

Clinical and genetic characteristics and therapeutic challenges in an infant with neonatal diabetes due to NKX2.2 mutation

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Introduction:

- Neonatal Diabetes Mellitus (NDM), is a rare disease presenting with persistent hyperglycemia requiring insulin therapy prior to 6 months of life¹.
- Within consanguineous Arab populations, the commonest etiologies for NDM differ from the ones in Caucasians².
- Treating a low weight infant with neonatal diabetes may be a challenging and frustrating process

Objective:

- To define the genetic etiology of a unique presentation of NDM in a SGA infant of consanguineous Palestinian parents.
- To elucidate the significant therapeutic and diagnostic challenges in the management of an extremely low birth weight (1.080 Kg) infant with early severe NDM..

Methods:

- Genetic studies: homozygosity mapping, sequencing of ABCC8, KCNJ11, INS and EIF2AK3 genes and exome sequencing.
- Therapeutic trials: continuous intravenous insulin, sulphonyl urea, subcutaneous Long Acting Insulin Analogues (LAIA) and continuous subcutaneous insulin (pump).

Results:

Homozygosity mapping identified three candidate genes: INS gene, RFX6 gene, and SLC19A2 gene but direct sequencing did not confirm any mutations in these genes. Exome sequencing revealed a c.356delG,p.P119 fs mutation in the NKX2-.2 gene (Figure 1). NKX2-2 is expressed in the CNS and pancreas and required for the final differentiation of pancreatic beta cells in mice. NKX2-2 mutation causes neonatal diabetes in human³.

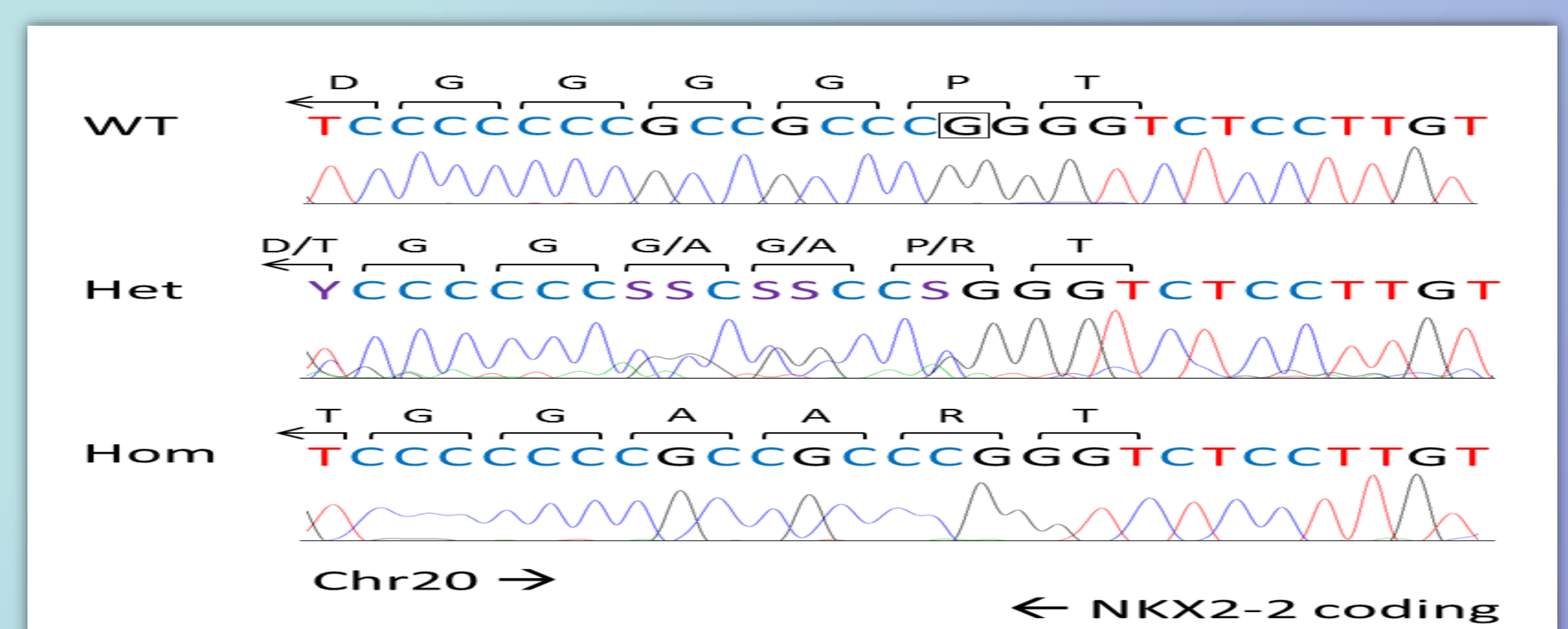
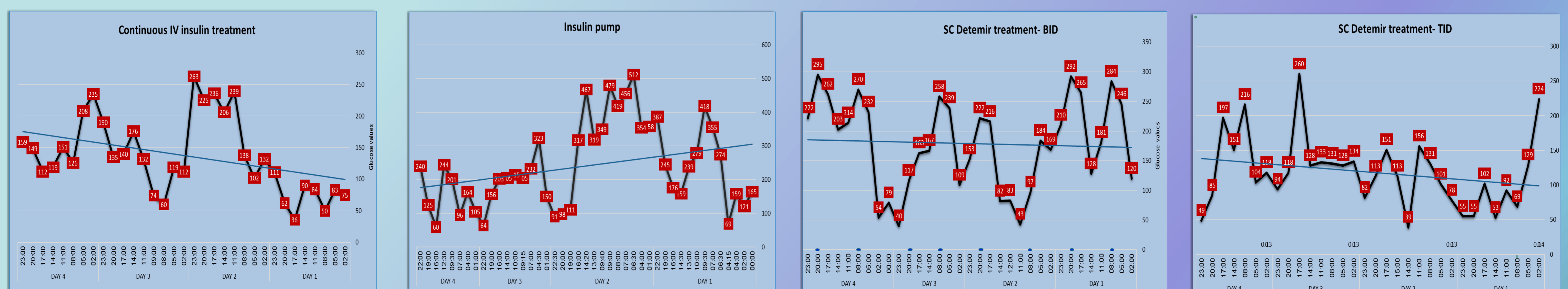


Figure 1: Sanger sequencing of NKX2-2 c.356delG p.P119fs mutation in genomic DNA of WT, heterozygote and homozygote individuals. Nucleotides and amino acid residues are indicated above the sequence chromatogram, c.356delG variant position is surrounded in a black box. Arrows below the sequence chromatograms indicate the coding of NKX2-2 from the negative strand of chromosome 20.

Therapeutically, the thin subdermal fat tissue in this case limited the use of insulin pump or continuous glucose monitoring. Sulphonylurea treatment showed no benefit, while the most non-fluctuate glycemc control was achieved by 3 daily doses of Long Acting Insulin Analogues (LAIA).



Glucometer readings at different modalities of insulin therapy :

A. Continuous IV insulin treatment (0.01-units/kg/hour) - unpredicted values, requiring frequent suspensions of insulin administration, resulted in severe hyperglycemia. **B. Continuous SC infusion by insulin pump** - prominent variability between reasonable glucose values and extreme hyperglycemia, technical issues attributed to thin sub-dermal fat. **C. Subcutaneous Detemir treatment (0.3 units/Kg/day) in 2 divided doses.** (Blue Dots=Detemir injections)- hyperglycemia prior and hypoglycemia following Detemir administration. **D. Subcutaneous Detemir treatment (0.3-0.4 units/day) in 3 divided doses-** reasonable glucose values, lower variability and possibility for home discharge.

Faster activity and shorter half life time of Detemir in very small infants with thin sub-dermal fat tissue should be considered

Conclusions

- The **c.356delG, p.P119fs** NKX2.2 mutation is associated with a severe IUGR and early extreme glucose instability.
- If insulin is required in these severe SGA cases LAIA in few daily doses are the optimal choice.
- As NDM in very low birth weight infants is a difficult therapeutic challenge a genetic diagnosis maybe mandatory for optimal choice of treatment modality.

¹ De León DD, Stanley CA. Permanent Neonatal Diabetes Mellitus. GeneReviews®[Internet]. Pagon RA, Adam MP, Ardinger HH, et al., editors. Seattle (WA): University of Washington, Seattle; 1993-2016.

² Habeb AM, Flanagan SE, Deeb A, Al-Alwan I, Alawneh H, Balafrej AA, Mutair A, Hattersley AT, Hussain K, Ellard S. Permanent neonatal diabetes: different aetiology in Arabs compared to Europeans. Arch Dis Child. 2012 Aug;97(8):721-3.

³ Flanagan SE, De Franco E, Lango Allen H, Zerah M, Abdul-Rasoul MM, Edge JA, Stewart H, Alamiri E, Hussain K, Wallis S, de Vries L, Rubio-Cabezas O, Houghton JA, Edghill EL, Patch AM, Ellard S, Hattersley AT. Analysis of transcription factors key for mouse pancreatic development establishes NKX2-2 and MNX1 mutations as causes of neonatal diabetes in man. Cell Metab. 2014 Jan 7;19(1):146-54.