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BRIEF REPORT

Sotos syndrome, infantile hypercalcemia, and nephrocalcinosis: a contiguous gene syndrome

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Abstract Sotos syndrome is characterized by overgrowth, a typical facial appearance, and learning difficulties. It is caused by heterozygous mutations, including deletions, of *NSD1* located at chromosome 5q35. Here we report two unrelated cases of Sotos syndrome associated with nephrocalcinosis. One patient also had idiopathic infantile hypercalcemia. Genetic investigations revealed heterozygous deletions at 5q35 in both patients, encompassing *NSD1* and *SLC34A1* (*NaPi2a*). Mutations in *SLC34A1* have previously been associated with hypercalciuria/nephrolithiasis. Our cases suggest a contiguous gene deletion syndrome including *NSD1* and *SLC34A1* and provide a potential genetic basis for idiopathic infantile hypercalcemia.

Keywords Idiopathic infantile hypercalcemia · Nephrocalcinosis · SLC34A1 · Sotos syndrome

Introduction

Sotos syndrome is an autosomal dominant overgrowth syndrome with length or head circumference typically greater than two standard deviations from the mean at birth and characteristic facial features [1]. The majority of patients also exhibit some form of developmental delay, which can range from mild to severe. Additional features may include advanced bone age, seizures, cardiac and renal anomalies, and scoliosis. The majority of cases are caused by mutations in NSD1 (nuclear receptor SET domain-containing protein), which occur mostly de novo and up to 10% of cases are caused by micro-deletions of 5q35 [2]. Genitourinary abnormalities are reported in approximately 15% of patients, most commonly vesico-ureteric reflux [1]. Here, we report on two cases of Sotos syndrome complicated by nephrocalcinosis plus infantile hypercalcemia in one patient. The identification of a chromosome 5q35 microdeletion in both cases encompassing *SLC34A1* and *NSD1*, provides a potential explanation for this extended phenotypic spectrum of Sotos syndrome.

Methods

We performed a retrospective note review of two patients with Sotos syndrome and concomitant nephrocalcinosis. Genetic investigations were performed as part of their clinical care [3].

Array comparative genomic hybridization was performed using the Nimblegen 135 K Whole Genome Tiling array (Roche NimbleGen, Inc, Madison, USA) according to the manufacturer's instructions. Array CGH analysis was performed using InfoQuant CGHFusion Software (InfoQuant, London, UK) using an average Log-ratio threshold of 0.35.

Sequencing of SLC34A1 was performed with 13 amplicons covering the coding regions and splice sites of the gene (primer sequences available on request).

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Case reports

Case 1

A 6-month-old female infant girl was referred for genetic evaluation with macrosomia (head circumference, weight, and height above 97th percentile), developmental delay, hypotonia, a Duane anomaly, and scoliosis. She was the fifth child of healthy non-consanguineous white British parents, and there was no significant family history. Her facial features were suggestive of Sotos syndrome. Her bone age was advanced. There were no clinical features of rickets. At the age of 15 months she had a severe febrile convulsion associated with a urinary tract infection. Renal ultrasound scanning showed diffuse enlargement of kidneys with evidence of nephrocalcinosis. A cystogram showed a normal bladder and no reflux. Biochemistries at the age of 3 years were normal (Table 1).

Case 2

A 10-day-old girl presented with recurrent vomiting and constipation. The pregnancy had been uncomplicated. She was the third child of healthy, non-consanguineous Romanian parents, and there was no family history of note. There were no clinical features of rickets. Investigations revealed hypercalcemia (Table 1) and a subsequent abdominal ultrasound showed nephrocalcinosis (Fig. 1a). She was treated with a low-calcium feed and plasma calcium normalized by 1 year of age and diet was liberalized. An MRI of the brain showed non-specific changes (lack of bulk of white matter). She was referred for genetic evaluation at 1 year of age, by which time developmental delay had also become apparent. Height was on the 25th, weight on the second, and head circumference on the 98th percentile. Her facial features were consistent with a diagnosis of Sotos syndrome.

Molecular investigations in both cases revealed micro-deletions of 5q35, defined by array comparative genomic hybridization, which encompassed *SLC34A1* and *NSD1* (Fig. 1). Sequencing of *SLC34A1* revealed a hemizygous 21-bp deletion (c.271_291del; p.91del7) in patient 2. This deletion has been previously described as a polymorphism [4]. No other sequence variations in *SLC34A1* were identified in both patients.

Discussion

Sotos syndrome is characterized by overgrowth and typical facial features, but additional features may be present, potentially as a consequence of micro-deletions encompassing other genes in addition to *NSD1* [5, 6]. Previously reported kidney-related findings were mainly genitourinary abnormalities, especially vesicoureteric reflux [1]. Our two cases extend the phenotypic spectrum to include nephrocalcinosis.

The inclusion of *SLC34A1* within the deleted region at chromosome 5q35 in our patients suggests an intriguing explanation for the nephrocalcinosis. *SLC34A1* encodes the main sodium-phosphate co-transporter (also called NaPi2a) in the proximal tubule. Recessive mutations in this gene were recently described as a cause of Fanconi syndrome with hypophosphatemic rickets [7]. Heterozygous mutations in this gene have been reported by Prie et al. in patients with nephrolithiasis and osteoporosis [8]. Moreover, heterozygous mutations in a related phosphate transporter SLC34A3 (NaPi2c) are associated with hypercalciuria [9]. It is thought that the impaired renal phosphate reabsorption leads to hypophosphatemia with subsequent activation of vitamin D and in turn, increased intestinal absorption of calcium and phosphate, resulting in hypercalciuria [10, 11]. However, there are some uncertainties about the applicability of this mechanism to our patients:

Table 1 Biochemical data

	Case 1			Case 2		
Age (years)	3.6	4.6	16.0	0.04	0.8	1.4
Plasma						
Corrected total calcium [mmol/l]	2.51	2.57	2.58	**3.1**	**2.71**	2.44
Phosphate [mmol/l]	1.44	1.48	1.04	ND	1.5	1.33
Creatinine [μmol/l]	43	40	83	59	25	46
PTH [pmol/l]	1.8	ND		ND	1.5	2.6
25-OH Vit D [nmol/l]	ND	ND		50	162	ND
1,25-OH Vit D [pmol/l]	ND	ND		ND	99	ND
Urine						
Calcium/creatinine [mmol/mmol]	0.85	0.55		ND	1.33	1.38
TmP/GFR	ND	1.35		ND	ND	**1.08**

Summary of biochemistries obtained in the two cases. Values outside the age-appropriate reference range are shaded *bold*. *ND* not determined

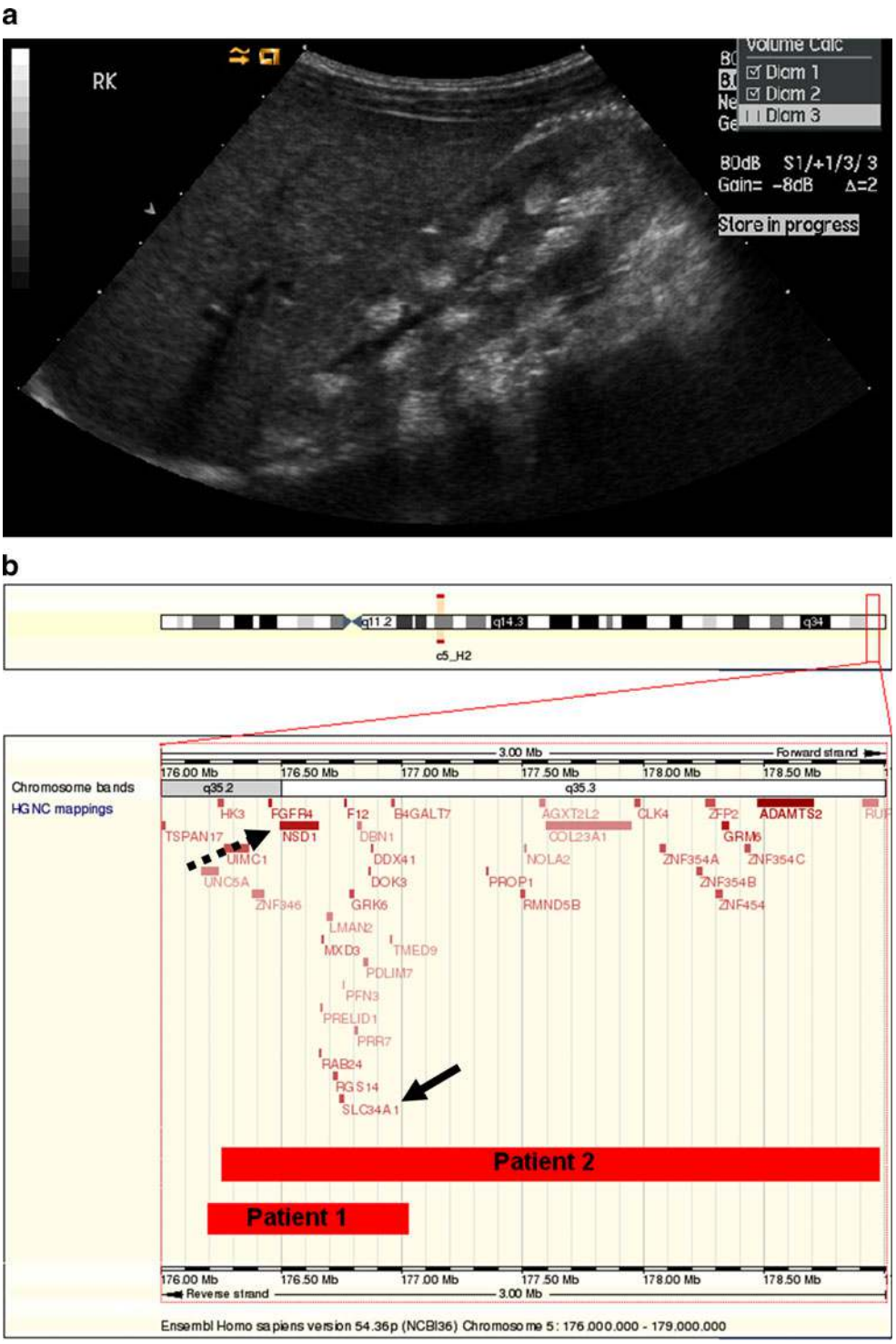

Fig. 1 Ultrasound and molecular findings. **a** Longitudinal image of the right kidney of case 2 showing medullary nephrocalcinosis. **b** Extent of the micro-deletions in both patients. *Arrows* denote *NSD1* and *SLC23A1*

1. SLC34A1 mutations identified in Prie's patients were missense, thought to exert a dominant negative effect, whereas our two cases harbor a whole gene deletion.
2. Patients described by Prie et al. were adults, suffering from nephrolithiasis, whereas our patients presented in early childhood with nephrocalcinosis. Moreover, Prie's patients had persistent hypophosphatemia with a decreased maximal capacity for renal phosphate reabsorption, whereas our patients had (borderline) normal phosphate values.
3. Vitamin D levels were only obtained in patient 2 and were normal during infancy (Table 1).

A potential explanation for these discrepancies is the developmental changes in renal phosphate handling, so that haploinsufficiency may only manifest during infancy when the demand on renal phosphate reabsorption is highest, due to higher plasma levels and the phosphate requirement of the growing skeleton. Unfortunately, renal phosphate handling was assessed in our patients only beyond infancy. Yet at 1.4 years of age, the maximum tubular phosphate reabsorption (TmP/GFR) in patient 2 was borderline low. Indeed, an infant with Sotos syndrome and renal phosphate wasting and a micro-deletion including *NSD1* and *SLC34A1* was recently reported and phosphate levels improved with age [12].

The co-deletion of *SLC34A1* may also provide an explanation for the diagnosis of idiopathic infantile hypercalcemia (IIH) in patient 2. IIH is a rare condition, characterized by resolution after infancy. Familial occurrence has been reported, suggesting a genetic basis [13]. However, no gene has been identified yet and a recent candidate approach was unsuccessful [14]. A recent clinical study using ketoconazole as an inhibitor of 1-α hydroxylase implicated excess vitamin D in the pathogenesis of IHH [15]. This would be consistent with the proposed mechanism here of vitamin D mediated hyperabsorption of calcium and phosphate due to renal phosphate loss (see above). Unfortunately, no biochemical data from infancy are available for our first patient to substantiate the association of IIH and *SLC34A1* deletion. An interesting further aspect is the identification of the deletion polymorphism in patient 2. This 21-bp in-frame deletion has been described and investigated previously: it was identified in six out of 96 Caucasian control chromosomes and calcium and phosphate indices were similar in carriers and non-carriers [4]. However, in that study, no individuals could be identified that were homozygous for the deletion to assess renal phosphate handling. In vitro, the deletion significantly affected SLC34A1-mediated phosphate currents. Since our patient is hemizygous for this deletion, it is conceivable that it may have functional significance. Yet, since bi-allelic mutations in *SLC34A1* are associated with renal Fanconi syndrome, which was not present in our patients, it is unlikely that variations in the remaining allele severely disrupt function. Further careful clinical observations of patients with SLC34A1 deletions and their calcium/phosphate handling are needed to delineate the association with nephrocalcinosis and IIH.

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