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# A novel mutation in the *SLCO2A1* gene presenting as persistent hypoproteinaemia and refractory iron deficiency anaemia due to chronic enteropathy: a case report

Sachith Mettananda[1,2*], PKBUC Bandara[1], Manissha Rajeindran[3] and Padmapani Padeniya[4]

## Abstract

**Background** The *SLCO2A1* gene encodes a prostaglandin transporter and we report a novel mutation causing hypoproteinaemia and refractory anaemia due to chronic enteropathy.

**Case presentation** An 18-year-old boy of consanguineous parents was investigated for hypoproteinaemia and anaemia. He was short, pale and had generalised oedema. Investigations revealed haemoglobin 5.8 g/dL; hypochromic microcytic anaemia; low serum protein, albumin, globulin, ferritin and iron. Bone marrow aspiration revealed low iron stores. Upper and lower gastrointestinal endoscopies showed moderate gastritis, duodenitis, and non-specific patchy inflammation in the rectum. The whole exome sequencing revealed a homozygous missense mutation in *SCLO2A1* gene (NP_005621.2:p.Arg97Cys; rs761212094). Sanger sequencing of the sibling with milder phenotype revealed same homozygous mutation, and carrier father was heterozygous.

**Conclusion** We report a novel mutation of *SLCO2A1* gene causing severe persistent hypoproteinaemia and refractory iron deficiency anaemia due to chronic enteropathy helping to delineate genotype-phenotype correlation of *SLCO2A1* variants.

**Keywords** *SLCO2A1*, Chronic enteropathy, Hypoproteinaemia, Refractory iron deficiency anaemia

## Background

Solute carrier organic anion transporter family member 2A1 (*SLCO2A1*) gene encodes a prostaglandin transporter that mediates the uptake and clearance of prostaglandins in numerous tissues [1]. Prostaglandin plays a vital role in modulating mucosal integrity of the alimentary tract, and loss-of-function mutations in *SLCO2A1* are reported to cause chronic enteropathy [2]. Here, we report an adolescent with a novel *SLCO2A1* mutation presenting with severe persistent hypoproteinaemia and refractory iron deficiency anaemia due to chronic enteropathy.

*Correspondence:
Sachith Mettananda
sachith.mettananda@kln.ac.lk
[1]Colombo North Teaching Hospital, Ragama, Sri Lanka
[2]Department of Paediatrics, Faculty of Medicine, University of Kelaniya, Thalagolla Road, Ragama 11010, Sri Lanka
[3]Department of Bionformatics, Credence Genomics (Pvt) Ltd, Colombo, Sri Lanka
[4]Department of Anatomy, Faculty of Medicine, University of Kelaniya, Colombo, Sri Lanka

## Case presentation

An eighteen-year-old Sri Lankan boy was investigated for recurrent episodes of oedema and pallor since he was two years old. His illness started at two years when he presented with pallor and generalized body swelling for the first time. He did not have haematemesis, melaena, per-rectal bleeding or other bleeding manifestations. His bowel habits were unaltered, and he did not show features of a chronic liver pathology. Urine output, colour and frequency were normal.

He was the youngest child of healthy but consanguineous parents with three children. His mother died when he was fifteen years old due to an accident. His oldest sibling was healthy; however, the second sister had been having persistent asymptomatic anaemia since childhood.

At eighteen years, his height was 148 cm (below −3SD) and his BMI was 16.5 kg/m$^2$ (between −2SD to -3SD). He was severely pale and had facial swelling and pitting ankle oedema (Fig. 1). There was no jaundice, lymphadenopathy or bleeding manifestations. Abdominal examination revealed ascites, but there was no hepatomegaly or splenomegaly. Cardiovascular, respiratory and neurological examinations were normal.

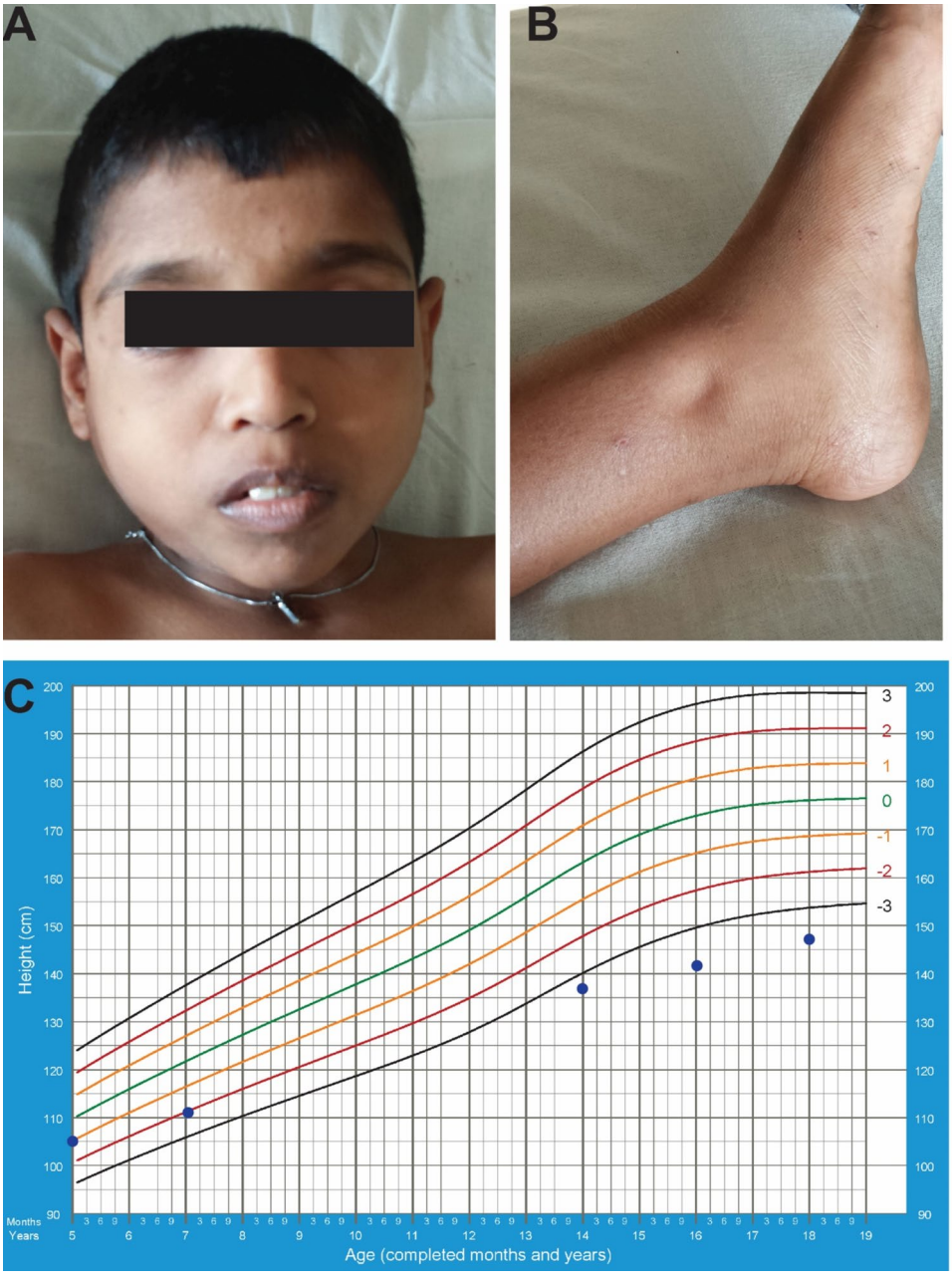


**Fig. 1** Photographs of the child demonstrating (**A**) facial swelling and (**B**) pitting ankle oedema. (**C**) Serial heights plotted in WHO height for age chart

Investigations done during the most recent admission to the hospital revealed haemoglobin- 5.8 g/dL (normal 11.0–15.0), mean corpuscular volume- 63fL (normal 80–100), mean corpuscular haemoglobin- 16pg (normal 27–32), white cells $9.2\times10^9$/L (normal 4.0–11.0), neutrophils- $5.2\times10^9$/L (normal 2.5-7.0), lymphocytes- $1.4\times10^9$/L (normal 1.0-4.8) and platelet count- $359\times10^9$/L (normal 150–400). The blood picture showed hypochromic and microcytic red blood cells and a few polychromatic cells, and the reticulocyte count was 4% (normal 0.5-2.0). The erythrocyte sedimentation rate was 3 mm/hr (normal < 15), and the direct agglutination test was negative. Serum iron profile revealed; ferritin- 5ng/mL (normal 28–397), serum iron- 43 µg/dL (normal 59–158), total iron binding capacity– 141 µg/dL (normal 291–430) and transferrin saturation- 30% (normal 20-50%). Haemoglobin electrophoresis showed haemoglobin (Hb) A- 89%, $HbA_2$-2.8% (normal 2.0-3.4) and HbF-0.5% (normal <2.0). His total serum protein was 2.9 g/dL (normal 6.0–8.0), albumin 1.6 g/dL (normal 3.5-5.0) and globulin 1.3 g/dL (normal 2.0-3.5). Urine analysis did not show proteinuria, and his liver profile, including transaminases, alkaline phosphatase, bilirubin, and prothrombin time and renal function tests were normal. Ultrasound scan of the abdomen was normal except for ascites. Abdominal paracentesis and ascitic fluid analysis was not performed as it was clear that the ascites was caused by hypoproteinaemia.

The results of several investigations done in the past to elucidate the cause of his hypoproteinaemia and anaemia were available. His anti-tissue transglutaminase antibodies, antinuclear antibodies, 24-hour urinary protein excretion, and Mantoux test were negative. Bone marrow aspiration and trephine biopsy revealed mildly hypercellular marrow fragments with increased erythropoiesis with micro-normoblastic maturation. Bone marrow iron stores were very low. Upper and lower gastrointestinal endoscopies done at three and five years were normal. However, upper gastrointestinal endoscopy done at seven years showed moderate gastritis and duodenitis, and the lower gastrointestinal endoscopy at the same age showed non-specific patchy inflammatory changes only in the rectum (Fig. 2). *Helicobacter pylori* antigen test was negative.

His anaemia showed a partial response to high doses of oral iron (120 mg elemental iron twice daily), and he had received leukodepleted packed red blood cell transfusions every 2–6 monthly. Despite receiving over 50 blood transfusions, his serum ferritin and serum iron remained low, and he did not show clinical or biochemical features of iron overload and organ dysfunction related to iron deposition. He had repeated episodes of generalised oedema due to hypoalbuminemia, which were managed by repeated infusions of salt-free 20% albumin 1 g/kg/day for 2–3 days at 3–4 monthly intervals. He also adhered well to the nutritional advice of a high-protein diet.

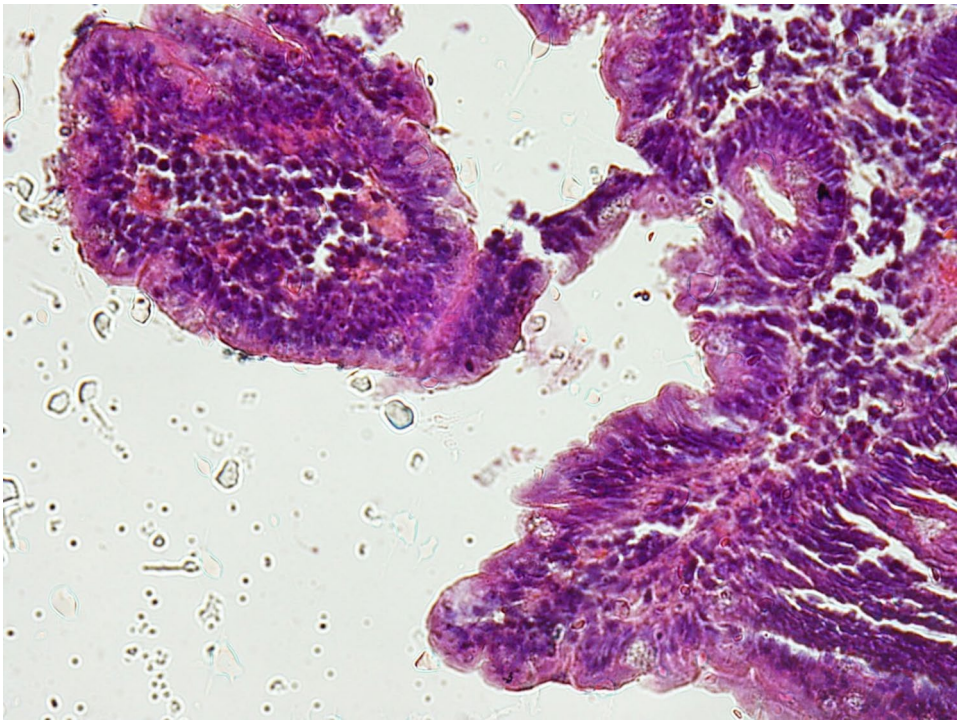

**Fig. 2** Microscopy image of the duodenal mucosa showing moderate duodenitis (H & E x 100)

His 20-year-old sister had a milder phenotype of the same condition. She had asymptomatic hypochromic microcytic anaemia and persistently low serum ferritin. She had received three blood transfusions in early childhood but had responded well to high-dose oral iron treatment (120 mg elemental iron twice daily) and subsequently did not require blood transfusions. She had mild hypoproteinaemia; total protein-3.9 g/dL, albumin- 2.5 g/dL and globulin- 1.4 g/dL. She never had oedema requiring albumin transfusions.

The presence of consanguinity in parents, having a sibling with a similar phenotype, the persistent symptoms since early childhood and the inconclusive findings in specific investigations prompted us to consider a rare genetic disease as the cause of the clinical syndrome. Whole exome sequencing was carried out in the index patient, revealing a homozygous missense mutation in exon 3 of *SCLO2A1* gene (rs761212094). The coding sequence variant is G>A (NC_000003.12:g.133973771G>A) with a protein change from arginine to cysteine (NP_005621.2:p.Arg97Cys). According to the American College of Medical Genetics and Genomics mutation classification guidelines, this mutation is a variant of uncertain significance (VUS). Nonetheless, in silico analysis by mutation tester and SIFT tools predict that the mutation is deleterious with a significant protein change. Then, we performed Sanger sequencing on the sibling with a milder phenotype. The affected sister had the same homozygous mutation in the *SLCO2A1* gene, and the carrier screening of their father revealed the same heterozygous mutation in the *SLCO2A1* gene (Fig. 3). Clinical correlation, in silico prediction, and family screening confirmed chronic enteropathy associated with *SCLO2A1* in the index patient.

## Discussion

In this case report, we described two siblings of the same family affected by persistent hypoproteinaemia and refractory iron deficiency anaemia due to a novel mutation in the *SLCO2A1* gene. The index patient had a very severe phenotype with persistent generalised oedema due to hypoproteinaemia requiring albumin transfusions and refractory iron deficiency anaemia requiring frequent blood transfusions. The elder sibling had a milder phenotype with asymptomatic microcytic anaemia and hypoproteinaemia.

*The SLCO2A1* gene encodes a prostaglandin transporter, a membrane-spanning protein that mediates the uptake and clearance of prostaglandins in numerous tissues [1]. Prostaglandins play many roles in human tissues, including modulating the mucosal integrity of the alimentary tract. At physiologic pH, prostaglandins traverse biological membranes poorly, and their entry into many tissues depends on the prostaglandin transporter [2].

The loss-of-function mutations of the *SLCO2A1* gene are reported to cause chronic enteropathy [1, 3, 4]. This entity, renamed chronic enteropathy associated with the *SLCO2A1* gene, shares many clinical features but is clinically distinct from Crohn's disease [5]. It is characterized by persistent blood and protein loss from the small intestine through chronic nonspecific multiple small intestine ulcers. In our patient, the upper gastrointestinal endoscopy and colonoscopy did not show macroscopic lesions, but inflammation features were present in the histology, suggesting an enteropathy. A capsular endoscopy was not performed due to limited resources. Another differential diagnosis for this clinical presentation is intestinal lymphangiectasia. However, our patient did not have classic clinical and laboratory features of intestinal lymphangiectasia like diarrhoea, steatorrhea and lymphopenia [6]. Also, *SLCO2A1* gene mutation is not reported to be associated with intestinal lymphangiectasia.

Our patients had previously not described mutation in the *SLCO2A1* gene. Although the mutation is classified as a VUS, in silico analysis by mutation tester and SIFT (Sorting Intolerant From Tolerant) tools predicted the mutation is deleterious with a significant protein change.

In conclusion, we described a novel mutation of the *SLCO2A1* gene presenting with severe persistent hypoproteinaemia and refractory iron deficiency anaemia due to chronic enteropathy. It adds to the clinical descriptions of rare phenotypes of chronic enteropathy associated with *SCLO2A1* and helps delineate the genotype-phenotype correlation of *SLCO2A1* gene variants.

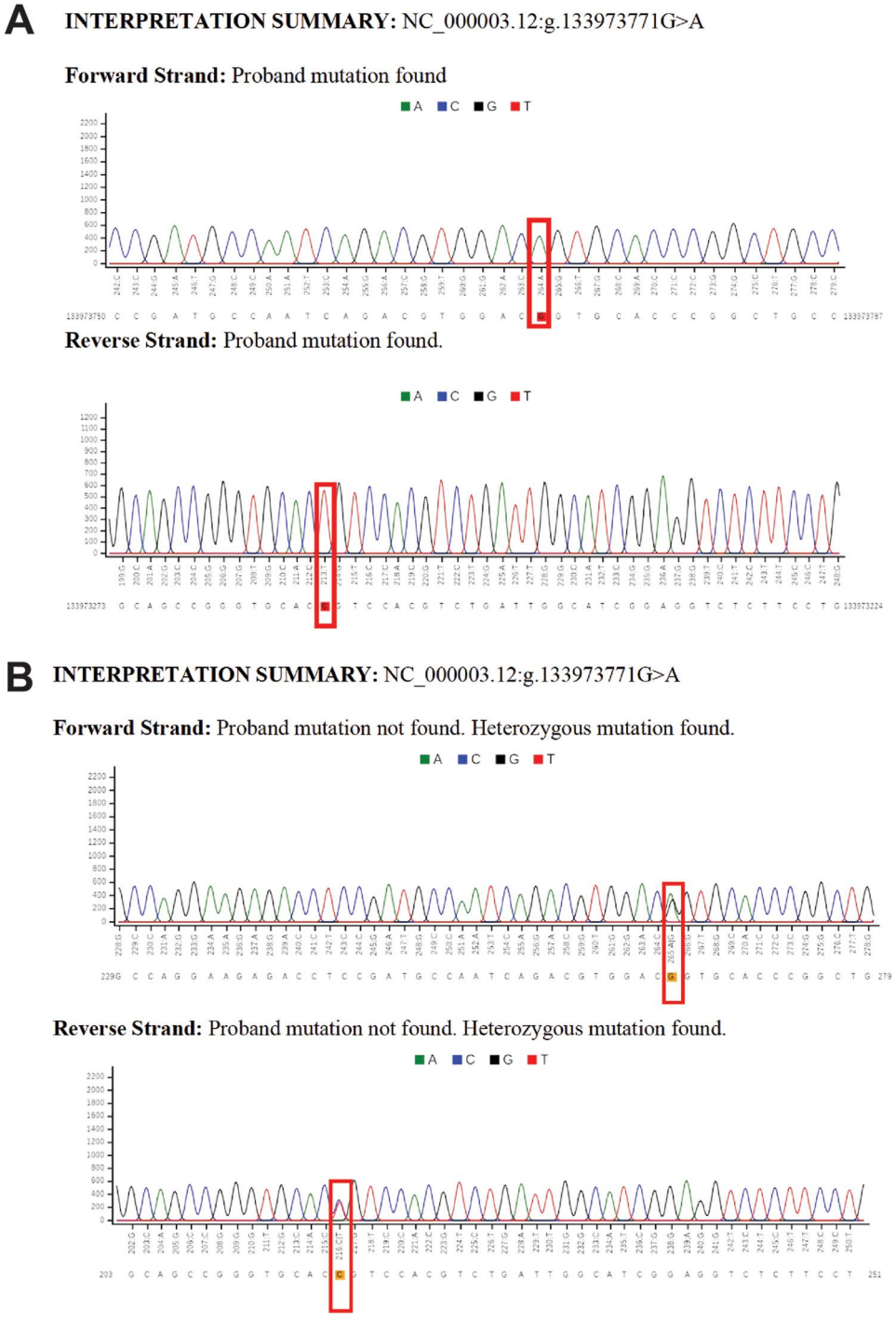


**Fig. 3** Sanger sequencing result of (**A**) affected sister with the same homozygous mutation and (**B**) carrier father with the same heterozygous mutation in the SLCO2A1 gene

**Abbreviations**

| | |
|---|---|
| SLCO2A1 | Solute carrier organic anion transporter family member 2A1 |
| VUS | Variant of uncertain significance |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12887-024-05252-6.

Supplementary Material 1

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**Author contributions**
SM, PB, MR and PP participated in making the diagnosis and management of the child. SM, PB and PP wrote the manuscript. All authors read and approved the final manuscript.

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**Data availability**
The datasets generated and analysed during the current study are available in the Genome Sequence Archive (accession number: HRA009137) at https://bigd.big.ac.cn/gsa-human/browse/HRA009137.

## Declarations

**Ethics approval and consent to participate**
Informed written consent was obtained from the patient.

**Consent for publication**
Written informed consent was obtained from the patient for the publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**Competing interests**
The authors declare no competing interests.

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