on insulin doses, but now her condition is under control.

The baby from Kolkata was diagnosed with neonatal diabetes, a rare condition affecting infants below six months.

Despite insulin doses four times a day, the baby's sugar levels remained high. It was then her blood sample was sent for genetic testing to Dr. Mohan's Diabetes Specialities Centre.

After being diagnosed with neonatal diabetes, which occurs due to a gene mutation, the child, admitted to the Centre, was slowly taken off insulin doses and switched to oral diabetics tablets.

NEW START: *Baby Ivana Das with her mother*
— PHOTO: B. JOTHI RAMALINGAM

Prasanth Das, the child's uncle, said: "The condition was diagnosed when she developed fever at just 15 days. She is more active now." Baby Ivana will be discharged soon.

V. Mohan, chairman of Dr. Mohan's Diabetes Specialities Centre, said genetic testing is essential to identify and treat neonatal diabetes among infants like Ivana.

డాక్టర్ మోహన్స్ డయాబెటిస్‌లో అరుదైన చికిత్స

విలేకరుల సమావేశంలో మాట్లాడుతున్న డాక్టర్ మోహన్

కొరుక్కుపేట:

డాక్టర్ మోహన్స్ డయాబెటిస్ స్పెషాలిటీస్ సెంటర్‌లో పుట్టిన 15 రోజుల శిశువుకు అరుదైన చికిత్స చేశారు. పుట్టుకతోనే న్యూయోనేటల్ డయాబెటీస్‌తో బాధపడుతున్న ఆ శిశువుకు ఇన్సులిన్, ఓరల్ యాంటీ డయాబెటిక్ ట్యాబ్లెట్స్‌తో చికిత్స చేసి సాధారణ స్థితి తీసుకు వచ్చినట్లు డాక్టర్ మోహన్స్ డయాబెటిస్ ఆస్పత్రి నిర్వాహకులు మద్రాసు డయాబెటిస్ రీసెర్చ్ ఫౌండేషన్ ప్రెసిడెంట్ డాక్టర్ వి.మోహన్ పేర్కొన్నారు. ఈ మేరకు గురువారం స్థానిక గోపాలపురంలోని డాక్టర్ మోహన్స్ డయాబెటిస్ ఆస్పత్రిలో విలేకరుల సమావేశం నిర్వహించారు. డాక్టర్ మోహన్ మాట్లాడుతూ కోల్‌కతాకు చెందిన ఆడశిశువు పుట్టుకతోనే జ్వరం రావటంతో పరీక్షలు చేయగా హైబ్లడ్ షుగర్ ఉన్నట్లు గుర్తించిన వైద్యులు తమ ఆస్పత్రి డాక్టర్ మోహన్ స్పెషాలిటీస్ సెంటర్‌కు వెళ్లాలని శిశువు తల్లిదండ్రులకు సూచించారని తెలిపారు. దీంతో ఇక్కడకు చేరుకున్న 15 రోజుల శిశువుకు జెనిటిక్ పరీక్షలు నిర్వహించగా న్యూయోనేటల్ డయాబెటిస్ (కెసిఎన్ జె11) ఉన్నట్లు గుర్తించామని దీంతో ప్రతి రోజు తక్కువ మోతాదులో ఓరల్ యాంటీ డయాబెటిక్ ట్యాబ్లెట్లతో పాటుగా ఇన్సులిన్ ఇచ్చామని అన్నారు. ఇన్సులిన్ తగ్గిస్తూ చికిత్స అందించగా శిశువు 382 ఎంజి/డిఎల్ ఉన్న బ్లడ్ షుగర్ లెవల్స్ క్రమంగా మూడు రోజులకు 84 ఎంజి/డిఎల్‌కు తగ్గించామని అన్నారు. మూడు రోజుల తరువాత ప్రస్తుతం శిశువుకు బ్లడ్ షుగర్ సాధారణ స్థితికి చేరుకుందన్నారు. చిన్నపిల్లల్లో జెనిటిక్ సమస్యల వల్ల అరుదుగా న్యూయోనేటల్ డయాబెటిస్ వస్తుంటాయన్నారు. ప్రారంభ దశలో గుర్తించగలిగితే ఖచ్చితంగా నయం చేయవచ్చన్నారు. పుట్టిన ఆరు నెలల్లోపు శిశువుకు ఖచ్చితంగా జెనిటిక్ పరీక్షలు చేయించాలని వివరించారు.

NDM is a monogenic form of diabetes mellitus that occurs in the first 6 months of life. A 3-month-old girl child presented with uncontrolled high blood glucose levels. She was on multiple daily insulin (MDI) treatment, but glycaemic control remained poor. Genetic analysis of NDM associated genes, revealed the presence of a heterozygous mutation p. Gly334Val (p. G334V) in *KCNJ11* gene, which has earlier

been shown to be associated with response to sulfonylurea therapy. The child was started on glibenclamide, a dose of 0.6 mg/kg/day initially and was increased to 1 mg/kg/day, and the insulin was tapered off and eventually stopped. The blood glucose levels were well maintained with the oral sulfonylurea therapy. This work is a demonstration of successful transition from insulin to oral drugs and precision diabetes.

5. Balamurugan K, Kavitha B, Yang Z, Mohan V, **Radha V**, Shyng SL (2019) Functional characterization of activating mutations in the sulfonylurea receptor 1 (ABCC8) causing neonatal diabetes mellitus in Asian Indian children. Pediatr Diabetes. 20(4):397-407.

This was the first functional characterization study from Indian NDM children carrying activating mutations in ABCC8 gene and the study offered insights into the mechanistic basis of genotype-phenotype relationships.

Gain-of-function of ATP-sensitive K+ (KATP) channels because of mutations in the genes encoding SUR1 (*ABCC8*) or Kir6.2 (*KCNJ11*) is a major cause of neonatal diabetes mellitus (NDM). The purpose of this study was to determine molecular defects in KATP channels caused by *ABCC8* mutations in Asian Indian children with NDM by *in vitro* functional studies. The processing efficiency and surface expression of the mutant channels and their response to intracellular ATP and ADP were analysed. Five SUR1 missense mutations, D212Y, P254S, R653Q, R992C, and Q1224H altered channel response to intracellular nucleotides to enhance channel activity, and two mutations, D212Y and P254S, also severely impaired channel biogenesis and surface expression. The novel finding that two L0 mutations have a profound effect on channel sensitivity to ATP inhibition, combined with recent high resolution structures of the channel, sheds new light on the importance of SUR1-L0 in ATP-induced Kir6.2 channel closure.

6. DeForest N, Kavitha B, Hu S, (…), Olefsky J, **Radha V,** Majithia AR. Human gain-of-function variants in HNF1A confer protection from diabetes but independently increase hepatic secretion of atherogenic lipoproteins. Cell Genom. 2023; 3(7):100339.

This is one of the unique, pioneering work where we have performed functional experiments to understand the causal role of gene variants at a larger scale. It emphasizes the need to use high throughput techniques and shows how to implement them in monogenic diabetes to help in clinical practice.

Hepatocyte nuclear factor 1 alpha (HNF1A) is a lineage-determining transcription factor expressed in several tissues including the liver and pancreas. Rare, complete loss-of-function (LOF) mutations in *HNF1A* have been shown to cause an autosomal dominant monogenic form of diabetes (MODY3) through deficiencies in pancreatic insulin secretion via a haploinsufficient genetic mechanism. Population based genetic association studies have corroborated associations between HNF1A and T2D, serum lipoproteins, and hsCRP12 but do not provide insight into mechanism, as most of the associated variants (SNPs) have minimal experimentally observable consequences on protein function.

To address this gap in knowledge, we examined the full allelic series of protein-coding variants in HNF1A using deep mutational scanning, a high-throughput approach that has been successfully utilized to characterize protein-coding variants in clinically important genes. All possible single amino acid substitutions in HNF1A were tested for transcriptional activity in human hepatocytes. These comprehensive data were analyszed together in order to relate variant to function to phenotype for metabolic disease-associated factors and disease outcomes including T2D and CAD. We discover gain-of-function (GOF) variants that, while conferring protection from T2D, promote pro-inflammatory/thrombogenic gene expression and an atherogenic lipid profile through liver specific enhancement of *HNF1A* target genes.This is a very unique work as for the first time in the world the entire gene has been studied by saturation mutagenesis. The outcome of the study shows that such prospective studies can be performed in all the clinically relevant diabetes disease genes helping in sharp and precise treatment.

7. Wall JD, Stawiski E, Ratan A, (...), **Radha V**, Mohan V, Majumder PP, Seshagiri, Seo SJ, Schuster S, Peterson AS (2019). The Genome Asia 100K Project: Enabling Genetic Discoveries across Asia. Nature 576(7785):106-111.

The invitation to join the GenomeAsia consortium is one of the greatest recognitions to the work done at my Molecular Genetics lab. The paper above describes the formation of the GenomeAsia consortium and the pilot phase of the GenomeAsia 100K Project in which we participated.

The underrepresentation of Asians in human genetic studies limited the diversity of individuals in genomic datasets and led to reduced medical relevance for a large proportion of the world's population. Population-specific reference genome datasets that would be useful for the complex populations of Asia led to the formation of the GenomeAsia consortium (http://www.genomeasia100k.com). The consortium serves to facilitate and coordinate sequencing efforts among consortium members to

maximize the value of the genomic sequence data that is produced and to facilitate efforts by national or other regional groups. The ultimate goal of the project is to provide a useful genomic resource and facilitate genetic studies in Asia.
The GenomeAsia Pilot (GAsP) project analysed the whole-genome sequencing data of 1,739 individuals from 219 population groups across Asia including 598 sequences from India. The data that was generated in this pilot study was used to analyse population structure and history, disease associations and founder effects. The data showed that the South Asian ancestry is enriched for putative loss of function (pLOF) variants, with number of novel homozygous protein truncating variants identified varying largely across the various South Asian groups. Some South Asian groups demonstrated strong genetic founder effects. Many novel cancer predisposing variants were identified in the GenomeAsia dataset. Upon evaluation of the utility of the pilot dataset for imputation, it was found that the GAsP reference panel had imputation accuracies ranging from 93 to 95%. To accelerate evaluation and broad utility, the data has been placed on the Michigan Imputation Server. The GenomeAsia project formed the basis for many larger-scale genomic studies in Asia and worldwide.

8. **Radha V,** Ek J, Anuradha S, Hansen T, Pedersen O, Mohan V. Identification of novel variants in the hepatocyte nuclear factor-1alpha gene in South Indian patients with maturity onset diabetes of young. J Clin Endocrinol Metab. 2009; 94(6):1959-65.

This was one of the first systematic studies on HNF1A gene mutations in Maturity-onset diabetes of the young (MODY) patients from South Asia. It showed that HNF1A gene comprises about 9% of clinically diagnosed MODY subjects in southern India.

Mutations in the HNF 1A gene are the most common cause of MODY in most populations. The aim of the study was to analyse what percentage of patients classified clinically as MODY have mutations of HNF1A gene and to look for novel gene mutations in our south Indian population. The HNF1A gene was sequenced in 96 unrelated south Indian subjects who were clinically classified as MODY. Nine novel variants comprising seven mutations (one novel mutation -538G>C in promoter region and six novel coding region mutations) and two polymorphisms were identified in the HNF1A gene. Functional studies revealed reduced transcriptional activity of the *HNF1A* promoter for the promoter variant. Two important findings from this work are that mutations in the *HNF1A* gene (MODY 3 subtype) comprise about 9% of clinically diagnosed MODY patients in south Indian

population and that there are several previously undescribed novel variants in the HNF1A gene in our population of which one novel coding region mutation Arg263His cosegregates with MODY in a family of 30 individuals.

9. Jahnavi S, Poovazhagi V, Kanthimathi S, (…), Kaur T, Mohan V, **Radha V**. Novel ABCC8 (SUR1) gene mutations in Asian Indian children with Congenital hyperinsulinemic hypoglycemia. Annals of Human Genetics, 2014: 78: 311–319.

This was the first study which reported on the genetics of Congenital hyperinsulinemic hypoglycemia in Asian Indian children.

Congenital hyperinsulinemic hypoglycemia (CHI) is a genetic disorder of pancreatic β-cell characterized by persistent hypoglycemia due to unregulated secretion of insulin. Inappropriate management may result in seizures, brain damage and death and therefore, the disorder requires immediate detection and treatment. This study screened 22 Asian Indian children with CHI for mutations in the genes that are most commonly associated with CHI (*KCNJ11*, *ABCC8*, *GCK*, *HNF4A* and *GLUD1*). Molecular abnormality was identified in 45.4% of the study population and all the mutations were present only in the *KCNJ11* and *ABCC8* genes. There were ten novel and two known mutations in the *ABCC8* gene. Mutations were identified in 88.9% of diazoxide unresponsive cases and in 11.1% of children who were treated with diazoxide. Most of the children (58.3%) who were not harbouring mutations in any of the genes studied responded well to pharmacological therapy, whereas true diazoxide responsiveness was not seen in children with mutations. We showed that genetic testing assists in understanding the nature of the molecular abnormality and in most cases the timely prediction of the type of hyperinsulinemia is likely to aid in avoiding hypoglycemia related brain damage.

10. Kavitha B, Srikanth K, Singh D, Gopi S, Mohan V, Chandra N, **Radha V**. A novel stop-loss mutation in NKX2-2 gene as a cause of neonatal diabetes mellitus: molecular characterization and structural analysis. Acta Diabetol. 2024;61(2):189-194.

This was the first study to report a stop loss mutation in NKX2-2 gene leading to NDM. This is also the first study where functional characterization and structural studies were performed to understand the biological effect of this mutation.

The aim of the study was to identify the genetic etiology of neonatal diabetes in an infant and to elucidate the molecular mechanism of the identified mutation underlying the pathogenesis. Direct sequencing of known etiological genes of NDM and syndromic forms of NDM such as *ABCC8*, *KCNJ11*, *INS*, *GCK*, *PDX1*,

EIF2AK3, *WFS1*, *NKX2-2*, *RFX6* and *AGPAT2* was performed. A novel homozygous frameshift mutation c.772delC, p.Q258SFs*59 in the *NKX2-2* gene was identified in this patient with neonatal diabetes. This mutation leads to translation of elongated protein sequence of 42 amino acids due to the loss of termination codon. Functional studies revealed that this elongated protein is likely to be involved in the disruption of secondary structure of protein leading to reduced DNA binding activity of the protein which in turn leads to reduced transactivation of target gene such as *GLUT2*, which in turn leads to reduced insulin secretion causing hyperglycemia. Structural analysis suggested alterations in the protein's tertiary structure, likely contributing to its dysfunction. These findings emphasize the importance of functional and structural characterization to understand the biological consequences of such mutations. This comprehensive analysis provides insights into the molecular mechanisms underlying NDM and its clinical phenotype, which may aid in better diagnosis and management of patients with similar variants in the future.