HHS Public Access

Author manuscript

Am J Med Genet A. Author manuscript; available in PMC 2023 January 31.

Published in final edited form as:

Am J Med Genet A. 2021 December ; 185(12): 3762–3769. doi:10.1002/ajmg.a.62449.

Expanding the phenotypic spectrum of Mendelian connective tissue disorders to include prominent kidney phenotypes

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Abstract

Heritable connective tissue disorders are a group of diseases, each rare, characterized by various combinations of skin, joint, musculoskeletal, organ, and vascular involvement. Although kidney abnormalities have been reported in some connective tissue disorders, they are rarely a presenting feature. Here we present three patients with prominent kidney phenotypes who were found by whole exome sequencing to have variants in established connective tissue genes associated with Loeys-Dietz syndrome and congenital contractural arachnodactyly. These cases highlight the importance of considering connective tissue disease in children presenting with structural kidney disease and also serves to expand the phenotype of Loeys-Dietz syndrome and

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AUTHOR CONTRIBUTIONS

Alanna Strong evaluated the patients clinically, helped in variant interpretation, and drafted the manuscript. Elaine Zackai, Stacey Drant, Kevin Meyers, Susan Furth, and Sonya Lopez each evaluated a subset of the patients, guided appropriate genetic, cardiac and kidney evaluations, imaging studies and clinical care, and recognized each patients' atypical presentations. Nina Gold and Jessica Gold provided references for the pathophysiology of kidney disease in connective tissue disorders. They also critically reviewed the manuscript. Reed Pyeritz guided phenotype evaluation and variant interpretation, and critically reviewed and edited the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

possibly congenital contractural arachnodactyly to include cystic kidney disease and cystic kidney dysplasia, respectively.

Keywords

congenital contractual arachnodactyly; kidney cysts; kidney dysplasia; Loeys-Dietz syndrome

1 | INTRODUCTION

Connective tissue is composed of diverse proteins that interact to form an extensive extracellular matrix for embryogenesis and organ development and function (McKee et al., 2019). Pathogenic variants in genes encoding connective tissue components can cause diverse diseases associated with skin, bone, joint, organ, and vascular deformity and instability (Hoffjan, 2012; Pyeritz, 2019; van Loon et al., 2020). These disorders can be inherited in an X-linked dominant, X-linked recessive, autosomal recessive, and autosomal dominant manner with variable penetrance and expressivity (Murphy-Ryan et al., 2010; Renner et al., 2019).

Loeys-Dietz syndrome (LDS) and congenital contractural arachnodactyly (CCA) are two examples of connective tissue disorders with diverse organ system involvement. LDS is an autosomal dominant disorder caused by pathogenic variants in *TGFBR1, TGFBR2, TGFB2, TGFB3, SMAD2*, and *SMAD3* (Loeys & Dietz, 2021; MacCarrick et al., 2014; Schepers et al., 2018; Verstraeten et al., 2016). LDS is clinically characterized by hypertelorism, bifid uvula, cleft palate, scoliosis, vertebral malformations, pectus abnormalities, pes planus, dural ectasia, allergic/autoimmune features (predisposition to environmental and food allergies, eczema, asthma, eosinophilic esophagitis, inflammatory bowel disease, sinusitis, and recurrent otitis media), aortic dilation, dissection and aneurysm, and arterial tortuosity of variable penetrance and expressivity (Loeys et al., 2005; Loeys & Dietz, 2021).

CCA is also an autosomal dominant disorder of variable penetrance and expressivity caused by pathogenic *FBN2* gene variants (Putnam et al., 1995). CCA is characterized by tall stature, dolichostenomelia, arachnodactyly, joint contractures, scoliosis, pectus abnormalities, and crumpled ears (Callewaert et al., 2009; Meerschaut et al., 2020; Tunçbilek & Alanay, 2006). Congenital heart disease, aortic disease, and gastrointestinal tract atresias have been reported, but are rare, and the vascular disease is typically less severe than that seen in LDS (Currarino & Friedman, 1986; Wang et al., 1996).

Although CCA is generally less severe, LDS and CCA have significant overlap in their clinical features (Meerschaut et al., 2020; Woolnough et al., 2017), likely stemming from their shared biology. Specifically, *FBN2* implicated in CCA encodes fibrillin-2, a protein critical for microfibril formation. In addition to their roles in tissue structural integrity, microfibrils also modulate transforming growth factor beta (TGFB) signaling by controlling ligand availability and activity (Hubmacher et al., 2006). The causal genes for LDS encode ligands, receptors, and transcription factors in the TGFB family. Thus, both conditions result in TGFB pathway dysregulation.

Here we report three patients who presented with prominent organ malformations including cystic kidney abnormalities and cystic kidney dysplasia found by whole exome sequencing to have inherited variants in *SMAD2, FBN2*, and *TGFBR1* consistent with diagnoses of LDS and CCA. These cases highlight the variability of these diseases within families and suggest that kidney disease can be a presenting feature of these connective tissue disorders.

2 | PATIENT PRESENTATIONS

2.1 | Patient 1

Patient is a 12-year-old male with a history of heterotaxy syndrome with complex congenital heart disease (right atrial isomerism, unbalanced right dominant atrioventricular septal defect, double outlet right ventricle, pulmonary atresia, infra-diaphragmatic total anomalous pulmonary venous return, right aortic arch, and bilateral superior vena cavas), asplenia, aspiration, feeding intolerance, osteopenia, iatrogenic adrenal insufficiency, kidney cysts, and developmental delay. He was born at 37 weeks gestational age via vaginal delivery weighing 3.15 kg (25%). Pregnancy was complicated by prenatal ultrasound findings concerning for heterotaxy syndrome with complex congenital heart disease, congenital cystic adenomatoid malformation (CCAM), and nonimmune hydrops. CCAM and nonimmune hydrops resolved before delivery. First cardiac surgery was at Day 4.

Clinical course has been complicated by intestinal malrotation, asplenia, poor oral intake with G-tube dependence, velopharyngeal insufficiency, developmental delay, and chronic hypoxemic respiratory failure requiring combined heart and lung transplantation at 4 years and 11 months of age. Post-transplant course was complicated by parainfluenza infection, resulting in respiratory failure requiring tracheostomy placement and acute kidney failure. Chromosomal microarray and heterotaxy gene panel (PreventionGenetics) were nondiagnostic.

The patient was referred to Clinical Genetics at 12 years of age due to the new incidental discovery of multiple, bilateral cortical kidney cysts. There was no family history of kidney cysts or kidney disease. Family history was notable for multiple food and environmental allergies and sporadic skin rashes in father, a paternal grandmother and paternal aunt with osteoarthritis, and a paternal grandfather who died in his 6th decade from a cerebral aneurysm. Examination showed a weight of 32.7 kg (6%), a height of 132 cm (<3%; 50% for 8.5 years of age), and a normal head circumference. He had mildly protuberant ears, pectus excavatum, mild scoliosis, multiple surgical scars, doughy and soft skin, and extremity hypermobility (Figure 1). Exome sequencing was sent to GeneDx for concern for underlying ciliopathy and was notable for a paternally inherited pathogenic *SMAD2* splice variant, c.997+1G>A, consistent with a diagnosis of *SMAD2*-spectrum disease/LDS. Paternal grandmother was also found to harbor the familial variant. As *SMAD2* variants are typically not associated with cystic kidney disease, targeted *PKD1, PKD2*, and *PKHD1* testing of the proband was performed and was negative.

Due to the association of LDS with arterial abnormalities, a CT angiogram of the head and neck was performed, which showed mild tortuosity of the internal carotid arteries, intracranial vertebrobasilar system, vertebral arteries at the C2-C3 level, and at the proximal

left V1 segment of the vertebral arteries. The left brachiocephalic trunk and the aortic arch were mildly dilated. Of note, the proximal aortic root is donor-derived.

The patient's father had a normal echocardiogram. MRA of the head, neck, chest, abdomen, and pelvis were normal. The paternal grandmother was deceased at the time of genetic testing, so phenotypic evaluation including vascular studies and echocardiogram could not be performed.

2.2 | Patient 2

Patient 2 is an 8-year-old male with a history of prematurity, developmental delay, bicuspid aortic valve, dilation of the aortic root and ascending aorta, and bilateral cystic kidney dysplasia. He was the product of a naturally conceived pregnancy to a 25 year-old G3P0→1 mother. Pregnancy was complicated by oligohydramnios and prenatal ultrasounds concerning for kidney dysplasia. Prenatal karyotype and microarray were nondiagnostic. Family history was notable for two prior pregnancies complicated by kidney dysplasia and oligohydramnios, both with fetal demise at 28 and 36 weeks gestation, respectively.

Patient was born at 29 weeks gestational age via emergency caesarian section for fetal distress. Birth weight was 1.29 kg (50%–75%). Patient remained in the NICU for 5 months for management of kidney dysplasia, cerebral hemorrhage, feeding immaturity status-post G-tube placement, patent ductus arteriosus status-post surgical ligation complicated by chylothorax, retinopathy of prematurity status-post laser surgery, and bilateral inguinal hernias status-post repair.

Patient is currently 8 years old. Clinical course has been complicated by progressive moderate to severe dilation of the aortic root and ascending aorta detected at 1 year of age monitored annually via cardiac MRI, vesicoureteral reflux and end-stage kidney disease status-post kidney transplant at 5 years of age, coxa valga, and bilateral hip subluxation. Development is globally delayed with sitting achieved at 12 months of age, and independent standing achieved at 4 years. Patient currently ambulates with a gait trainer and is nonverbal.

Growth parameters at 8 years of age were notable for a weight of 20.1 kg (3%) and a height of 114 cm (<1%; 50% for 5.5 years). Clinical genetics evaluation via telehealth at 8 years of age showed microcephaly, ptosis, epicanthus, upslanted palpebral fissures, high palate, thin lips, widely spaced teeth, and prominent ears with thin superior helices (Figure 2). Trio exome sequencing was sent to GeneDx and was notable for a maternally inherited nonsense variant of uncertain significance in *TGFBR1* (c.428T>A; p.Leu143*). Maternal echocardiogram was normal; however, she was noted to have long limbs with a short torso, mild scoliosis, and pectus excavatum. Kidney ultrasound showed two right renal arteries.

2.3 | Patient 3

Patient 3 is a 16-year-old male with a history of cystic kidney dysplasia, mild aortic root dilation and facial asymmetry. He was born at 37 weeks gestational age weighing 2.95 kg (50%). Prenatal ultrasounds showed unilateral structural kidney abnormalities and oligohydramnios. Kidney function was initially compromised after birth, but resolved within 7 days. Postnatal abdominal ultrasound showed a small right kidney with decreased

corticomedullary differentiation and cortical cysts, and a small, cystic dysplastic left kidney with absent corticomedullary differentiation.

Clinical Genetics evaluation at 6 months of age showed right hemifacial microsomia and preauricular skin tag, suggestive of Goldenhar syndrome or Townes-Brock syndrome. Sequencing of *SALL1* was negative. Radiology of the spine was normal, echocardiogram showed mild aortic root dilation, and ophthalmologic examination done for concern for Goldenhar syndrome showed a right dermoid cyst.

The patient demonstrated normal development without support. He developed end-stage kidney disease requiring kidney transplant at 14 years of age. The post-transplant course was complicated by neutropenia and mucositis, felt to be medication-related. Because of his complex and unusual course, Clinical Genetics was reconsulted at age 15 years. Review of the family history was notable for a father with tall stature (193 cm) and an inability to extend or supinate his arms at the elbows, a paternal uncle with pectus excavatum who died at 15 years from complications of transposition of the great arteries, a paternal great-uncle through the paternal grandfather with cleft palate and iris colobomas who died in infancy, and a paternal cousin with tall stature (greater than 183 cm) and pectus excavatum.

Growth parameters at 15 years showed a weight of 48.1 kg (8%) and a height of 166 cm (17%). Physical examination via telehealth showed right hemifacial microsomia, mild ptosis, ear asymmetry with the right ear larger than the left, partial stenosis of the left ear canal, pectus excavatum, and arachnodactyly (Figure 3). Due to concern for connective tissue disorder with atypical features, chromosomal microarray and trio exome sequencing were sent to GeneDx, which showed a paternally inherited variant of uncertain significance in *FBN2* (c.1616G>A; p.(C539Y)), consistent with a possible diagnosis of CCA. Cascade familial testing was declined.

3 | DISCUSSION

Connective tissue disorders are highly diverse and affect multiple organ systems with extreme inter- and intrafamilial variability (Hakim & Sahota, 2006; McKee et al., 2019; Pope et al., 2019). Prompt recognition of this class of disorders is imperative, as it permits early screening for known vascular and organ complications. Here we report three cases of well-known connective tissue disorders, LDS and CCA, that presented with atypical features of multi-system involvement, especially kidney abnormalities, including kidney cysts and dysplasia (Figure 4). We highlight these cases to emphasize the atypical presentations these diseases can have and the need to image the kidneys.

Patient 1 presented with heterotaxy-spectrum disease and was found to have a pathogenic variant in *SMAD2*. *SMAD2* encodes a transcription factor in the transforming growth factor B (TGFB) signaling pathway, which plays a critical role in organ morphogenesis and vascular development (Goumans et al., 2009). Pathogenic *SMAD2* variants have been identified in individuals with syndromic aortic aneurysm, LDS, complex congenital heart disease, heterotaxy-spectrum disease, and developmental delay (Cannaerts et al., 2019; Granadillo et al., 2018; Schepers et al., 2018; Zaidi et al., 2013). Our patient's splice

variant has been previously reported in an individual with complex congenital heart disease, heterotaxy-spectrum, asplenia, and intestinal malrotation (Zaidi et al., 2013). Of note, the reported patient's variant arose de novo, and our patient's variant is inherited from a father with a structurally normal heart, and he inherited this variant from a mother with no known congenital heart differences. It is unknown why our patient presented with such a severe phenotype relative to his family. Possible explanations include a contribution from variants in other morphogen genes, or dominant expression of the mutation-bearing *SMAD2* allele during development due to transcriptional stochasticity or epigenetic modification.

Kidney involvement has not been reported in *SMAD2*-spectrum disease. It is possible that this feature is variant-dependent, and the reported patient with the same variant is too young to have developed this sign. Kidney cysts have been reported in the related connective tissue disorder Marfan syndrome caused by pathogenic variants in *FBN1* (Chow et al., 2007; Nicot et al., 2019; von Kodolitsch et al., 2019). *SMAD2* is expressed in the developing kidney (Vrljicak et al., 2004), and *SMAD2* is suspected to play a role in cystogenesis in cystic kidney disease, consistent with a relationship between *SMAD2* and kidney cysts (Chatterjee et al., 2017; Hassane et al., 2010; Leonhard et al., 2016).

Patient 2 similarly presented with multi-organ involvement including dilation of the aortic root and ascending aorta and kidney dysplasia. Trio exome sequencing showed a maternally inherited nonsense variant of uncertain significance in *TGFBR1*. *TGFBR1* encodes a receptor for the TGFB family upstream of *SMAD2* and also plays a critical role in organogenesis and vascular patterning (Goumans et al., 2009). *TGFBR1* is also expressed in the developing kidney (Dumbrava et al., 2021). Pathogenic *TGFBR1* variants have been identified in individuals with LDS and familial thoracic aortic aneurysm (Loeys et al., 2006). Mother has some features of connective tissue disease, including scoliosis, pectus excavatum, and long limbs; however, it is unclear why her vasculature and kidneys are unaffected in contrast to her son. It is also unknown whether the two previous pregnancies affected by kidney dysplasia also harbored this variant. Importantly, the identified variant is a variant of uncertain significance. *TGFBR1* is a highly conserved gene with a pLI of 0.85, and the identified variant is absent in gnomAD, 1000 genomes and ExAc. Although *TGFBR1* missense variants are typically associated with connective tissue disease, splice site and nonsense variants have been reported, and a haploinsufficient mouse model has severe vascular malformations (Fujiwara et al., 2018; Fujiwara et al., 2019; Renard et al., 2014). Loss-of-function is an established mechanism for *TGFBR1*-spectrum disease (MacFarlane et al., 2019).

Patient 3 presented with cystic kidney dysplasia and physical features consistent with Goldenhar syndrome and was found to have a paternally inherited variant of uncertain significance in *FBN2*, consistent with a possible diagnosis of CCA. Paternal family history is notable for multiple individuals with tall stature and pectus deformities as well as individuals with complex congenital heart disease, cleft palate, joint contractures, and iris colobomas, all features described in CCA (Callewaert et al., 2009; Meerschaut et al., 2020; Tunçbilek & Alanay, 2006). Facial asymmetry has been reported in CCA as well as in other congenital contracture syndromes; however, kidney dysplasia has not been reported (Hall et al., 1983; Jaman & Al-Sayegh, 2016). The classic features of CCA, described

first by Beals and Hecht in 1972, do not include kidney abnormalities, but the majority of patients suspected of CCA do not have imaging of the abdomen (Hecht & Beals, 1972). Like *SMAD2* and *TGFBR1, FBN2* is also expressed in the developing kidney (Quondamatteo et al., 2002).

Kidney disease due to pathogenic variants in genes encoding components of the connective tissue has been reported, most notably in Alport syndrome (AS). AS is a heritable connective tissue disorder characterized by hematuria, hearing loss and variable progression to end-stage kidney disease caused by pathogenic variants in genes encoding components of the glomerular basement membrane, including *COL4A3, COL4A4*, and *COL4A5* (Nozu et al., 2019). Of note, there are typically not overt connective tissue findings such as tall stature, hypermobility, scoliosis, pes planus or pectus deformities, nor is congenital heart disease an associated feature. Kidney dysplasia has also been reported in classic connective tissue disorders (Kaplan et al., 1995, 1997).

Although the detected *FBN2* variant is classified as a variant of uncertain significance, *FBN2* is a highly conserved gene with a pLI of 1, the identified variant affects a cysteine residue and is predicted to affect disulfide bonding, and in silico models predict a deleterious effect on protein structure and function. Most of the causal *FBN2* variants associated with CCA localize to exons 24-35, in contrast to our patient's variant, which maps to exon 12 (Park et al., 1998). It is possible that variant geography is dictating our patient's atypical presentation.

Although highly provocative that these three patients have prominent kidney features and concern for connective tissue disease, these cases do not definitively establish causality. It is possible that these patients' kidney disease is coincidental, caused by variants in multiple genes with small effect size, or by environmental triggers and exposures. Also possible is a separate genetic diagnosis not revealed by exome. Indeed, multiple genetic diagnoses identified by exome is well established, even though not detected in our patients (Balci et al., 2017; Hannah-Shmouni et al., 2021; Posey et al., 2016; Smith et al., 2019; Trujillano et al., 2017). Further studies are required to truly establish this association.

In summary, we present three cases of connective tissue disorders with atypical presentations that include kidney disease. We propose a low threshold for screening for kidney abnormalities in individuals with LDS and CCA, especially those with atypical features and structural differences.

ACKNOWLEDGMENTS

The authors would like to thank the patients and their families for allowing us to participate in their care and permitting publication of their cases. We would also like to acknowledge our funding sources: Medical Genetics Research Training Grant 5T32GM008638-22 (Alanna Strong).

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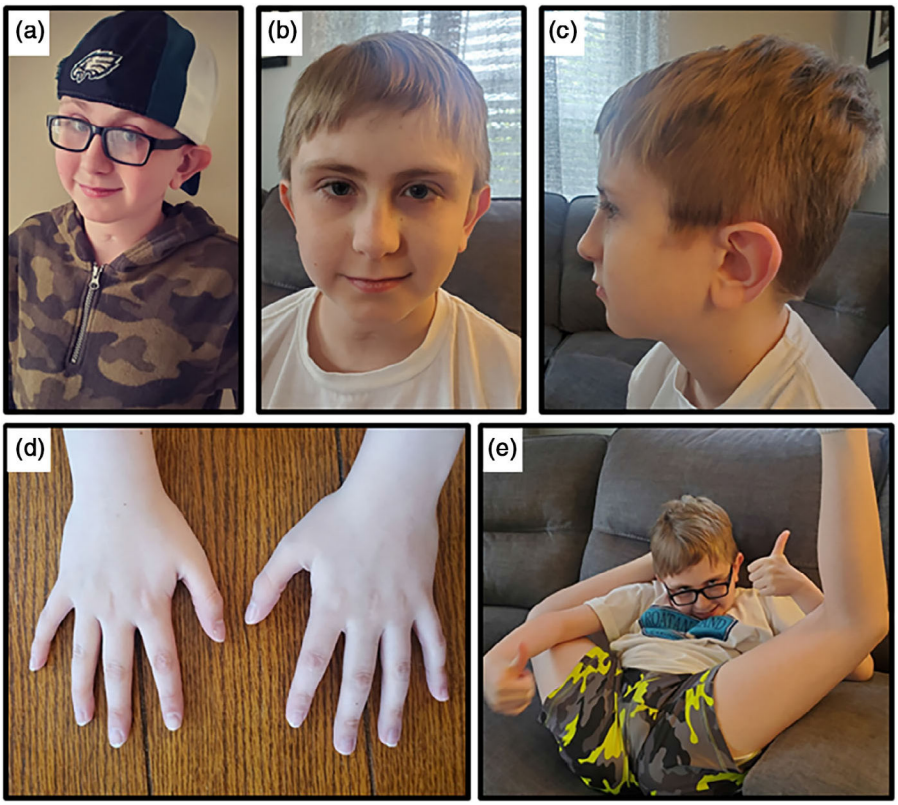

FIGURE 1.

Patient 1: (a) facial view with nondysmorphic features, thin upper lip, and slightly protuberant ear; (b) facial view again demonstrating thin upper lip and mildly protuberant ears; (c) profile view demonstrating slightly protuberant ear and normal midface; (d) hands with no arachnodactyly; (e) patient demonstrating his flexibility

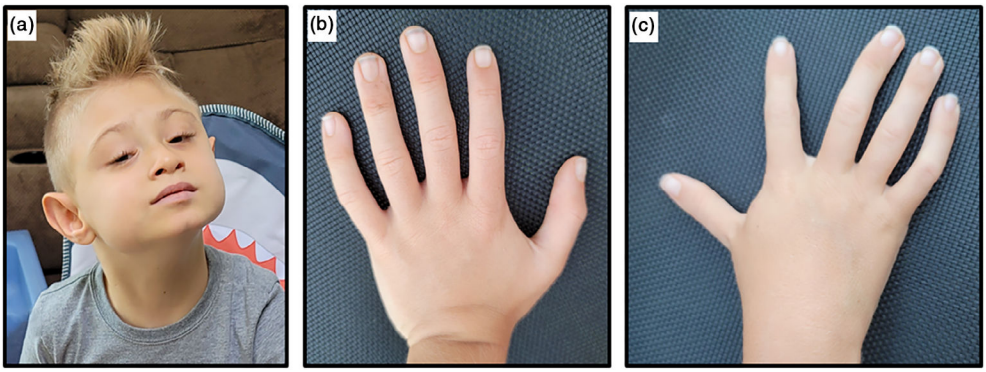

FIGURE 2.

Patient 2: (a) facial view demonstrating microcephaly, bilateral ptosis, epicanthus, upslanting palpebral fissures, and prominent ears with thin superior helices; (b) left hand demonstrating arachnodactyly; (c) right hand demonstrating an anteriorly-placed, hypoplastic thumb, and curved fifth finger

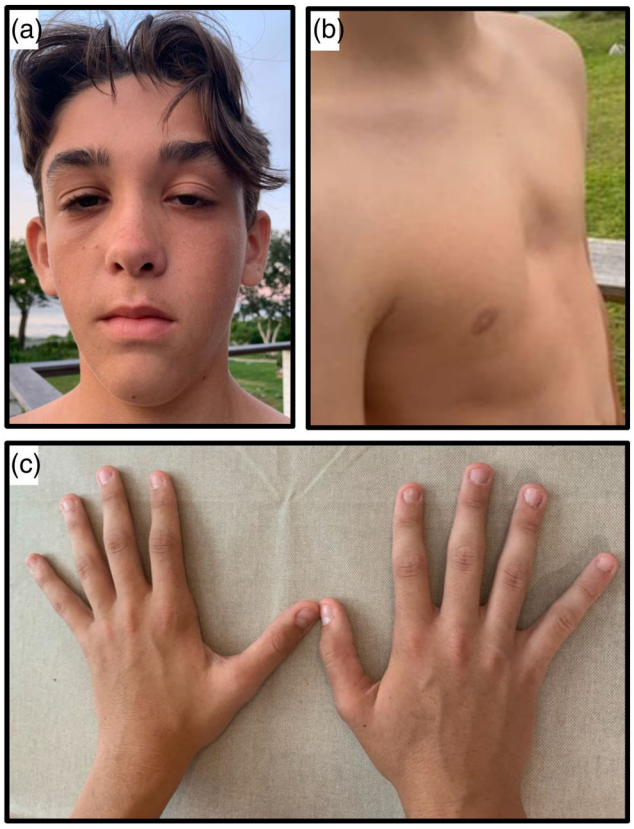

FIGURE 3.
Patient 3: (a) Facial view demonstrating smaller left ear and smaller right cheek; (b) Chest view demonstrating pectus excavatum; (c) Hands with no arachnodactyly

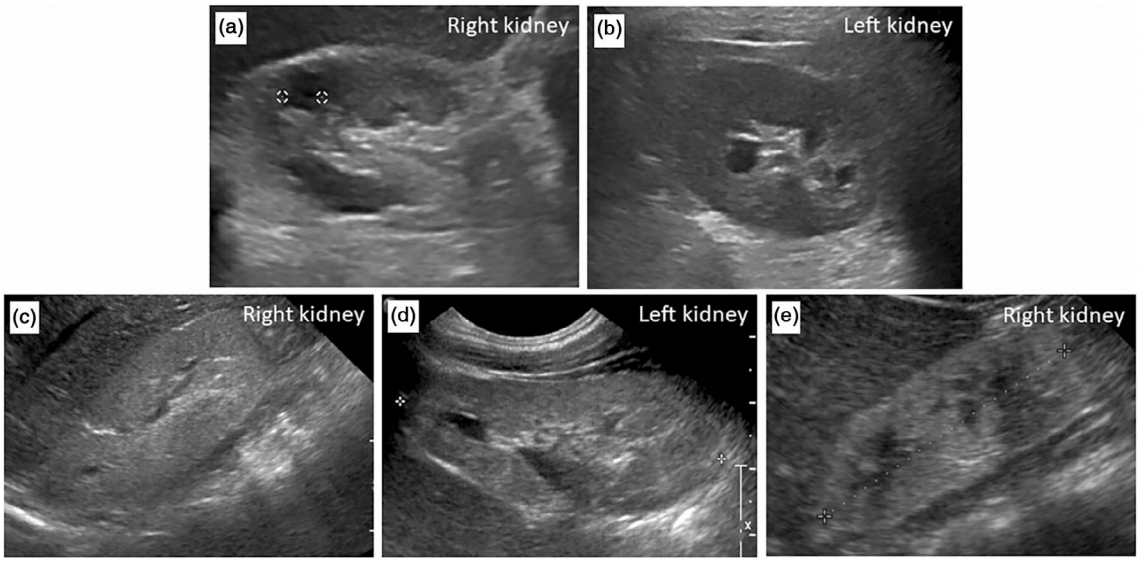

FIGURE 4.

(a, b) Patient 1 kidney ultrasound at 12 years of age demonstrating bilateral cortical cysts with normal parenchymal thickness, echogenicity, and corticomedullary differentiation. (c, d) Patient 2 kidney ultrasound at 14 months of age demonstrating echogenic kidneys with loss of corticomedullary differentiation and small cyst indicative of medical renal disease. (e) Patient 3 kidney ultrasound at 8 months of age demonstrating absent left kidney and right kidney with diffusely increased echogenicity, mild cortical thinning, and possible small, peripheral cysts