# Clinical Characterisation of a novel *RFX6* mutation - a rare cause of neonatal diabetes syndrome

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## BACKGROUND

Mitchell Riley syndrome is a rare syndrome caused by mutations in the *RFX6* gene, a winged helix transcription factor that is expressed in the developing pancreas and in the gut endoderm

**Clinical Features:**
**Neonatal diabetes**
**Intestinal atresia**
**Pancreatic abnormalities**
**Biliary hypoplasia**

Previous eight case reports highlight poor outcomes with usually a fatal course in infancy.

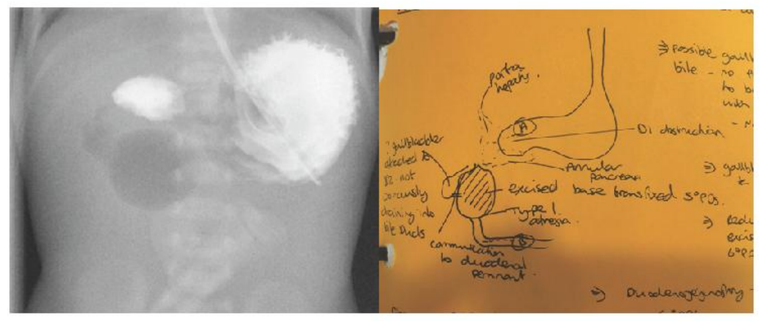

FIGURE 1

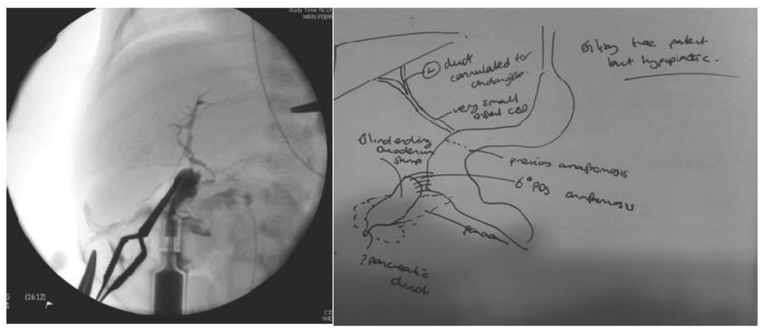

FIGURE 2

## CASE PRESENTATION

Twin 2 of a dichorionic diamniotic IVF pregnancy was antenatally diagnosed with duodenal atresia.
On day 2 of life, at planned repair of this defect, she was noted to have an annular pancreas and absent gallbladder (figure 1). Preoperatively, pigmented stool and bile were noted, but postoperatively she became acholic with rising conjugated hyperbilirubinaemia. Subsequent investigation revealed a patent but hypoplastic biliary tree with absence of gallbladder (figure 2).
She was also diagnosed with neonatal diabetes and difficult to control initial blood glucose levels. Feed intolerance and poor weight gain were also problematic, complicated by stricture formation at the site of the duodenal atresia repair. Pancreatic exocrine insufficiency was excluded. Surgical intervention helped to improve feed tolerance but she remains PN-dependent due to presence of malabsorptive diarrhoea to achieve adequate nutrition.

Currently, aged 1 year, conjugated hyperbilirubinaemia has resolved (figure 3), weight gain is improving, and neuro-development is appropriate (figure 4). Diabetes is well controlled with insulin pump therapy (HbA1C of 6.3%).

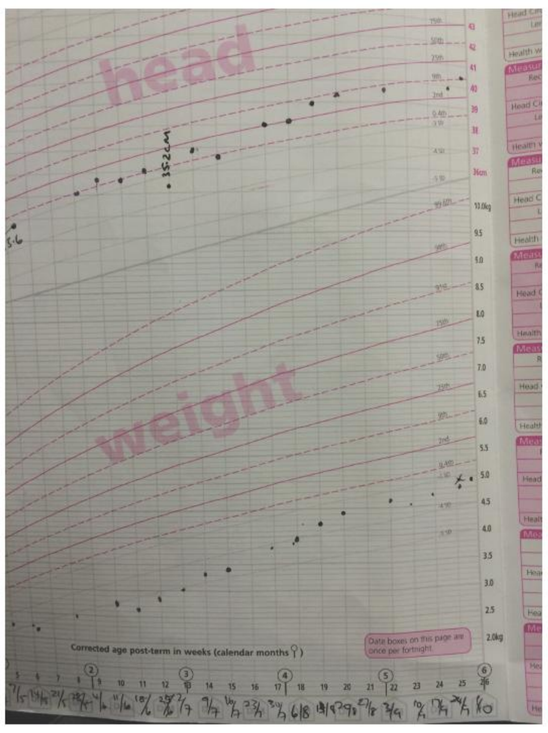


FIGURE 4

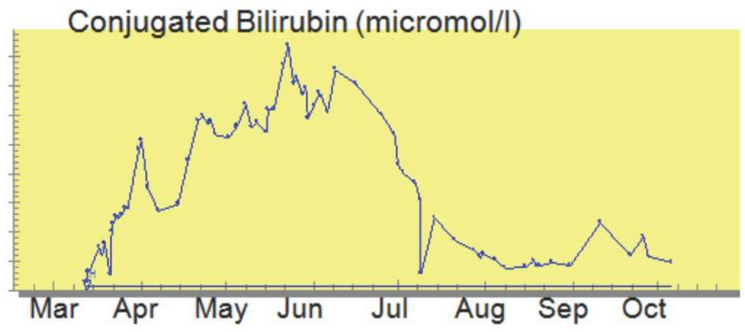


FIGURE 3

## GENETICS

Genetic analysis identified a novel homozygous intronic mutation, c. 1556-40T>G in *RFX6*. This mutation is predicted to create a cryptic splice acceptor site in intron 14 and cause aberrant splicing

## REFERENCES

**Soyer et al** (2010) Rfx6 is an Ngn3-dependent winged helix transcription factor required for pancreatic islet cell development. *Development 137, 203-212*
**Mitchell et** al (2004) Neonatal diabetes, with hypoplastic pancreas, intestinal atresia and gall bladder hypoplasia: search for the aetiology of a new autosomal recessive syndrome. *Diabetologia 47:2160–2167*
**Pearl et al** (2011) Functional analysis of Rfx6 and mutant variants associated with neonatal diabetes. *Dev Bio* 351:135-145
**Concepion et al** (2014) Neonatal diabetes, gallbladder agenesis, duodenal atresia, and intestinal malrotation caused by a novel homozygous mutation in *RFX6. Pediatric Diabetes 15: 67–72*
**Spiegel et al** (2011) Clinical Characterization of a Newly Described Neonatal Diabetes Syndrome Caused by RFX6 Mutations. *Am J Med Genet Part A 155:2821–2825.*
**Martinovici et al** (2010) Neonatal hemochromatosis and Martinez-Frias syndrome of intestinal atresia and diabetes mellitus in a consanguineous newborn. *European Journal of Medical Genetics 53: 25-28*
**Smith et al** (2010) Rfx6 directs islet formation and insulin production in mice and humans. *Nature* **463**:775-780
**Chappell et al** (2008) A Further Example of a Distinctive Autosomal Recessive Syndrome Comprising Neonatal Diabetes Mellitus, Intestinal Atresias and Gall Bladder Agenesis. *American Journal of Medical Genetics 146A:1713–1717*
**Taleb et al** (2011) RFX6 is needed for the development and maintenance of the beta cell phenotype. *Islets 3:291-293*

## CONCLUSIONS

Mutations in *RFX6* are a rare cause of neonatal diabetes associated with poor prognosis. Death within 6 months of life has been reported in 5/8 cases reported so far, mostly due to end stage liver disease and multi-organ failure. This report describes the clinical characteristics of a new case due to a novel homozygous splice site mutation in *RFX6.* It also illustrates that careful management of the critical phase in early infancy may be followed by a relatively favourable outcome than previously reported.

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