TITLE

Clinical characteristics and long term follow up of 17 patients with permanent neonatal diabetes due to PTF1A distal enhancer mutations

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OBJECTIVES

•Pancreas transcription factor 1 alpha (PTF1A), encoded by *PTF1A* gene is a beta helix loop (bHLH) protein

•Involves in the development of pancreas and cerebellar neurogenesis.

•Mutations of *PTF1A* cause permanent neonatal diabetes (PNDM), pancreas agenesis and cerebellar agenesis,

•*PTF1A* enhancer mutations have been reported to cause PNDM and isolated pancreas agenesis.

•We evaluate the phenotype and genotype characteristics and long-term follow up of 17 patients with PNDM and isolated pancreas agenesis due to *PTF1A* distal enhancer mutation.

METHODS

- Neonatal diabetes was defined as diabetes presented within the first 6 months of life.
- Presenting clinical and biochemical characteristics were reviewed from the hospital files of the patients.
- A molecular genetic analysis was performed to all the patients and their parents who a DNA sample was available.
- The latest growth, developmental milestones and metabolic characteristics were re-evaluated once applicable.

Table 1. Presenting and follow up characteristics of 17 cases with distal enhancer PTF1A mutation

	Median	Range (Min-max)
Age of diagnosis (day)	6.5	1-60
Gestational age (week)	36	28-40
Birth weight (SDS)	-3.1	-6.67-0.24
Blood glucose at presentation (mg/dl)	406	242-800
C-peptid (ng/ml)	0.1	0.01-0.5
Current age (months)	39.5	8-115
Ferritin (mg/dl)	1562	451-2000
Latest height (SDS)	-2.52	-4.17-(-0.99)
Curent insulin dose (U/kg/day)	0.8	0.5-1.0
Latest HbA1c (%)	9.9	8.0-12.1

RESULTS

- Number of patients recruited was 17.
- Presenting and follow up characteristics of patients are summarized in Table 1
- Majority of cases had severe IUGR
- Birth weight SDS was negatively correlated with gestational age (r=0.827; p=0.000).
- All patients had clinical signs of exocrine pancreas insufficiency and pancreas agenesis/hypoplasia in radiological imaging.
- A low faecal elastase was measured in 8 out of 9 patients.
- Insulin therapy and pancreas enzyme replacement were introduced to all patients.
- A transient, but **markedly elevated ferritin level** was detected in all patients who ferritin levels had been measured at the neonatal period.
- In the molecular genetics analysis, the most common mutation was (Figure 1);
- *PTF1A* distal enhancer g.23508437A>G which was detected in 12 cases.
- *PTF1A* distal enhancer g.23508363A>G mutation was detected in 2 cases,
- *PTF1A* distal enhancer g.23508365A>G in 2 cases
- *PTF1A* distal enhancer g.23508336G>T mutation in a single case

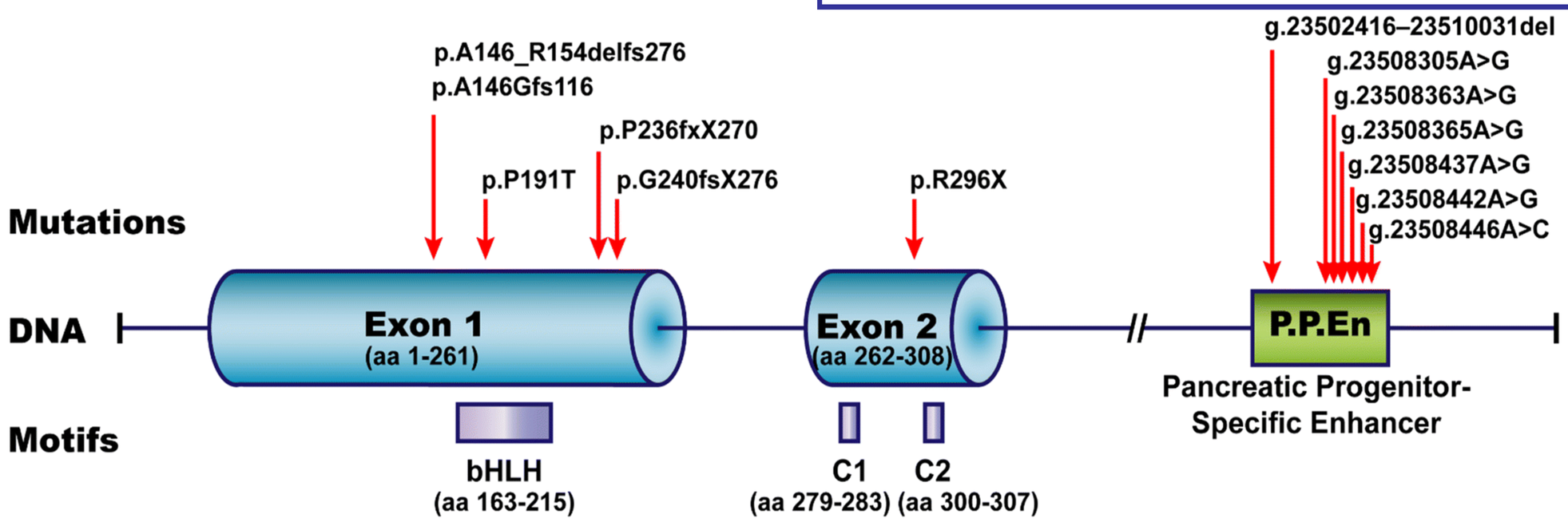

Figure 1. PTF1A gene motif and sites of mutations detected so far

CONCLUSIONS

- In this large series of 17 cases with PNDM due to homozygous distal enhancer *PTF1A* mutations, presence of severe IUGR, isolated pancreas agenesis/hypoplasia and exocrine pancreas insufficiency in all cases suggested a good phenotype-genotype correlation.
- Although was not measured in all subjects, **markedly elevated ferritin level** and its role in the phenotype of patients remain unknown and require to be further elucidated.
- Finally, although, all were replaced using pancreas enzyme, majority of cases failed to catch up growth.
- This can be attributed to poor compliance to the enzyme replacement, but, still requires further investigations to clarify the underlying exact mechanism

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Fetal, neonatal endocrinology and metabolism (to include hypoglycaemia)

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