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Review Article

# Neonatal diabetes with complete agenesis of the pancreas: new missense mutation of the gene PDX1

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## ABSTRACT

The purpose of this original clinical case is to report for the first time in the literature a new PDX1 missense mutation, p.(Arg175Leu) associating resulting in complete agenesis of the pancreas with a Neonatal Diabetes exocrine pancreatic insufficiency.

## INTRODUCTION

Neonatal diabetes mellitus (NDM) has an estimated incidence of 1: 300 000 to 1: 400 000 live births [1]. Mutations in the genes KCNJ11, ABCC8 and INS account for nearly 70% of the single-gene causes of permanent neonatal diabetes mellitus [2]. PDX1 mutations are a rare cause of NND permanent neonatal diabetes which can be isolated or associated with pancreatic agenesis [3]. The authors reports a case of permanent neonatal diabetes with involvement of the exocrine pancreas secondary to complete pancreatic agenesis

## CLINICAL CASE

S.H. , is a female infant 3rd of 3 sibling (two healthy sisters) from consanguineous parents, with a well-followed pregnancy, conducted at 36 WA with cesarean delivery for intrauterine growth retardation (IUGR), Birth weight was= 1300gThe father of S.H. insulin was diagnosed with diabetes at the age of 31 years and on insulin treatmentH. was hospitalized at birth in a neonatal unit for hypotrophy with a hyperglycemia detected the first day of lifeShe was initially treated with regular insulin only for 4 months for hyperglycemia as part of an IUGRThe cause of IUGR is unexplored, and she was referred to the Children's Hospital of Rabat at 4 months of age for hypotrophy and hyperglycemia.Clinical examination: At the age of 4 months, S.H. is tonic, reactive; without signs of Weight: 2.4 Kg (-4 DS), height : 50 cm (-4 DS), and cranial perimeter : 35 cm (-4 DS)She has no facial dysmorphism ,and the Capillary Glycemia: 2.3 g / l(mmol/l)The blood test showed a Glycemia: 2.5 g / l, HCO3-: 17 mEq / l, Cholesterol : 1.09 g / l, LDL: 0.33 g / l, Na +: 135 mEq / l, K +: 5.37 mEq / l , HbA1c: 8.4% (DCA200), urea: 0.07 g / l, and creatinine: 4.7 mg / l. As part of the etiological review of neonatal diabetes, a C-peptide was undetectable, Anti GAD and Anti Islet Antibodies negative

Abdominal ultrasound did not visualize pancreas As part of the collaboration since 2007 with the Molecular Genetics Laboratory at Exeter Hospital, a Genetic Study was conducted with the following conclusions:

S.H. is homozygous for a new missense mutation PDX1, p.Arg175Leu. This mutation affects a highly conserved residue in the homeobox PDX1 domain. The father of S.H. is heterozygous for the new missense mutation PDX1, p.Arg175Leu. It is unclear whether the father's diabetes is caused by the mutationThe measurement of fecal elastase <15 µg / g. This very low rate result, associated with an abdominal MRI confirmed the complete agenesis of the pancreas

### Therapeutic management was based

- At 4 months old, an MDI insulin regimen (Aspart and Détémir) was initiated at a dose between 0.5 and 0.8 U /Kg / day /; and a parallel follow-up in pediatric gastroenterology consultation for the management of its exocrine pancreatic insufficiency: prescription of pancreatic extracts and vitamin therapy and dietary advice.

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## DISCUSSION

The PDX1 gene (Pancreatic and duodenal homeobox 1) is a homeotic gene located on chromosome 13, and is a major regulator of pancreatic development and islet b-cell differentiation. In mature B cells, PDX1 regulates the expression of critical genes including insulin, glucokinase and glucose transporter [2].

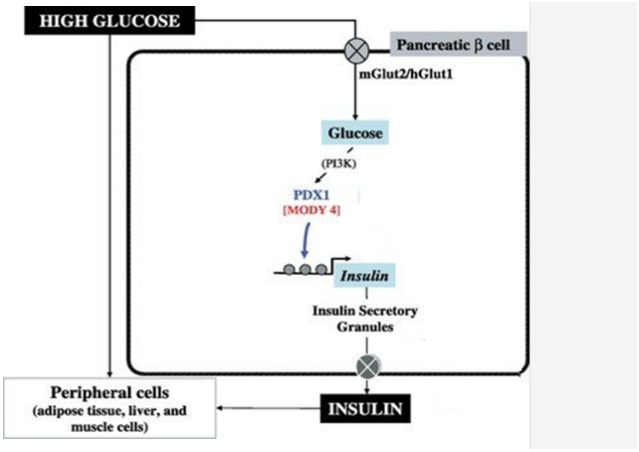
In the literature, publications reporting neonatal diabetes with agenesis or hypoplasia of the pancreas are very rare. About ten cases have been reported with different phenotypes.

The latest publication from 2017 reported by Abhishek Kulkarni et al (5) reported a mutation, p.(XX), of the PDX1 gene with permanent neonatal diabetes, an annular pancreas and duodenal atresia with exocrine pancreatic insufficiency.

Other cases have also been reported in the literature, Stoffers, et al. [6] reported a patient with pancreatic agenesis with deletion of a single nucleotide in codon 63 of the human IPF1 (PDX1) gene (13q12.1). Schwitzgebel, et al. [7] reported two mutations affecting the IPF gene (PDX1) causing pancreatic agenesis. The largest cohort of five patients with mutations of the PDX1 gene has been described by De Franco, et al. who found bi-allelic mutations in three patients with normal pancreas formation and no exocrine involvement [3]. Nicolino, et al. [8] reported two patients with mutations resulting from the E178G substitution in PDX1 homeodomain. Both patients had permanent neonatal diabetes with subclinical exocrine insufficiency.

Our patient is homozygous for a new missense mutation PDX1, p.Arg175Leu, never reported in the literature and this is the first case reported. This mutation is the cause of the patient's pancreatic agenesis.

Permanent neonatal diabetes secondary to agenesis of the pancreas is often diagnosed in the 2 first days of life and persists then without any phase of remission. Clinically, IUGR is almost constant (93%), ketonuria is rare and there is exocrine pancreatic insufficiency associated with diabetes. Treatment consists of lifetime insulin therapy with pancreatic extracts and vitamin supplementation.




## CONCLUSION

Advances in molecular genetics have identified many genes associated with various subtypes of diabetes.

Genetic analysis can now be used as diagnostic tools and dictate optimal treatment. As for this new original observation with neonatal diabetes on complete agenesis of the pancreas following a new mutation of the PDX1 gene suggests the need to look for mutations of the PDX1 gene in neonatal diabetes in the absence of known and frequent mutations and to detect the involvement of exocrine pancreas despite the absence of suggestive clinical signs

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