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CLINICAL REPORT

# Further delineation of *SLC9A3*-related congenital sodium diarrhea

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**Abstract**

**Background:** Congenital sodium diarrhea (CSD) is a rare enteropathy displaying both broad variability in clinical severity and genetic locus and allelic heterogeneity. Eleven CSD patients were reported so far with *SLC9A3* variants that impair the function of the encoded intestinal sodium-proton exchanger 3 (NHE3).

**Methods:** We report a 4-year-old patient, born prematurely in the 35th week of gestation, with antenatal polyhydramnios and dilated intestinal loops, and with diarrhea of congenital onset, 2–6 times a day, and with polydipsia. She thrived age-appropriately under a normal family diet. Serum sodium levels were repeatedly normal but urinary sodium excretion was low. Exome sequencing revealed compound heterozygous variants in *SLC9A3* as the likely cause of the congenital diarrhea.

**Results:** While exome sequencing did not reveal pathogenic or likely pathogenic variants in other genes that cause syndromic or non-syndromic forms of congenital and intractable diarrheas, we identified novel compound heterozygous variants in *SLC9A3*, a complex allele with two missense changes, NP_004165.2:p.[Ser331Leu;Val449Ile] and in-trans the missense variant p.(Phe451Ser).

**Conclusion:** The clinical phenotype here appears to localize to the milder end of the known CSD spectrum, and the identified variants suggest that this is the twelfth patient reported to date with CSD due to mutations in *SLC9A3*.

**KEYWORDS**

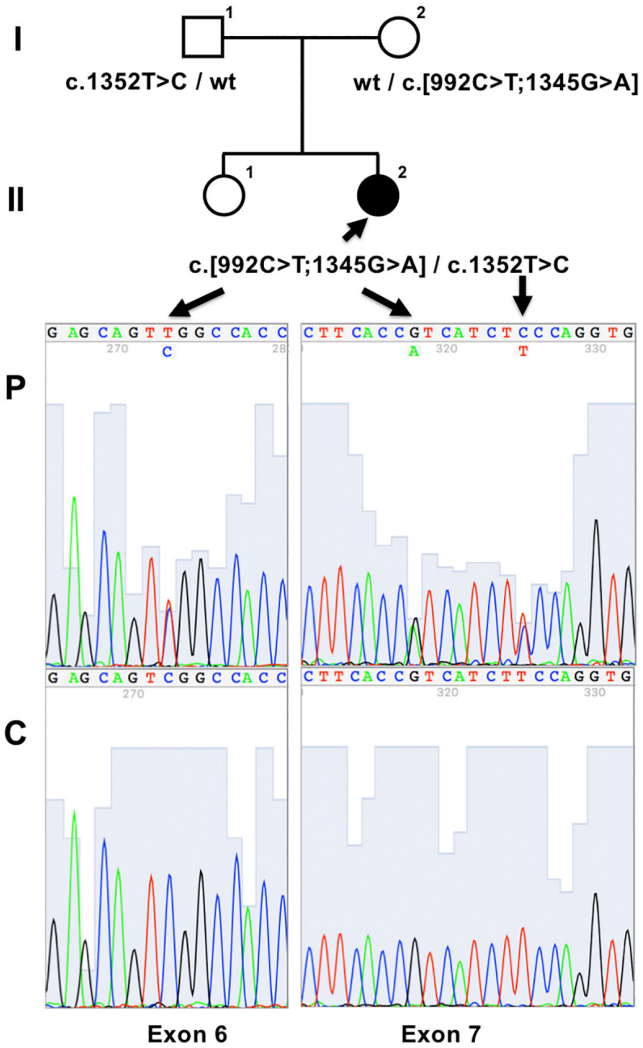
compound heterozygous, CSD, NHE3, parenteral nutrition, SLC9A3, urinary sodium

## 1 | INTRODUCTION

Congenital diarrheal disorders (CDDs) or congenital diarrheas and enteropathies (CODE) are terms that refer to a clinically and genetically heterogeneous group of conditions manifesting perinatally or in the first months of life with intractable diarrhea or bowel dysmotility (Thiagarajah et al., 2018). One of those individually rare disorders is the congenital sodium diarrhea (CSD), for which until now less than 60 patients have been reported in literature (Janecke et al., 2016). CSD is clinically and genetically heterogeneous. A syndromic form of the disease with

tufting enteropathy is caused by biallelic mutations in the SPINT2 (OMIM *605124) gene (Heinz-Erian et al., 2009; Holt-Danborg et al., 2019). Non-syndromic forms of CSD can be due to dominant *GUCY2C* (OMIM *601330) mutations (Müller et al., 2016) or biallelic mutations in *SLC9A3* (Janecke et al., 2015). The SLC9A3 gene (solute carrier family 9, subfamily A, member 3, OMIM *182307) encodes sodium-proton exchanger 3 (NHE3) which is located in the apical membrane of enterocytes and is important for intestinal sodium absorption and pH maintenance. NHE3 is extensively regulated by numerous hormones, growth factors as well as by extracellular osmolarity, the state of filamentous actin assembly, membrane curvature, and surface charge (Alexander & Grinstein, 2009; Donowitz et al., 2009; Prasad & Visweswariah, 2021). Clinical symptoms typically start prenatally with polyhydramnios and dilation of bowel loops. Intractable watery diarrhea with excessive fecal sodium loss and metabolic acidosis manifests soon after birth. It was first described in 1985 in two sporadic patients (Booth et al., 1985; Holmberg & Perheentupa, 1985), in whom impaired jejunal, pH-dependent sodium resorption was demonstrated in 1990 (Keller et al., 1990), and in whom *SLC9A3* variants were first identified in 2015 (Janecke et al., 2015).

Global NHE3 knockout in mice leads to diarrhea, metabolic acidosis, dilation of the intestinal tract and




| Mutated | L | I S |
|---|---|---|
| H.sapiens | KYVKANISEQSATTVRYTMKM | STTIIVVFFTVIFQGLTIKPL |
| M.musculus | KYVKANISEQSATTVRYTMKM | STTLIVVFFTVIFQGLTIKPL |
| D.rerio | KYINANMDEKSVTCLRYSLKV | GTTLIVVYFTVILQGITMKPL |
| X.tropicalis | KYVKANISEQSATTVRYTMKM | STTIIVVYFTVIFQGLTIKPL |
| D.melanogaster | HYTYNNLSEDSRQRTK-Q-IF | TATSLIVIFTVVI-QGGA--A |
| S.cerevisiae | HYAYYNMSRRSQITIKY--IF | ATVLVVVVLTVII-FGGT--T |

**FIGURE 1** A genealogical tree of the investigated family is shown with the segregation of identified SLC9A3 variants, and Sanger sequencing traces depicting the identified SLC9A3 variants are shown beneath the tree, and finally a partial alignment of SLC9A3 orthologues from selected species shows the high conservation of mutated amino acid residues. C, control; P, patient.

a high mortality rate subsequent to weaning (Bradford et al., 2009), and tamoxifen-inducible intestinal epithelial cell-specific NHE3 knockout causes watery, alkaline diarrhea in combination with a swollen small and large intestine, and a ~25% mortality rate in adult mice 3 weeks after tomixifen administration (Xue et al., 2020), mimicking the phenotype of individuals with CSD carrying SLC9A3 mutations.

## 2 | CLINICAL REPORT

This female patient is the second child of healthy, unrelated Caucasian parents (Figure 1). Their first daughter is healthy and there is no family history of protracted diarrhea. Routine ultrasound examinations in the third trimester of her pregnancy had shown a polyhydramnios and multiple dilated bowel loops. Due to a premature rupture of the membranes she was born with a gestational age of 35 weeks and 3 days weighing 2960 g and with a birth length of 48 cm.

Upon delivery, an abdominal distention was noted. Abdominal ultrasound and a radiograph showed marked dilatation of fluid- and air-filled small and large bowel loops that caused a mechanical obstruction of the small intestine. The patient developed an intractable watery diarrhea immediately after her birth. She presented with 2–6 liquid stools per day, and with an extended abdomen and flatulence. The diarrhea persisted under both breast and bottle feeding, and at rest and can be classified with HPO terms (https://hpo.jax.org/app/) (HP:0002041) intractable diarrhea, (HP:0002028) chronic diarrhea, (HP:0005208) secretory diarrhea, (HP:0012603) abnormal urine sodium concentration.

Serum electrolytes, acid–base metabolism, red and white blood counts, kidney and liver function tests were repeatedly normal (Supporting Information). Fat-soluble vitamins were in the normal range. There was no indication as to a systemic or local inflammation. Fecal pancreatic elastase levels values were in the lower range as a result of the watery stools; fetal calprotectin was repeatedly normal in the watery stool. Stool investigation showed no evidence for an infectious etiology of the diarrhea, stool contained neither blood nor mucus. Abdominal ultrasound was normal at age 17 months. Oral food intake was tolerated with adequate growth in height and weight, but the diarrhea persisted for the next years so that further investigations and genetic testing were initiated at the age of 2.5 years. Gastroduodenoscopy and colonoscopy were performed, which showed normal histopathological,

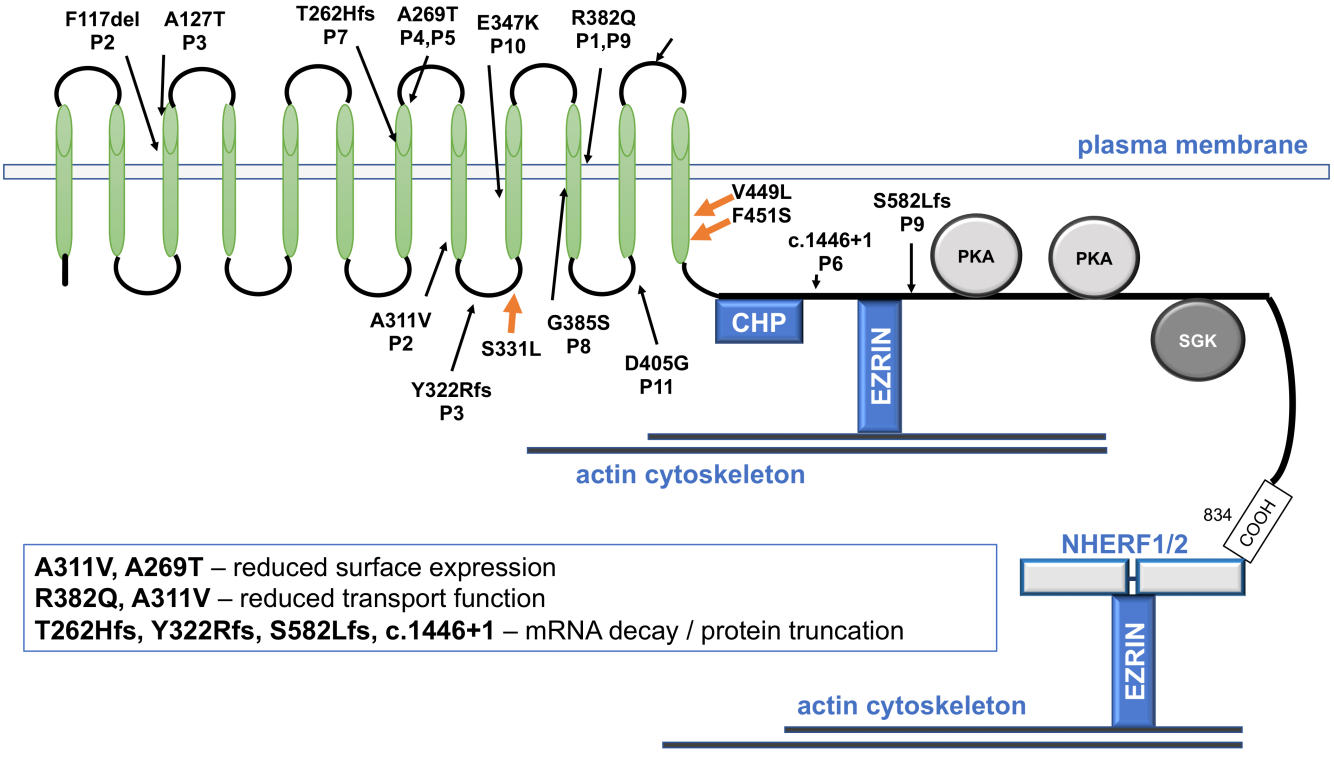



FIGURE 2 Schematic of the NHE3 protein encoded by SLC9A3. Transmembrane domains (residues 1–454) and a cytosolic C-terminal domain (residues 455–831) with known interactions as well as the sites of known variants identified in reported CSD patients are indicated. CHP, calcineurin homology protein; NHERF1/2, sodium hydrogen exchanger regulatory factor 1 and 2; P1–P11, patient 1–11, one whole-gene deletion identified in patient P1 is not displayed; PKA, protein kinase A; SGK, serum and glucocorticoid kinase.

**TABLE 1** Clinical and genetic findings in reported CSD patients with biallelic SLC9A3 variants

| Parameter | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 | Patient 6 |
|---|---|---|---|---|---|---|
| Consanguinity | No | No | No | Yes | Yes | Yes |
| Nationality | Canadian Caucasian | German/Finish | British Caucasian | Turkish | Turkish | Turkish |
| Current age (years) | 2.5 | 37 | 33 | 1.5 | Neonate | 6.5 |
| Sex | F | F | F | F | M | M |
| Gestational age (weeks) | 37 | 33 | 36 | 33 | 32 | 33 |
| Birth weight (g) | 2285 | 2530 | 2800 | 2560 | 2160 | 3210 |
| Weight (kg, centile) | 12, 25th | n, i | n, i | 1.34, 90th | 2.84, 75th | 32.7, >97th |
| Height (cm, centile) | 83.2, >10th | n, i | n, i | 63, 50–70th | 48, 25–50th | 119, 50th |
| Poly = hydramnios | Yes | Yes | Yes | Yes | Yes | Yes |
| Parenteral fluids till (weeks) | Intermittent | None | 5 | 3 | 2 | 237 |
| Current treatment | Oral | Oral | Oral | Oral | Oral | Oral + i, v |
| Current Na supplement (mmol/kg/d) | None | 4 | n, i | n, i | None | 6.5 |
| Outcome | Growth retardation | Mild watery diarrhea | Mild watery diarrhea | Watery diarrhea, hyper-aldosteronism | Normal, fully breastfed | Watery diarrhea, partial PN, ileal ulcerations since the age of 4 years |

macroscopic, and electron microscopic findings. In particular, there was no evidence for inflammatory bowel disease, structural mucosa defects like microvillus inclusion disease or Tufting enteropathy. At this point, low serum ferritin and vitamin B12 levels prompted intravenous iron and oral vitamin B12 substitution.

Low urinary sodium excretion was found and oral sodium supplementation with sodium citrate and potassium citrate was started. The girl shows age-appropriate growth (length 101.5 cm (37th pc.), weight 16.3 kg (52nd pc.), BMI 15.8 kg/m$^2$ (62nd pc.)), and psychomotor development at age 4 years. She has watery stools 3–5 times per day.

## 3 | GENETIC TESTING

Ethical compliance: All patient data were extracted from her medical routine records. Written informed consent for molecular genetic studies and publication of data was obtained from both parents. This approach was approved by the ethics committee of the Medical University of Innsbruck. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Given the suspected diagnosis of a hereditary congenital diarrheal disease, clinical exome sequencing was performed, focusing the targeted bioinformatic analysis on 91 genes that are contained in the clinical exome enrichment and that are known to cause intestinal transport or digestive enzyme defects, structural mucosa defects, enteroendocrine deficiencies, immunodeficiencies, and metabolic disorders with early or prominent intestinal involvement. Clinical exome sequencing was performed with the patient's DNA sample using the Nextera Rapid Capture kit (TruSightTM One Panel Expanded, Illumina) and a NextSeq sequencer (Illumina). Paired-end reads were aligned to the human reference genome with Burrows–Wheeler transformation (Li & Durbin, 2009). Polymerase chain reaction (PCR) duplicates were removed with PICARD (http://picard.sourceforge.net) and single nucleotide substitutions, and small indels were called with SAMtools software. All variants were submitted to SeattleSeq (http://snp.gs.washington.edu/SeattleSeqAnnotation/) for annotation, categorization, and filtering against public variant databases. Copy number variants were called with the CNV Detective software. Generated sequence data resulted in an average 152-fold coverage of the target with 98.5% being covered at least 20X. An evaluation of variants was restricted to our CODE panel of 91 genes (*ADA, ADAM17, AICDA, AIRE, ANGPTL3, ANTXR2, AP1S1, APOB, ARX, BLNK, BTK, CD19, CD40, CD40LG, CD55, CD79A, CD79B, CD81, CFTR, CLMP, CR2, CTLA4, CYBA, CYBB, DCLRE1C, DGAT1, EGFR, EPCAM, FLNA, FOXP3, GUCY2C, ICOS, IGHM, IGLL1, IL10, IL10RA, IL12RB1, IL21, IL2RA, IL2R, JAK3, KMT2D, LCT, LRBA, LRRC8A, MPI, MS4A1, MTTP, MYO5B, NCF1, NCF2, NCF4, NEUROG3, NFKB2, NHEJ1, NPC1L1, PCSK1, PCSK9, PIK3R1, PTPRC, RAG1, RAG2, RFX6, SAR1B, SBDS, SI, SKIV2L, SLC10A2, SLC26A3, SLC2A2,*

| Patient 7 | Patient 8 | Patient 9 | Patient 10 | Patient 11 | Patient 12 |
|---|---|---|---|---|---|
| Yes | No | No | Yes | Yes | No |
| German Caucasian | Serbian Caucasian | Canadian Caucasian | Moroccan African | South-Asian | German Caucasian |
| 4 | 19 | 1.5 | 1.5 J | 1.3 | 3 |
| M | M | M | M | F | F |
| 34 | 34 | 34 | 36 | 40 | 35 |
| 2615 | 2125 | 2700 | 3290 | 3740 | 2960 |
| 16, 25th | 72, 50th | 9.02, 10th | 10, 50th | n, i | 16.3, 50th |
| 102, 10th | 175, 50th | 80, 25th | 7, 50th | n, i | 101, <50th |
| Yes | Yes | Yes | Yes | Yes | Yes |
| 20 | None | Current | None | Yes | No |
| Oral | Oral | i, v | Oral | Oral | oral |
| None | None | 13 | 9 | n, i | Yes |
| Mild watery diarrhea | Mild watery diarrhea, budesonide treatment | Total parenteral nutrition, growth retardation | Normal growth, diarrhea since the 3rd life month | Normal growth | Mild watery diarrhea, normal growth |

*SLC2A7, SLC30A2, SLC39A4, SLC5A1, SLC7A7, SLC9A3, SPINK1, SPINT2, STXBP2, TCN2, TERT, TNFRSF13B, TNFRSF13C, TREH, TTC37, TTC7A, UBR1, UNG*, and *XIAP*).

Clinical variant prioritization included filtering with respect to population allele frequencies (MAF <0.1% in 1000 g and ExAC), effect (nonsense, splicing, missense, and CNV) and in-silico evaluation scores (CADD, PolyPhen2, and Protean). Sanger sequencing of *SLC9A3* exons 6 and 7 was performed in the parental samples to determine the segregation of the variants identified in the proband. *SLC9A3* PCR primer sequences were based on the NCBI reference sequence for mRNA (NM_004174.4) and genomic DNA (NG_046804.1). Primer sequences and PCR conditions are available from the authors upon request. Nucleotide numbering reflects cDNA numbering with +1 corresponding to the A of the ATG translation initiation codon in the reference sequence. Orthologue alignments for NHE3 proteins were obtained from the Ensembl database entry for *SLC9A3*.

Clinical exome sequencing in the proband and Sanger sequencing of exons 6 and 7 in SLC9A3 showed that the patient is compound heterozygous for a complex allele, NM_004174.3:c.[992C > T,1345G > A] (NP_004165.2:p.[Ser331Leu;Val449Ile]), inherited from her mother, and an allele with a c.1352T > C (p.(Phe451Ser)) variant inherited from her father (Figure 1). All three identified variants are rare in the general population as concluded from allele frequencies of 1/204666 for p.Ser331Leu, 14/281638 for Val449Ile (including one homozygous individual of unknown status), and zero for Phe451Ser listed in the gnomAD database. Also, all three variants are predicted to be pathogenic by MutationTaster, Protean, Polyphen2, and CADD algorithms. A multispecies alignment showed a high or invariant conservation of the mutated amino acids among species (Figure 1). The location of all reported SLC9A3 (NHE3) variants is shown in Figure 2, and their relation to reported patients and reported or indicated functional assessments.

## 4 | DISCUSSION

We report a patient with intractable diarrhea of congenital onset. Extended investigations including a gastroduodenoscopy and colonoscopy produced normal findings. Although serum electrolytes and acid–base metabolism were repeatedly in the normal range, absolute urinary sodium excretion, and urinary sodium-creatinine ratio were low in our patient. Collectively, our findings suggested a form of congenital sodium diarrhea in this patient. In line with this hypothesis, the sequencing of 91 congenital diarrhea genes revealed rare, biallelic and likely functionally relevant variants only in the SLC9A3 gene in our patient. We consider these *SLC9A3* variants as the likely cause of the congenital diarrhea in our patient, which is supported

by formal scoring of the variants by ACMG criteria that would categorize all variants as likely pathogenic (PS4, PM2, PP2, PP3, and PP4).

In order to evaluate our conclusion further, we compiled our clinical and genetic findings with those of all 11 previously reported CSD patients with SLC9A3 variants (Table 1; Dimitrov et al., 2019; Gupta et al., 2019; Janecke et al., 2015). Of note, 11 out of 12 patients (of which are 6 males, 6 females) were born before term, within the 32nd to 37th week of gestation, and polyhydramnios was noted in all pregnancies, making these typical findings of this disorder. Our patient never required parenteral nutrition, which would be a rare finding in most forms of congenital diarrheas, but fits well with observations in patients with *SLC9A3*-related diarrhea who required no parenteral nutrition, or only for few weeks, and very rarely, for longer periods of time (Table 1). Patients with *SLC9A3*-related diarrhea did not or required only low amounts of sodium supplementation, and 10 out of 12 patients thrived well without a special diet. While sodium supplementation is warranted to avoid any sodium depletion of the body, it is not suited to abolish the chronic diarrhea.

As inflammatory bowel disease developed in 2 out of 12 patients described at ages of 6.5 and 19 years so far, with 8 out of 12 patients reported only at young ages of 4 years or less (Janecke et al., 2015), and changes in SLC9A3 expression are frequently observed in sites of active inflammation in many patients with inflammatory bowel disease (Prasad & Visweswariah, 2021), monitoring of patients with *SLC9A3*-related disease for signs of intestinal inflammation seems indicated. Inflammatory bowel disease affects at least 18% of patients with the more frequent but clinically similar chloride diarrhea caused by defects in the intestinal chloride-bicarbonate transporter SLC26A3, which is coupled to SLC9A3 (Priyamvada et al., 2015), and associated with gut microbiota dysbiosis (Norsa et al., 2021).

Given the patient's antenatal history, clinical symptoms, and genetic findings, we conclude that the patient presented here has CSD caused by *SLC9A3* variants.

## AUTHOR CONTRIBUTIONS

Thomas Müller and Andreas R. Janecke participated in the conception of the study. Ema Bogdanic and Andreas R. Janecke drafted the manuscript. All authors collected and analyzed data, interpreted the results, and revised the manuscript. All authors read and approved the final manuscript.

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None.

## CONFLICT OF INTEREST

The authors declare that they have no competing interests.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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