Hypertrophic pyloric stenosis masked by kidney failure in a male infant with a contiguous gene deletion syndrome at Xp22.31 involving the steroid sulfatase gene: case report

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Abstract

Background: Contiguous gene deletion syndrome at Xp22.3 resulting in nullisomy in males or Turner syndrome patients typically encompasses the steroid sulfatase gene (STS) and contiguously located other genes expanding the phenotype. In large deletions, that encompass also the Kallmann syndrome 1 gene (KAL1), occasionally infantile hypertrophic pyloric stenosis (IHPS) and congenital anomalies of the kidney and urinary tract (CAKUT) have been reported.

Patient presentation: We report on a male newborn with family history in maternal uncle of renal abnormalities and short stature still without ichthyosiform dermatosis. The baby presented CAKUT with kidney failure and progressive vomiting. Renal bicarbonate loss masked hypochloremic and hypokalemic metabolic alkalosis classically present in IHPS and delayed its diagnosis. Antropyloric ultrasound examination and cystourethrography were diagnostic. After Fredet-Ramstedt extramucosal pyloromyotomy feeding and growing was regular and he was discharged home. Comparative whole-genome hybridization detected a maternal inherited interstitial deletion of 1.56 Mb on Xp22.31(6,552,712_8,115,153) × 0 involving the STS gene, but not the KAL1 gene.

Conclusions: Aberrant cholesterol sulfate storage due to STS deletion as the underlying pathomechanism is not limited to oculocutaneous phenotypes but could also lead to co-occurrence of both IHPS and kidney abnormalities, as we report. Thus, although these two latter pathologies have a high incidence in the neonatal age, their simultaneous association in our patient is resembling not a chance but a real correlation expanding the clinical spectrum associated with Xp22.31 deletions.

Keywords: Case report, Xp22.3 nullisomy, Congenital anomalies of the kidney and urinary tract, Gastric outlet obstruction, Digestive system abnormalities

Background

Contiguous gene deletion syndrome at Xp22.3 resulting in nullisomy in males or Turner syndrome patients is characterized by the combination of one or more monogenic disorders and clinical findings as short stature...
(short stature homeobox gene, SHOX), chondrodysplasia punctata (aryl sulfatase genes - ARSD, ARSE, ARSF), X-linked ichthyosis (aryl sulfatase C or steroid sulfatase gene, STS), ocular albinism type 1 (OA1) and elements of X-linked neurodevelopmental disorders and Kallmann syndrome (KAL1; reduced hypothalamic and pituitary function with resulting hypogonadotropic hypogonadism and hypoplasia of the olfactory bulb) [1], whereas the term Rud’s syndrome should no longer be used [2]. FG syndrome 3 is also mapped to this region [3]. In large deletions, occasionally cardiac arrhythmia [4], periventricular nodular heterotopia [5], acute lymphoblastic leukemia [6], end-stage renal failure [7] and infantile hypertrophic pyloric stenosis (IHPS) [3, 4, 8–12] were also reported. The most critical region of deletion breakpoints, characterized by a low frequency of interspersed repeats and a low GC content [13], encompasses the STS gene (MIM*300747) resulting in microsomal enzyme deficiency with an incidence about 1:1500 in males [14].

This membrane-bound enzyme is ubiquitously expressed and hydrolyzes several 3-beta-hydroxysteroid sulfates, which serve as metabolic precursors for estrogens, androgens, and cholesterol [15]. Despite the widespread enzyme deficiency, patients apparently have abnormalities only of the stratum corneum where increased cholesterol sulfate concentrations are causing abnormal desquamation, decreased corneodesmosomal degradation and retention hyperkeratosis of the skin mostly a few weeks after birth, but conatal collodion is also reported [12]. There might be associated cardiac arrhythmia and benign Pre-Descemet corneal dystrophy characterized by cholesterol sulfate accumulation and punctiform opacities without vision impairment on the one side, as well as cryptorchidism and neurobehavioral disorders due to deficient (neuro-) steroids on the other side [4, 16]. Despite the escape of lyonization, some female deletion carriers also have corneal opacities and can present parotid disturbances and cervical dystocia due to lacking placental production of estriol [4, 14]. Congenital anomalies of the kidney and urinary tract (CAKUT) have been reported rarer in STS limited microdeletions or point mutations than in larger deletions of Xp22.3 that encompass also the KAL1 gene, a neighboring gene important for urogenital development [7, 12, 13, 17, 18].

We report on a male newborn with family history in maternal uncle of renal abnormalities and short stature still without ichthyosiform dermatosis. The baby presented CAKUT with kidney failure and progressive vomiting. Renal bicarbonate loss masked hypochloremic and hypokalemic metabolic alkalosis classically present in IHPS and delayed its diagnosis. This report of associated STS deletion and IHPS further define and expand the clinical spectrum associated with CNV in this region and provide support for the role of modifiers contributing to phenotypic variability.

**Patient presentation**

This male term newborn is the second son of healthy non consanguineous Caucasian parents. His maternal uncle suffering from nephropathy had undergone a kidney transplant. Fetal sonographic assessment revealed hydronephrosis bilaterally, and oligohydramnios inducted to Cesarean section. At birth baby’s weight was 2710 g (−1.07 SDS/10th centile), length 46 cm (−1.82 SDS/3rd centile), and head circumference 33 cm (−1.09 SDS/14th centile). During the first week of life, he developed severe acidosis and was referred to our department. Physical examination was unremarkable except for pale skin and hyporeactive aspect; male genitals were normal. There were no edemas. Diuresis, and blood pressure were normal. Laboratory investigations diagnosed renal insufficiency by low bicarbonates 15 mmol/l, augmented creatininemia 3.12 mg/dl, urea 89 mg/dl, chlor 120 mEq/l, moderate proteinuria 327 mg/l, glucosuria 500 mg/l and microhematuria, while anion gap, albuminemia, proteinemia and uric acid were preserved. Abdominal ultrasound and subsequent voiding cystourethrogram showed renal hypoplasia on the left and renal dysplasia on the right as well as moderate hydronephrosis due to grade IV vesicoureteral reflux. X-ray, cranial and cardiac ultrasounds and electrocardiogram were normal. He started intravenous rehydration and bicarbonate supplementation. Refeeding by breast milk and a special powdered feed with low levels of potassium for renal impairment (Kindergen® 1g in 5ml water) was initiated after 12h. He tended to have regurgitations attributed to a urinary infection and treated on the fifth day of the hospital stay with oral amoxicillin switched to oral cefixime on day 14 (sensitive to Escherichia coli) until negative urinary cultures were reported. Persistent regurgitation did not ameliorate by trials of smaller, more frequent feeds, thickened formula, and anti-Trendelenburg positional management. At 1 month of age, intermittent nonbilious vomiting increased markedly, he weighed 3110 g (−0.4 centile), creatininemia and urea were halved, bicarbonates kalium and chlor were normal.

Antypyloric ultrasound examination revealed hypertrophied muscular layer of 4.6 mm and elongation of the pyloric canal of 19 mm (diameter 14 mm). In retrospect, some frame of the cystourethrogram had already shown an air-filled stomach with undulating contours known as “Caterpillar sign” (Fig. 1). Fredet-Ramstedt extramucosal longitudinal pyloromyotomy was performed. Afterwards, feeding and growing was regular and he was discharged home 45 days old. All treatment options have been discussed with both parents. Erythropoietin treatment
and clinical multidisciplinary follow-up are ongoing. At 6 month of age, large polygonal, brownish scales appeared particularly on the anterior aspect of the lower extremities.

Comparative whole-genome hybridization was performed during hospitalization using the Agilent® 8x60K microarray and detected a maternal inherited interstitial deletion of 1.56 Mb on arr [hg19] Xp22.31(6,552,712_8,115,153) × 0 involving the genes STS, variable charge X-linked (VCX; *300229), pseudouridine 5′-phosphatase (PUDP; *306480), Patatin like phospholipase domain containing-4 (PNPLA4; *300102) and microRNA MIR4767 and MIR651.

Discussion and conclusion
We report on a male newborn with nonaccidental association of IHPS, kidney failure and maternal Xp22.3 deletion involving the STS gene.

IHPS is the most common form of gastrointestinal obstruction in infancy (1:700), five times more frequent in males than in females and hereditarily is high as 87% [19, 20]. Isolated and syndromic IHPS are described [21]. The exact etiology of isolated IHPS is unknown, although neuronal nitric oxide synthase (NOS) upregulation and an extracellular matrix abnormality have been reported in subsets [21]. Various potential genetic loci have been investigated, as well as various environmental factors (maternal smoking or young age, firstborn, feeding practice, post-natal erythromycin use) without producing conclusive data. Interestingly, reducing erythromycin indications and increasing dietary intake of omega-3 fatty acids in Western countries during the last decade probably decreased the incidence of isolated IHPS [20, 22].

By studying syndromic IHPS (Table 1) it was evidenced that the lipid metabolism plays a fundamental role in etiopathogenesis [23]. The risk of IHPS is inversely and significantly associated with total cholesterol level with an Odds ratio of 0.77 (95% CI, 0.64–0.92; p = 0.005) per 10 mg/dL [24]. Indeed, there are higher incidence of IHPS in syndromes affecting the lipid metabolism. A classic example is the Smith-Lemli-Opitz syndrome, an autosomal recessive congenital disorder caused by mutations in the 7-dehydrocholesterol reductase (DHCR7) gene at 11q13. Affected individuals are unable to complete the final step in cholesterol biosynthesis with accumulation of aberrant 7-dehydrocholesterol in developing tissues causing a wide range of metabolic and developmental abnormalities, including IHPS in 10–15% of cases [21]. In congenital generalized lipodystrophy type IV (CAVIN1 gene at 17q21) diffuse skeletal and smooth muscle hypertrophy are leading to cardiac arrhythmia and IHPS [21, 25]. In syndromes associated with hypotonia, as in FG syndrome 3 (Xp22.3) or Down syndrome (critical region 21q22.3), the IHPS incidence is about 7% [3, 21]. Other syndromes frequently associated with IHPS are connective tissue disorders in which abnormal or excess of connective tissue in the pylorus gradually develop mechanic obstruction [21]. Furthermore, biopsies have shown not only muscle layer hypertrophy but also accumulation of extracellular matrix molecules (chondroitin-sulfate proteoglycan and fibronectin) [26]. This is also the underlying cause for unsuccessful non-surgical conservative treatment with oral or intravenous administration of atropine, leaving the surgical extramucosal pyloromyotomy as the gold standard [27].

STS alterations as in our case report, can lead to disturbed intracellular metabolism of cholesterol and to storage phenomenon of cholesterol sulphate. It was

![Fig. 1 At 24 days of life, voiding cystourethrogram is showing absence of bladder (B) and urethral abnormalities, but right-sided vesicoureteral reflux with moderate dilation of the ureter (U), renal pelvis (R) and calyces and blunting of fornices as well as accidental finding of persistent distended stomach (S) with undulating contours known as Caterpillar sign, virtually pathognomonic for hypertrophic pyloric stenosis](image-url)
### Table 1: Differential diagnosis of syndromic infantile hypertrophic pyloric stenosis (IHPS) and renal anomalies as variable features (Bioinformatics were obtained from open-source GeneCards.org and Malacards.org and from Peeters et al. [21])

| Cytogenetic region/gene(s) | n. of IHPS cases | Mode of inheritance | Phenotype |
|---------------------------|------------------|--------------------|-----------|
| 1p36/SKI, SPEN, RERE, PRDM16, GABRD, HSPG2 | 1–4 | AD | 1p36 deletion syndrome (craniofacial dysmorphism, hydrocephalus, genitourinary and neurodevelopmental disorders) |
| 2q22.3/ZE82 | 1–4 | AD | Mowat-Wilson syndrome (craniofacial dysmorphism, deep set eyes, Hirschsprung disease, hydrenephrosis) |
| 2q37.3/HDAC4 | 1–4 | AD | 2q37 microdeletion syndrome (round face, multicystic kidneys, neurodevelopmental disorders) |
| 3p25 | 1–4 | AD | 3p25 microdeletion syndrome (trigonocephaly, microcephaly, cardiac and genitourinary malformations, neurodevelopmental disorders); Noonan syndrome 5 (3p25.2/RAF1 mutations) |
| 4q22.1/PKD2 | 1–4 | AD | Polycystic kidney disease 2, lateralization defects |
| 5p13.2/NIPBL | 11–50 | AD | Cornelia de Lange syndrome (microbrachicephaly, synophrys, growth retardation, genitourinary malformations, cardiac and neurodevelopmental disorders) |
| 6p12.3-p12.2/PKHD1 | 1–4 | AR | Polycystic kidney disease 4, Caroli disease |
| 6p24.3/TFAP2A | 1–4 | AD | Branchiooculofacial syndrome (orofacial clefts, hearing loss, renal agenesis or cystic anomalies) |
| 6q15/MAP 3K7 | 1–4 | AD | Frontometaphyseal dysplasia 2, cardiac and genitourinary malformations |
| 7q21.2/PEX1 | 1–4 | AR | Zellweger syndrome (extreme hypotonia, seizures, renal and hepatic cysts/disfunction) |
| 8q12.2/CHD7 | 1–4 | AD | CHARGE syndrome (coloboma, heart anomaly, choanal atresia, genitourinary and ear malformations); Kallmann syndrome (anosmia, hypogonadotropic hypogonadism) |
| 10q24.32/NFKB2 | 1–4 | AD | Common variable immunodeficiency-10, nephrotic syndrome |
| 10q26/FGFR2 | 1–4 | AD | Apert syndrome (craniosynostosis, complete syndactyly, hydrenephrosis); Beare-Stevenson syndrome (craniosynostosis, cutis gyrata) |
| 11p13/WT1 | 1–4 | AD | Derys-Drash syndrome (genitourinary malformations and neoplasia) |
| 11p15.5/HRAS | 5–10 | AD | Costello syndrome (fetal overgrowth, craniofacial dysmorphism, periorificial papillomatia, echogenic kidneys, cardiomyopathy, neurodevelopmental disorders) |
| 11q13.4/DHCR7 | 11–50 | AR | Smith-Lemli-Opitz syndrome (short stature, craniofacial dysmorphism, cleft palate, genitourinary malformations, syndactyly of second and third toes, cardiac and neurodevelopmental disorders) |
| 12q23.2/PAH | 5–10 | AR | Phenylketonuria (microcephaly, pale pigmentation, neurodevelopmental disorders if not recognized) |
| 12q24.11/UBE3B | 1–4 | AR | Kaufman oculocerebrofacial syndrome (facial dysmorphism, cardiac, genitourinary malformations and neurodevelopmental disorders) |
| 12q24.13/PTPN11 | 1–4 | AD | Noonan syndrome 1 (short stature, facial dysmorphism, wolly hair, webbed neck, cardiac and genitourinary malformations) |
| Trisomy 13 | 1–4 | AR | Patau syndrome (hypotelorism, orofacial clefts, polydactyly, aplasia cutis, visceral malformations) |
| 14q13.2/PPP2R2C | 1–4 | AR | Gonadal dysgenesis, dysmorphic facies, retinal dystrophy, myopathy |
| 14q32 | 1–4 | AD | Temple syndrome (short stature, maternal disomy) |
| 16p13.3 | 1–4 | AD | Polycystic kidney disease 1, intracranial aneurysm |
| 16q22.2/DHODH | 1–4 | AR | Miller syndrome (postaxial acrofacial dysostosis, genitourinary malformations) |
| 17q12/HNF1B | 1–4 | AD | HNF1B-related tubulointerstitial kidney disease, diabetes |
| 17q21/CAVIN1 | 5–10 | AR | Congenital generalized lipodystrophy type IV (muscular dystrophy, arrhythmia, phlebothrombolympathy) |
| 17q21.31/KANSL1 | 1–4 | AD | Koolen-De Vries syndrome (craniofacial dysmorphism, cardiac and genitourinary malformations) |
| Trisomy 18 (18p) | 5–10 | AD | Edwards' syndrome (craniofacial dysmorphism, omphalocele, vertical talus, visceral malformations) |
| 18p11/PIEZO2 | 1–4 | AD | Marden-Walker syndrome (microcephaly, blepharophimosis, arthrogryposis, genitalinary malformations) |
| 18q21.32/CCBE1 | 1–4 | AR | Hennekam lymphangiectasia-lymphedema syndrome |
| 19q13.12/NPHS1 | 5–10 | AR | Nephrotic syndrome type 1, hyperlipidemia |
| 19p13.2/ZNF699 | 1–4 | AR | DEGCAGS syndrome (neurodevelopmental disorders, visceral malformations) |
evidenced that age of onset of ichthyosis or absent/mild forms of XLI, frequently found in Southern European countries, are not related to width of Xp22.3 deletion [12, 18]. The late-onset of cutaneous presentation in our newborn is possible and clinical follow up have to direct the functional significance of these genes remains under investigation. VCX, PUDP and mitochondria-related PNPLA4 have been implicated in neurocognitive development, although the functional significance of these genes remains under debate [11, 13]. KAL1 gene, implicated in urogenital development, is not deleted in our case.

Vomiting and growth failure present a clinical challenge in neonatal age. Major causes are severe gastroesophageal reflux, neonatal sepsis, anatomical and functional gastrointestinal obstructions including IHPS and pylorospasm; less frequent are food allergy, inborn errors of metabolism, congenital adrenal hyperplasia, intracerebral abnormalities such as subdural hemorrhage or hydrocephalus, drugs or toxic agents and/or renal tubular acidosis. This spectrum widens in case of CAKUT, as in our patient, including renal impairment, risk of urosepsis and renal adapted diet. A concomitant edema could involve also the functional significance of these genes remains under debate [11, 13]. KAL1 gene, implicated in urogenital development, is not deleted in our case.

| Cytogenetic region/gene(s) | n. of IHPS cases | Mode of inheritance | Phenotype |
|----------------------------|------------------|---------------------|-----------|
| 19ql3.2/UTBP4              | 1–4              | AR                  | Cuts laxa type lc (hydronephrosis, bladder diverticula) |
| 20q13.33/SOX18             | 1–4              | AD                  | Glomerulonephritis, hypotrichosis, lymphedema, telangiectasia |
| Trisomy 21                 | > 50             |                     | Down syndrome (hypotonia, craniofacial dysmorphism, sandal gap, cardiac and gastrointestinal malformations, neurodevelopmental disorders) |
| 21q22.3/COL18A1            | 1–4              | AR                  | Knobloch syndrome (eye and CNS abnormalities, aplasia cutis, duplex kidneys or ureters) |
| 22q11.2/BCR, MAPK1         | 1–4              |                     | Cornelia de Lange syndrome (microbrachicephaly, synophrys, genitourinary malformations, neurodevelopmental disorders) |
| Xp11/SMC1A                 | 11–50            | XL                  | X-linked ichthyosis; FG syndrome (hypotonia, macrocephaly, craniofacial dysmorphism, anorectal malformations); Kallmann syndrome (anosmia, hypogonadotropic hypogonadism) |
| Xp11.4/BCOR                | 1–4              | XL                  | Lenz microphthalmia, genitourinary malformations |
| Xp22/STS, FG53, KAL1       | 5–10             | XL                  | X-linked ichthyosis; FG syndrome (hypotonia, macrocephaly, craniofacial dysmorphism, anorectal malformations); Kallmann syndrome (anosmia, hypogonadotropic hypogonadism) |
| Xq11.2/AMER1               | 1–4              | XL                  | Osteopathia striata, macrocephaly, cranial sclerosis, multicystic kidneys, male lethality |
| Xq13/MED12                 | 5–10             | XL                  | FG syndrome type 1 also known as Opitz-Kaveggia (hypotonia, macrocephaly, anorectal malformation) |
| Xq26.2/GPC3                | 1–4              | XL                  | Overgrowth, organomegaly |
| Xq28/FLNA, NAA10           | 1–4              | XL                  | Pseudobstruction, hydrenephrosis, aortic valvular dysplasia; Lenz microphthalmia; frontometaphyseal dysplasia |

Abbreviations: AD Autosomal recessive, AMER1 APC membrane recruitment protein 1, AR Autosomal recessive, BCOR corepressor for B-cell lymphoma 6, BCR Breakpoint cluster region, CAVIN1 Caveolae associated protein 1, CBBE1 Collagen and calcium-binding EGF domains 1, CHD7 Chromodomain helicase DNA binding protein 7, CNS Central nervous system, COL18A1 Collagen type XVIII alpha 1 chain, DHCR7 7-dehydrocholesterol reductase gene, DHH0H Dihydropyrrurate dehydrogenase gene, PKHD1 ciliary IPT domain containing fibrocytivor-polyductin, FGFR2 fibroblast growth factor receptor 2, FGF3 FG syndrome 3, FLNA Filamin A, GABRD Gamma-amino butyric acid type A receptor subunit delta, GPC3 Glypican 3, HDAC4 Histone deacetylase 4, HNF1B Hepatocyte nuclear factor-1-beta, HRAS HRas Proto-Oncogene, HSPG2 Heparan sulfate proteoglycan 2, KAL1 anosmin 1, KANSL1 KAT8 regulatory NSL complex subunit 1, LTBP4 Latent transforming growth factor beta binding protein 4, MAP3K7 Mitogen-activated protein kinase kinase kinase 7, MAPK1 Mitogen-activated protein kinase 1, MED12 Mediator complex subunit 12, NAA10 N-alpha-acetyltransferase 10 NatA catalytic subunit, NFKB2 Nuclear factor kappa B subunit 2, NRXN1 Nkx2-1, PDK2 Polyclastin, PPP2R3C Protein phosphatase 2 regulatory subunit B double prime gamma, PRDM16 PR/SET domain 16, PTEN Protein tyrosine phosphatase non-receptor type 11, RAF1 Raf-1 proto-oncogene, RERE Arginine-glutamic acid dipeptide repeats, SKI SKI proto-oncogene, SMCA1 Structural maintenance of chromosomes 1A, SOX18 SRY-box transcription factor 18, SPEN Spen family transcriptional repressor, ST5 Steroid sulfatase, TFFAP2 Transcription factor AP-2 alpha, UBE3B Ubiquitin protein ligase E3B, W1T Wilms tumor 1 transcription factor, XL X-linked, ZEB2 Zinc finger E-box binding homeobox 2, ZNF699 Zinc finger protein 699
In conclusion, aberrant cholesterol sulfate storage due to STS deletion as the underlying pathomechanism is not limited to oculocutaneous phenotypes but could also lead to co-occurrence of both IHPS and kidney abnormalities, as we report. Thus, although these two latter pathologies have a high incidence in the neonatal age, their simultaneous association in our patient is resembling not a chance but a real correlation expanding the clinical spectrum associated with Xp22.31 deletions.

Abbreviations
ARS2: Arylsulfatase gene D; CAKUT: Congenital anomalies of the kidney and urinary tract; CAVIN1: Caveolae associated protein 1; DHCR7: 7-dehydrocholesterol reductase; IHPS: Infantile hypertrophic pyloric stenosis; KAL1: Kallmann syndrome 1 gene; NGS: Nitric oxide synthase; OA1: Ocular albinism type 1; PKD: Polycystic kidney disease; PNPLA4: Patatin like phospholipase domain containing-4; PUDP: Pseudouridine 5'-phosphatase; SHOX: Short stature homeobox gene; STS: Steroid sulfatase gene; VCX: Variable charge X-linked.

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Authors' contributions
IAMS contributed in all parts of the study, concepted, and wrote the paper. MG contributed to clinical management and consulting and revised the manuscript. MC performed surgical consulting and instrumental investigation. MMDA performed the nephrological assessment. GS contributed to clinical management and follow-up. FF collected the patient data and revised the literature. VA contributed to the interpretation of genetic data. EP performed data analysis and interpretation, and critically revised the manuscript. GC performed genetical consulting, coordinated and supervised all parts of the study. All authors read and approved the final manuscript.

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Declarations

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Parent's informed written consent was provided.

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Not applicable.

Competing interests
Not applicable.

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