Severe Congenital Neutropenia Due To G6PC3 Deficiency Case Series of Five Patients and Literature Review

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Abstract

Glucose-6-phosphate catalytic subunit 3 (G6PC3) deficiency is characterized by severe congenital neutropenia with recurrent pyogenic infections, a prominent superficial venous pattern, and cardiovascular and urogenital malformations, caused by an alteration of glucose homeostasis, with increased endoplasmic reticulum stress and cell apoptosis. We describe five new cases from Mexico, and review 89 more patients reported in the past decade, to delineate the most frequent laboratory and genetic features, their treatment, and outcomes, and to expand the knowledge of syndromic and non-syndromic phenotypes in these patients.

Introduction

While rare diseases are individually infrequent, collectively they afflict around ten percent of the world population. Patients with rare diseases typically must endure a “diagnostic odyssey” that may take several years, before receiving a correct diagnosis and treatment. Inborn errors of immunity (IEI) are a group of rare congenital diseases caused by monogenic germline variants that result in the modification of protein expression or function, affecting the development, function, and homeostasis of the immune system (1). IEI comprise a wide spectrum of disorders that may manifest not only with increased susceptibility to infections, but also with inflammation, autoimmunity, allergy, or malignancy.

In 1950, Rolf Kostmann first described “hereditary agranulocytosis”, or severe congenital neutropenia (SCN), characterized by an early onset of recurrent bacterial and fungal infections of the mouth, umbilical stump, skin, gastrointestinal tract, bones, lungs, and lymph nodes (2).

Although pathogenic variants in *ELANE* are the most common genetic etiology of autosomal dominant (AD) SCN, several others have been described in the last two decades: X-linked *WAS* gain-of-function (GOF), autosomal recessive (AR) *HAX1*, *GFI1*, *CSF3R*, and *G6PC3* loss of function (LOF); and AD *TCIRG1* haploinsufficiency. The molecular cause is unknown in about 30% of patients with SCN.

In 2009, Boztug and Klein reported (3) a series of 12 patients with congenital neutropenia and various cardiovascular and urogenital developmental anomalies, who had homozygous and compound heterozygous variants in the gene encoding glucose-6-phosphatase catalytic subunit 3 (G6PC3 deficiency, also known as type 4 SCN, OMIM #612541), as well as prominent superficial veins (mainly in trunk and limbs). *G6PC3* is located on chromosome 17q21 and spans 6 exons.

Independently, a pair of Turkish siblings were reported with pulmonary arterial hypertension, and other abnormalities including cardiac, hematological, and skeletal defects (4). Over the last decade, the spectrum of the disease has continuously widened to include non-syndromic forms and new features (5). Here, we describe five patients from Mexico, and review the available literature for clinical features, genetic variants, treatment, and outcome of 89 more patients with G6PC3 deficiency.

Case Reports

Patient 1

A 3-month-old male, born to non-consanguineous parents from rural central Mexico, was born prematurely at 35 weeks and admitted to the neonatal intensive care unit for extensive edema and ecchymoses, with respiratory distress that required mechanical ventilation. He was started on intravenous antibiotics for pneumonia and sepsis.

Physical examination found low weight, a low-grade systolic murmur, hepatomegaly, and cryptorchidism; prominent superficial veins in thorax, abdomen and all four limbs were later noted. Laboratory work-up reported transient-variable anemia, lymphopenia, and thrombocytopenia; as well as severe persistent neutropenia and pan-hypogammaglobulinemia. An echocardiogram showed a persistent foramen ovale (4mm) with bidirectional shunt and pulmonary arterial hypertension at 58 mmHg. Abdominal ultrasound revealed pyloric stenosis and severe bilateral hydronephrosis.

Filgrastim (granulocyte-colony stimulating factor, G-CSF) was started at 3–5 µg/kg/d, with a spectacular but transient increase in neutrophil count, as well as prophylactic antibiotics (trimethoprim/sulfamethoxazole, itraconazole) and monthly intravenous immunoglobulin (IVIG) at 1g/kg. A homozygous single-nucleotide deletion in exon 1 of *G6PC3* (c.210delC, p.Phe71SerfsTer46), was identified through Sanger sequencing, a variant previously reported (6). In time, the dosage of filgrastim had to be increased up to 22 mg/kg/d, to achieve an acceptable neutrophil count. Due to this severe and early presentation, hematopoietic stem-cell transplantation (HSCT) was performed in this patient at the age of 15 months. Unfortunately, he developed neutropenic colitis and died of sepsis on day + 29.

Patient 2

A 15-year-old female, born to non-consanguineous parents from a small rural community (300 inhabitants), was admitted for a 6-year history of episodic diarrhea and intense-generalized abdominal pain, each episode lasting between 7 and 14 days, for which she had received multiple antibiotic treatments with slight improvement. Her past medical history also included pneumonia at 4 months old, as well as recurrent otitis media and other upper airway infections.

On admission, we found a severely undernourished patient, with prominent superficial veins, finger clubbing, brachymetatarsia of the third toes, and bilateral sensorineural hearing loss. Laboratory workup revealed anemia, intermittent neutropenia, and lymphopenia. Colonoscopy and histopathology were compatible with Crohn’s disease; echocardiography revealed mild tricuspid insufficiency.

She started treatment with mesalazine, trimethoprim-sulfamethoxazole (TMP-SMZ), prednisone, IVIG every 21 days, and filgrastim (G-CSF, 10mcg/kg/d). Through Sanger sequencing, a homozygous single-nucleotide deletion was found in exon 1 of *G6PC3* (c.210delC, p.Phe71SerfsTer46), the same variant

identified in Patient 1.

At age 16, she developed bronchopulmonary aspergillosis and was treated with voriconazole. Despite good adherence, complete remission of IBD was never achieved. At 17, she presented with acute abdominal pain, fever, and vomit; she died with abdominal sepsis after intestinal perforation. Remarkably, prior to this catastrophic event, she had been asymptomatic. The autopsy revealed severe extensive bowel inflammation, which was at odds with her clinical symptoms and signs.

Patient 3

A 3-month-old female patient, born to non-consanguineous Mexican parents, with a family history of three paternal uncles who died before the age of 5 years. She first presented with neonatal sepsis requiring intravenous antibiotics, after which she had 5 episodes of pneumonia and a surgically corrected rectovaginal fistula.

On physical examination, we found severe chronic malnutrition, prominent superficial veins in her abdominal wall, bilateral sensorineural hearing loss, and supplemental oxygen dependence. Her clinical assessment revealed severe neutropenia, atrial septal defect, and severe pulmonary damage due to multiple atelectasis and bronchiectasis, associated with pulmonary arterial hypertension. Whole-exome sequencing identified the same homozygous single-nucleotide deletion in *G6PC3* (c.210delC; p.Phe71SerfsTer46) as in patients 1 through 4. Patient 3 is currently 3 years old, alive, and well, under treatment with granulocyte colony stimulating factor (G-CSF, filgrastim) 30 mcg/kg/day.

Patient 4

A 9-year-old boy from northern Mexico, with no known consanguinity or family history of infections or early deaths. He started at age 3 months with suppurative otitis media and pneumonia that required admission to the intensive care unit (ICU) and was hospitalized for a month. Neutropenia was recorded since then, with absolute neutrophil counts (ANC) within the range of 450 to 790/mm3, which responded well to filgrastim (G-CSF).

However, despite the increase in neutrophil numbers, the patient persisted with multiple respiratory tract infections requiring frequent hospitalizations and parenteral antibiotics up to 5 years of age. He also presented with oral, finger and perianal abscesses, without any isolates. From 6 years on, the frequency of infections decreased to 1–2 per year. On physical examination, weight and height were normal; he had a prominent superficial venous pattern in trunk and limbs, as well as redundant skin folds in the neck, and a left inguinal hernia.

Laboratory workup reported intermittent thrombocytopenia and persistent lymphopenia; bone marrow aspirate showed myeloid cell hypoplasia and nonspecific findings. An echocardiogram revealed persistent foramen ovale (corrected percutaneously with an Amplatzer device), and pulmonary hypertension of 45mm/Hg, whereas a Doppler ultrasound of the liver documented compensated portal hypertension. Percutaneous liver biopsy reported sinusoid fibrosis and steatosis.

Sanger sequencing identified a compound heterozygous genotype, with variants in exons 1 and 4 of *G6PC3*: the same single-nucleotide deletion (c.210delC, p.Phe71SerfsTer46), and a nonsense transition (c.481C > T, p.Arg161*), respectively. The patient is currently alive and well, under treatment with granulocyte colony stimulating factor (G-CSF)

Patient 5

A 2-year-old female, born to non-consanguineous Mexican parents, was referred to our care for a history of cow's milk allergy, allergic asthma and rhinitis, recurrent otitis media, sepsis, urinary tract infection, autoimmune colitis and disseminated herpes zoster.

On physical examination, she did not have any syndromic features. Complete blood count reported severe neutropenia, anemia, intermittent lymphopenia, and thrombocytopenia. Through whole-exome sequencing analysis, a compound heterozygous genotype consisting of two single-nucleotide deletions in exons 1 and 4 of *G6PC3*, was identified (c.210delC, p.Ile70HisfsTer46) ; c.421del, p.Trp141GlyfsTer2); this second frameshift variant has not been previously described and is not found in gnomAD. The patient is alive under treatment with filgrastim (G-CSF) and prophylaxis with TMP-SMZ and fluconazole.

Ethics approval

This case series study was granted exemption by the National Institute of Pediatrics Research and Ethics Committee due to its retrospective design. All authors subscribe the 1964 Declaration of Helsinki by the World Medical Organization and its later amendments regarding human experimentation. All patients or their guardians consented to genetic diagnostic research and publication.

Review of the literature

We searched the PubMed/Medline database for the terms ("G6PC3 deficiency" OR "Dursun syndrome" OR "Severe congenital neutropenia type 4"), and selected articles published in English from 2009 to 2020. We found 89 patients reported from at least 14 countries in 4 continents (See tables. Not all reports included the country of origin). **Table 1** describes their origins, demographic, clinical and laboratory features, treatment, and outcome. **Table 2** collects their genetic variants. In **Table 3**, we summarize the most common features and findings.

Ninety-four patients were included in this review (whenever the denominator is less than 94, that attribute was not available for some patients). The distribution of the disease was similar between males (52/92, 56%) and females. Most cases were from Middle East countries (47.8%). None of the patients had adverse reactions to live vaccines such as BCG. All patients presented at least one severe infection prior to 2 years of age; however, only 28.5% (26/91) were diagnosed before the age of two.

Syndromic features were identified in 71/94 (75.5%) of the patients. The most frequent alterations were cardiovascular defects, mainly atrial septal defect in 52/94 (55.3%), valve disease 21/94 (22.3%), patent ductus arteriosus 10/94 (10.6%); and prominent superficial veins 58/94 (61.7%). Some of the cardiovascular malformations resulted in pulmonary hypertension secondary to pulmonary overflow. However, a group of patients had primary pulmonary hypertension not related to congenital cardiopathy. Thirty-seven patients (39.3%) presented with urological or genital malformations, which were more commonly seen in male patients, being cryptorchidism the most prevalent among those: 21/52 (40.53%). Other reported anomalies were urachal fistula, unilateral or bilateral inguinal hernia, hydronephrosis, genital dysplasia, and micropenis. Endocrine abnormalities were described in 28/94 patients (30%), with variable manifestations ranging from growth retardation in 12/94 (12.7%), to puberal delay (in 6/94, 6.3%), and growth hormone deficiency (4/94, 4.3%).

Other non-hematological features were sensorineural hearing loss in 12/94 (12.7%), developmental delay (11/94, 12%), and microcephaly (5/94, 5.3%). Inflammatory bowel disease was present in 10/94 (10.6%) of patients, with a higher prevalence in the syndromic group (70%); two of these patients also had oculocutaneous albinism, three had persistent lymphopenia, and one T cell lymphopenia, suggesting a more severe compromise. Splenomegaly was reported in 6/94 (6.3%).

Immunological analysis was not performed homogeneously in all patients; flow cytometry, immunoglobulins or lymphoproliferation were available only for 21/94. Although they all had severe neutropenia, some showed an intermittent increase in neutrophil counts. Intermittent thrombocytopenia was reported in 37/94 patients (39.3%), and 17 of 94 (18%) had lymphocyte counts below 1500/µl. Nineteen patients had their serum immunoglobulin levels measured, of which 9 (47.3%) presented with hypergammaglobulinemia and 2 hypogammaglobulinemia (10.5%).

Treatment was described in 76 patients; one patient did not require any pharmacological intervention, while 63/76 (82.8%) were given G-CSF, 2.6% received pegfilgrastim, and 3.9% received prophylactic co-trimoxazole as only treatment; IVIG was administered in 5/76 (6.5%) patients. Only 3 patients (4%) received hematopoietic stem cell transplant (HSCT). Patient 69 underwent HSCT due to severe IBD refractory to medical treatment and showed complete resolution of gastrointestinal symptoms; whereas patient 70 was transplanted because of the severe presentation of the disease and died from complications associated with the procedure. Long-term outcome was available for 79 patients, with survival at the time of publication of the original papers of 67/79 (84.8%) (**Table 1**).

Among the 94 reported patients, homozygous missense was the most frequent variant type (**Table 2**). Homozygous frameshift insertions, deletions, splice-site, or nonsense were also reported. Although the transition c.130C > T was associated with non-syndromic neutropenia in Pakistani patients, a genotype-phenotype correlation has not been confirmed.

Discussion

Including our five patients, a little over 100 G6PC3 deficiency cases have been described in the literature. They frequently present with recurrent and severe bacterial infections during the first year of life, such as otitis media, skin abscesses, urinary tract infections, sino-pulmonary infections, and sepsis. The diagnosis is suspected based on microbes (bacterial and fungal), infection sites (mouth, skin, bone, blood, lymph nodes, umbilical stump, respiratory and gastrointestinal tracts), and hematological findings: severe neutropenia was found in all reported patients; thirty-seven patients had intermittent thrombocytopenia without clinical bleeding. Bone marrow aspirates of patients with G6PC3 deficiency showed a great diversity of findings, including: normocellular or hypercellular bone marrow, maturation arrest, and even myelokathexis (7). So far, there is no evidence that G6PC3 deficiency is a preleukemic condition. In this review, we found only one case of leukemia (P70) (8); no other reports of malignant transformation, as has been described in other SCN syndromes (5) (9).

We have been able to include here most of the patients reported in the medical literature, expanding the phenotype, and describing the typical hematological and non-hematological features of G6PC3 deficient patients. The main limitations are the descriptive retrospective nature of the study, the fact that the information we rely upon is provided by different sources and authors, and lastly, the possibility of important data being lost throughout. Additionally, this is not a systematic review, and we are only including cases reported in English.

The activity of glucose-6-phosphatase is regulated by 3 genes: *G6PC1*, expressed in liver, small intestine and kidney, is related to the glycogenolytic and gluconeogenic pathways. *G6PC2*, expressed only in the pancreatic cells, is related to glucose level control; and *G6PC3*, ubiquitously expressed, hydrolyzes glucose-6-phosphate to glucose in the final step of gluconeogenesis and glycogenolysis (10) in the endoplasmic reticulum. G6PC3 is essential to control neutrophil viability (3); its loss of function is associated with neutropenia due to an increase of endoplasmic reticulum stress and abnormal glucose homeostasis that leads to an increased susceptibility to apoptosis of neutrophils, skin fibroblasts and myeloid cells (11)(12). The above findings suggest that G6PC3 deficiency is a quantitative and qualitative neutrophil disease (13).

The immunological features are diverse and include T cell lymphopenia, thymic hypoplasia, and dysgammaglobulinemia. Some articles suggest that the T cell lymphopenia found in patients with G6PC3 deficiency may be associated with thymic hypoplasia. Nevertheless, the mechanisms leading to this thymic alteration are unclear (14). Some G6PC3-deficient patients may have a more profound immunological defect, and might require a deeper approach, including T cell flow cytometry and lymphoproliferation assays. When abnormalities in the function of T and B cells are demonstrated, it is mandatory to consider immunoglobulin replacement (9). Progressive lymphopenia has also been reported; therefore, immunological long-term follow-up is required.

Non-hematological features are pivotal in differentiating G6PC3 deficiency from other causes of SCN: structural heart defects, prominent superficial veins, urogenital malformations, growth retardation, pubertal and developmental delay (15). The phenotypic spectrum of the disease is expanding, as it might be syndromic or non-syndromic, the latter group being harder to diagnose given the absence of non-hematological features. (16). In this review, 23/94 (24.4%) of the patients did not have any syndromic association. Thus, G6PC3 deficiency should be considered in any SCN of unknown etiology.

The most frequent non-hematological features are cardiovascular malformations (17), atrial septal defect being the most common among those (55.3%). A wide range of cardiac abnormalities has been described in the literature, including heart valve abnormalities (mitral insufficiency, pulmonary valve stenosis, mitral and tricuspid insufficiency), followed by patent ductus arteriosus, coronary aneurysm, hypoplastic left ventricle and foramen ovale. The prominent superficial venous pattern was present in 58/94 (61.7%) of the patients reported, making it a frequent non-hematological feature. This alteration is less evident in childhood but becomes more prominent with age. These vascular changes have been attributed to increased cell apoptosis, and they can develop into varicose veins and ulcers during adulthood (11).

IBD has been reported in 10/94 reported patients with G6PC3 deficiency. Some authors suggest that autoinflammation through inflammasome activation may aggravate the IBD activity in G6PC3 deficiency (12). IBD is a common finding in phagocyte defects, such as chronic granulomatous disease and leukocyte adhesion deficiency; these patients show dysregulated and poorly controlled inflammation perpetuated by a breakdown in the mucosal homeostasis and defective bacterial recognition and clearance (18) (19) (20) (21). Fecal calprotectin is not a good marker of inflammation in these patients since the neutropenia may give false-negative results; stool α1 antitrypsin may be a more reliable marker (22). Hematopoietic stem cell transplant is a reasonable alternative for severe gastrointestinal manifestations resistant to conventional treatments (17).

The treatment most frequently used was filgrastim (G-CSF), leading to an increase in the number of neutrophils, together with an improvement in the patient's quality of life due to a decrease in the infection rate. In a murine G6PC3$^{-/-}$ model, G-CSF delayed, but did not prevent, neutrophil apoptosis. In that study, a five-day G-CSF treatment regime corrected neutropenia, stimulated glucose uptake and improved neutrophil function (23). Depending on the severity of the defect, some patients received prophylactic antibiotics; mild phenotypes were treated with co-trimoxazole alone. On the other hand, more severe phenotypes may require G-CSF, antibiotics and gammaglobulin replacement. In general, the reported survival is high, with a good quality of life as long as patients use filgrastim (G-CSF) and their malformations are surgically corrected. In recent years, therapeutic options other than G-CSF have emerged, such as SGLT2 inhibitor empagliflozin, a drug that decreases the concentration of 1,5-anhydroglucitol-6-phosphate (1,5AG6P) a toxic metabolite that accumulates in the plasma of G6PC3 patients (24); empagliflozin reduces the concentration of toxic metabolites allowing a recovery in neutrophil function (25). This novel treatment appears promising, although further studies are needed. So far, there is no recommendation to endorse or promote HSCT as a definitive treatment for the neutropenia. In this review, only 3 patients underwent HSCT, of which one died due to complications associated with the procedure.

We recommend the use of filgrastim (G-CSF), as it is considered safe and improves neutrophil counts, prevents the recurrence of infections, and it subjectively improved the quality of life in all reported cases. The dose and frequency of administration vary with the needs of each patient. We also recommend the use of oral ambulatory prophylactic antibiotics; co-trimoxazole is a cheap and safe choice to diminish the rate and severity of infections, particularly in countries where the access to G-CSF is limited. A small group of patients has a higher immune compromise, so we suggest that all patients who either continue to suffer recurrent infections despite having normal levels of neutrophils or who have persistent lymphopenia, should be further evaluated with immunoglobulin levels testing, flow cytometry and lymphoproliferation assays. So far, HSCT is only suggested in patients with IBD refractory to conventional pharmacological treatment, and is not routinely recommended, with most reports showing a good evolution with the exclusive use of filgrastim (G-CSF) and surgery to treat malformations.

Although G6PC3 deficiency is a rare disease, there is an increasing number of case reports around the world. This allows us to have a clearer idea of the clinical picture, the associated syndromic features, and the best treatment for these patients. Given a clinical suspicion of G6PC3, it is appropriate to carry out a complete medical history that includes consanguinity, type and number of infections, and microbiological isolates. An exhaustive physical examination is mandatory, searching for a triangular face, depressed nasal bridge, redundant neck skin, *cutis laxa*, prominent veins, cardiac murmur, overlapping toes and urogenital malformations, as they may be present in the syndromic phenotype.

All patients with suspected G6PC3 deficiency should have an echocardiogram and renal ultrasound. They must also have a close monitoring of weight, height, and growth velocity, with any alteration prompting measurements of growth hormone levels and an evaluation by an endocrinologist. Although it is an infrequent manifestation, the presence of loose stools or bloody diarrhea, tenesmus, or abdominal pain, suggests IBD. These patients should be evaluated with a complete blood count, erythrocyte sedimentation rate or C-reactive protein, albumin, fecal calprotectin, and upper endoscopy/colonoscopy with biopsies.

The c.210delC variant was present in all 5 Mexican patients from this report, and in most Hispanic patients reported to date. Banka and Newman (17) pointed out there might be some founder effects: Arg253His is frequent in the Middle East, Gly260Arg is more frequent in Caucasians from Europe, and Phe71SerfsTer46 (c.210delC) is common among unrelated individuals of Hispanic descent. With a frequency of 0.00011 in gnomAD (gnomad.broadinstitute.org/variant/17-42148542-TC-T?dataset = gnomad_r2_1), all 28 existing alleles (16 women and 12 men, all heterozygous) are from Latino/Admixed American individuals. Our 5 patients came from different regions of the country, mostly from Central and North Mexico. Although there was no known history of consanguinity, endogamy at small, geographically isolated communities, might explain the homozygosity in three of the families.

There are multiple unanswered questions about G6PC3-deficient patients. The cause for the heterogeneity of the bone marrow findings is currently unknown, as is the reason why some patients present with thymic hypoplasia, lymphopenia and hypogammaglobulinemia. Whether the neurodevelopmental delay and hearing loss described in some patients, are caused by prolonged hospitalizations and recurrent infections, or they are part of the disease phenotype, is also unclear. Other exceptional clinical features, such as oculocutaneous albinism, might result from different autosomal recessive gene defects in highly consanguineous populations.

In conclusion, we described 5 and reviewed 89 more cases of G6PC3 deficiency reported in the literature during the last 10 years, including clinical features, treatment, prognosis, and mutational analysis. It is a disease with a high heterogeneity, with syndromic and non-syndromic phenotypes. A possible G6PC3 deficiency should be considered in every patient with severe congenital neutropenia. The follow-up should include growth and development evaluation, as well as an assessment of complete blood count, echocardiogram, and renal ultrasound, while individualizing the needs of each patient, as clinical penetrance is

variable, and no genotype-phenotype has been described. The ongoing management of the disease should be conducted within a multidisciplinary team. We recommend treating with G-CSF and antibiotic prophylaxis, as they seem to improve the frequency of infections and quality of life. An increasing number of cases of G6PC3 deficiency in the world is likely to continue to be identified due to easier access to diagnostic methods, expanding our understanding of this disease.

List Of Abbreviations

GOF, gain of function; Severe congenital neutropenia (SCN), glucose-6-phosphate catalytic subunit 3 (G6PC3), inflammatory bowel disease (IBD), atrial septal defect (ASD), pulmonary hypertension (PH), granulocyte colony stimulating factor (G-CSF).

Declarations

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DISCLOSURE OF CONFLICTS OF INTEREST

APG works as medical manager at Glaxo-Smith Kline. GMCS used to be a medical advisor for Astra Zeneca. None related to this study.

AVAILABILITY OF DATA AND MATERIAL

The authors confirm that the data supporting the findings in this study are available within the article and in supplementary materials.

CODE AVAILABILITY

Not applicable

AUTHORSHIP CONTRIBUTIONS

Substantial contribution to the acquisition of the data was provided by N Velez-Tirado, MA Yamazaki-Nakashimada, E Lopez Valentín, A Partida-Gaytan, SC Scheffler-Mendoza, GM Chaia Semerena, A Alvarez-Cardona, and MA Suárez Gutiérrez, who also suspected the diagnosis and cared for the patients. Substantial contributions to the conception of the work, analysis of the data and drafting of the manuscript were provided by N Velez-Tirado, MA Yamazaki Nakashimada, and SO. Lugo Reyes. Substantial contribution to laboratory and genetic diagnoses were provided by EA Medina-Torres, P Baeza-Capetillo, T Hirschmugl, W Garncarz, SE Espinosa-Padilla, J Aguirre Hernández, C Klein, and K Boztug, who also revised the manuscript critically. All authors read and approved the final manuscript.

ETHICS APPROVAL

This case series study was granted exemption by the National Institute of Pediatrics Research and Ethics Committee due to its retrospective design. All authors subscribe the 1964 Declaration of Helsinki by the World Medical Organization and its later amendments regarding human experimentation.

CONSENT TO PARTICIPATE

Informed consent was obtained from all individual participants included in the study.

CONSENT TO PUBLISH

The participant has consented to the submission of the case report to the journal

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Tables

Table 1. Demographic, clinical and laboratory features of 94 patients with G6PC3 deficiency

Author	Individual	Country	Age (years)[a]	Sex[b]	Clinical remarks	Cytopenias	Immunoglobulins	Bone marrow
Boztug, 2009	P1	Turkish	6	M	ASD Cryptorchidism Increased venous marking Hepatoesplenomegaly	ANC 60-246 /µl Intermittent thrombocytopenia	NA	Maturatio stage of promyelo
Boztug, 2009	P2	Turkish	3	F	Cor triatriatum Malformation of pulmonary veins Increased venous marking Hepato/esplenomegaly Growth hormone deficiency	ANC 54-240/µl	NA	Maturatio stage of promyelo
Boztug, 2009	P3	Turkish	11	F	ASD Mitral insufficiency Increased venous marking Hepatoesplenomegaly	ANC 0-61/µl Intermittent thrombocytopenia	NA	Maturatio stage of promyelo
Boztug, 2009	P4	Turkish	6	M	ASD Cryptorchidism Increased venous marking	ANC 0-322/µl	NA	Maturatio stage of promyelo
Boztug, 2009	P5	Turkish	4	M	Increased venous marking Poor growth	ANC 25-84/µl Intermittent thrombocytopenia	NA	Maturatio stage of promyelo
Botzug, 2009	P6	Turkish	6	F	ASD Pulmonary valve stenosis Increased venous marking	ANC 90-612/µl	NA	NA
Boztug, 2009	P7	Greece	7	F	Inner ear hearing loss Increased venous marking	ANC 30-1280/µl	NA	NA
Boztug, 2009	P8	Germany	8	F	ASD Urachal fistula Microcephaly Increased venous marking	ANC 75-210/µl Intermittent thrombocytopenia	NA	NA
Boztug, 2009	P9	France	9	F	Myopathy Increased venous marking	ANC 200-500/µl	NA	NA
Boztug, 2009	P10	Germany	10	M	ASD Cryptorchidism Genital dysplasia Microcephaly Inner ear hearing loss Increased venous marking	ANC 0-3.000/µl Intermittent thrombocytopenia	NA	NA

					Growth retardation			
Boztug, 2009	P11	Persian	11	M	ASD PDA	ANC 250-440/μl	NA	NA
Boztug, 2009	P12	Lebanese	12	M	Cryptorchidism Bilateral inguinal hernia Cleft palate	ANC 615-2000/μl	NA	NA
Eghbali, 2009	P13	Iran	0	M	Hydronephrosis of the left kidney ASD and PDA	ANC 234/μl	IgG 672 mg/dl (350-1180) IgM 131 ml/dl IgA 48 mg/dl (36-165)	Maturatio myeloid s
Dursun, 2009	P14	Turkish	0.3	F	ASD Mild PH Hypertelorism Pectus carinatum Hypoplastic thymus	ANC 300-630/μl ALC 336-3800/μl Platelets 141.000 - 222.000/μl Hb 6.5 g/dl	NA	Hypocellu normal di series
Durson, 2009	P15	Turkish	0.2	M	ASD Mild PH Pectus carinatum Cryptorchidism Hypoplastic thymus	ANC 112-6000/μl ALC 154-3680/μl Platelets 35.000-446.000/μl Hb 7.8 g/dl	NA	Dysplasti lineages, changes i erythroid vacuoliza series.
Arostegui, 2009	P16	Moroccan	22	M	ASD Bilateral cryptorchidism Prominent subcutaneous venous circulation Poor growth	ANC 50-540/μl Hb 9.5 g/dL	NA	Paucity o series bey promyelo
Xia, 2009	P17	USA	NA	NA	ASD	Neutropenia Intermittent thrombocytopenia	NA	NA
Xia, 2009	P18	USA	NA	NA	ASD Coronary aneurysm	Intermittent thrombocytopenia	NA	NA
McDermott, 2010	P19	USA (Caucasian)	13	M	Permeable foramen ovale Mild PHT Cryptorchidism Prominent superficial veins Sensorineural hearing loss Heart valve abnormalities Poor growth Microcephaly Ligamentous laxity Bronchiectasias	ANC 50-900/μl	NA	Full myelo Increased CXCR4

McDermott, 2010	P20	USA (Caucasian)	9	F	ASD Prominent superficial veins Poor growth Microcephaly Sensorineural hearing loss Bronchiectasias	ANC 50-900/μl	NA	Full myelo Increased CXCR4
Germeshausen, 2010	P21	Turkish	24	F	Hypogonadotropic hypogonadism ASD Mild mitral and tricuspid insufficiency Prominent superficial venous pattern Learning difficulties	ANC 200-700 /μl Thrombocytopenia	NA	NA
Germeshausen, 2010	P22	Caucasian	20	M	Cryptorchidism Genital dysplasia Microcephaly ASD Prominent superficial venous pattern	ANC 0-30/μl Thrombocytopenia	Hypogammaglobulinemia	NA
Germeshausen, 2010	P23	Caucasian	5	M	Neurodevelopmental abnormalities	ANC 300-350 /μl	NA	NA
Hayee, 2011	P24	Pakistan	20	M	Recurrent oral ulceration	NA	NA	Normocel left-sided
Hayee, 2011	P25	Pakistan	28	M	ASD Granulomatous IBD Splenomegaly Digital cubbing Short stature	NA	NA	NA
Gatti, 2011	P26	Ecuador	10	M	ASD Mitral and tricuspid regurgitation Sensorineural hearing loss Right-sided cryptorchidism Prominent venous pattern	ANC 180/μl Platelets 18.000/μl Hb 9.6 g/dL	NA	Paucity of neutrophi megakary hyperplas
Cullinane, 2011	P27	USA (Caucasian)	32	F	ASD Oculocutaneous albinism IBD Fine telangiectasias on arms and chest Prominent superficial venous pattern on legs, varicose veins in legs PH	ANC 0/μl Platelets 21.000-57.000/μl	NA	Arrested r developm precursors increased
Banka, 2011	P28	Israel	29	F	Small for gestation at birth	ANC 700-1.300/μl	NA	Hypercellu myeloid h Increased

					Mild learning disability Prominent superficial venous pattern and varicose veins Mild kyphosis Clinodactyly Hypothyroidism	Platelets 38.000-140.000/μl		megakary like forms
Banka, 2011	P29	Israel	26	M	Small for gestation at birth Agenesis of left kidney Right kidney hydronephrosis Mild learning disability Prominent superficial venous pattern and varicose veins Hypothyroidism	ANC 200-600/μl Hb 9.9 gr/dL	NA	Mildly dec cells. Increased megakary
Banka, 2011	P30	Israel	25	F	ASD PDA Mild learning disability Prominent superficial venous pattern and varicose veins Poor growth Delayed menarche	ANC200-1.500/μl ALC 900-1.700/μl Hb 10.8 gr/dL	NA	Decreased dysmyelo with redu the cytopl increased
Banka, 2011	P31	Israel	2	M	Pulmonary valve stenosis ASD and PDA Cryptorchidism Mild-moderate development delay Prominent superficial venous pattern Pectus carinatum PH	ANC 400-7.700/μl Monocytosis Lymphopenia	NA	All stages seen with maturatio
Alizadeh, 2011	P32	Persian	0.2	M	ASD Failure to thrive	ANC 40-170 /μl		Maturatio myelocyte
Alizadeh, 2011	P33	Persian	4	M	ASD Unilateral hydronephrosis Prominent superficial venous pattern	ANC 28-450 /μl	NA	Maturatio myelocyte
Fernandez, 2012	P34	USA (Caucasian)	20	M	ASD Cryptorchidism Oculocutaneous albinism Mitral valve prolapse Inflammatory bowel disease Hepato/esplenomegaly	Intermittent thrombocytopenia Neutropenia	NA	NA
Smith, 2012	P35	Pakistan	9	M	ASD IBD Splenomegaly	ANC 100/μl	NA	NA

					Short stature			
Smith, 2012	P36	Turkey	NA	F	Patent foramen ovale Tricuspid insufficiency	ANC<100/μl	NA	NA
Smith, 2012	P37	Pakistan	13	M	No abnormalities	ANC 400 /μl	NA	Normocel
Smith, 2012	P38	Pakistan	3	M	No abnormalities	ANC 450 /μl	NA	Normocel morpholo
Boztug, 2012	P39	Arab	12	F	ASD Small PDA Prominent superficial venous pattern Discontinuous labia majora and minora	ANC 200/μl Platelets 58.000-414.000/μl	NA	Left shift reduced n mature ne
Boztug, 2012	P40	Hispanic	9	M	ASD Prominent superficial venous pattern Frontal bossing Upturned nose Bilateral cryptorchidism Growth hormone deficiency	ANC 0-123/μl Platelets 13.000-120.000/μl	NA	Left shift reduced n mature ne
Boztug, 2012	P41	Caucasian	9	M	ASD Prominent superficial venous pattern Hypoplastic nipples Micropenis Erythropachydermia	ANC 100/μl	NA	Not done
Boztug, 2012	P42	Caucasian	11	M	ASD PDA Bicuspid aortic valve Prominent superficial venous pattern Micropenis Cryptorchidism Erythropachydermia Mild developmental delay	ANC 276/μl Platelets 44.000-342.000/μl	NA	Left shift reduced n mature ne
Boztug, 2012	P43	Caucasian	7	M	ASD Prominent superficial venous pattern Growth hormone deficiency Triangular face Left inguinal hernia	ANC 0-2.200/μl Platelets 65.000-635.000/μl	NA	Hypocellu left shift with few neutrophi
Boztug, 2012	P44	Hispanic	11	M	ASD Mitral and tricuspid regurgitation Prominent superficial venous pattern Right cryptorchidism	ANC 180/μl Platelets 16.000-553.000/μl	NA	Maturatio myelocyte stage

					Bilateral inner ear hearing loss			
Boztug, 2012	P45	Hispanic	1	M	ASD Prominent superficial venous pattern Ambiguous genitalia Hydronephrosis Triangular face	ANC 40/μl	NA	Maturatio myelocyte stage
Boztug, 2012	P46	Caucasian	16	F	ASD Prominent superficial venous pattern	ANC 300/μl		NA
Boztug, 2012	P47	Persian	11	F	ASD Mild tricuspid regurgitation *Cutis laxa* Growth retardation Triangular face	ANC 220/μl Platelets 69.000-173.000/μl	NA	Maturatio myelocyte stage
Boztug, 2012	P48	Hispanic	12	F	Small ASD Prominent superficial venous pattern Growth hormone deficiency Triangular face	ANC 480/μl Platelets 25.000-362.000/μl	NA	Maturatio myelocyte stage
Boztug, 2012	P49	Hispanic	14	M	ASD Prominent superficial venous pattern Triangular face Osteoporosis Kawasaki disease Growth retardation Delayed puberty	ANC 60/μl Platelets 30.000-420.000/μl	NA	Maturatio myelocyte stage
Boztug, 2012	P50	Turkish	0	M	ASD Prominent superficial venous pattern Hydronephrosis *Cutis laxa* Triangular face Frontal bossing Micrognathia Bilateral hearing loss Growth retardation	ANC 41/μl	NA	Maturatio myelocyte stage
Boztug, 2012	P51	Persian	1	M	ASD Prominent superficial venous pattern	ANC 750-900/μl	NA	Maturatio myelocyte stage
Boztug, 2012	P52	Caucasian	18	M	ASD Bicuspid aortic valve Prominent superficial venous pattern Small kidneys Cryptorchidism	ANC<100/μl	NA	NA

					Delayed puberty Growth retardation Massive splenomegaly			
Boztug, 2012	P53	Pakistani	1	F	Hypoplastic left ventricle Congenital ptosis Growth retardation	ANC 200-400	NA	Left shift strongly r of mature
Boztug, 2012	P54	Caucasian	7	M	ASD Prominent superficial venous pattern Cryptorchidism Right ptosis Splenomegaly	ANC 200/μl Platelets 97.000-332.000/μl	NA	Left shift strongly r of mature
Aytekin, 2013	P55	Turkey	13	F	Mild mitral regurgitation Frontal bossing Depressed nasal bridge Upturned nose Retrognathia Prominent superficial venous pattern on neck, chest, abdomen Poorly developed secondary sexual characteristics	Hb 9.2 g/dL ANC 200/μl	Normal	Myelokath Hypercellu myeloid h without m
Banka, 2013	P56	Pakistan	10	F	No prominent superficial venous Normal echocardiogram	ANC 320-1.999/μl Platelets 131.000-201.000/μl	NA	Normocel
Banka, 2013	P57	Pakistan	13	F	No prominent superficial venous Normal echocardiogram	ANC 280-1080/μl	NA	Normocel
Banka, 2013	P58	Great Britain	8	F	No prominent superficial venous Normal echocardiogram	ANC 120-570/μl Lymphocytes 1070-1100/μl	NA	Normocel
Banka, 2013	P59	Great Britain	18	F	No prominent superficial venous Normal echocardiogram	ANC 110-670/μl Lymphocytes 660-1150/μl	NA	Normocel
Bégin, 2013	P60	Canada	0.6	F	Mitral valve insufficiency Prominent superficial venous IBD Growth delay	ALC 600 /μl (1.500-2.800) T-cell lymphopenia	IgG 2340 mg/dl (520-1520) IgA 117 mg/dl (65-400) IgM 183 mg/dl (22-280)	Normal he
Estévez, 2013	P61	Caucasian	11	M	Cryptorchidism Prominent superficial veins	ANC 45-1.200 /μl Intermittent thrombocytopenia	NA	
Alangeri, 2013	P62	Saudi Arabia	12	M	Asthma Bicuspid aortic valve	ANC 7-500/μl Intermittent thrombocytopenia	NA	Active trili hematopo evidence arrest.

					Inguinal hernia			
Alangeri, 2013	P63	Saudi Arabia	10	F	ASD Aphthous stomatitis Abdominal pain Asthma	ANC 210/μl Intermittent thrombocytopenia	NA	NA
Alangeri, 2013	P64	Saudi Arabia	NB	M	Septic shock	NA	NA	NA
Alangeri, 2013	P65	Saudi Arabia	9	F	Asthma	ANC 110-600/μl	Normal lymphocyte subsets	No matura
Alangeri, 2013	P66	Saudi Arabia	2	M	NA	ANC 180/μl		Active gra no matura
Arikoglu, 2014	P67	Turkey	3	F	ASD and PDA Frontal bossing Depressed nasal bridge Retrognathia Prominent superficial venous pattern on chest and abdomen Hepatomegaly Bilateral cortical renal cysts PH	ANC 600/μl Hb 6 g/dL Platelets 89000/μl	IgG 889 mg/dl (604-1940) IgA 50 mg/dl (26-296 mg/dl) IgM 130 mg/dl (71-235) IgE < 17 KU/L (0-100) CD4+ T cells 260-436 mm^3 (500-2400) CD19+ T cells 80-166 mm^3 (200-2100)	Normocel
Kaya, 2014	P68	Turkey	0.4	F	Patent foramen ovale Minimal tricuspid insufficiency Pancolitis, IBD	ANC 80/μl	Normal	Normal
Kaya, 2014	P69	Turkey	1	F	ASD Osteoporosis	ANC 100/μl	NA	NA
Desplantes, 2014	P70	France	NB	F	Aortic insufficiency Grade III RVU, urethral duplication Prominent veins *Cutis laxa* Frontal bossing Thick lips Hypothyroidism Neurodevelopment difficulties Leukemia	ANC 280/μl Mild thrombocytopenia Mild anemia	NA	NA
Desplantes, 2014	P71	France	NB	M	ASD Bilateral cryptorchidism Hypospadias	ANC 383/μl	NA	NA

					Prominent veins *Cutis laxa* Frontal bossing Thick lips Neurodevelopment difficulties			
Desplantes, 2014	P72	France	NB	F	ASD Bilateral grade I RVU Thick lips Prominent veins *Cutis laxa* Neurodevelopment difficulties	ANC 411/µl Mild thrombocytopenia Mild anemia	NA	NA
Desplantes, 2014	P73	France	NB	M	PDA overriding aorta Grade III RVU Right cryptorchidism Prominent veins IBD *Cutis laxa* PH Thick lips Neurodevelopment difficulties	ANC 550/µl Mild anemia	NA	NA
Desplantes, 2014	P74	France	NB	M	Cryptorchidism Bilateral RVU Megaureter Prominent veins *Cutis laxa* Bilateral hearing loss Prominent lips Neurodevelopment difficulties	ANC 314/µl Mild anemia	NA	NA
Desplantes, 2014	P75	France	0.7	M	Prominent veins Kabuki syndrome like Cerebral palsy	ANC 540/µl Mild anemia	IgG 1870 mg/dl (608-1229) IgA 170 mg/dl (33-200) IgM 170 mg/dl (46-197) CD3+ 1960 (2100-6200) CD4+ 812 (1300-3400) CD8+ 756 (490-1300) CD19 364 (390-1400)	NA
Desplantes, 2014	P76	France	NB	M	Aortic insufficiency Cryptorchidism Micropenis	ANC 405/µl Mild thrombocytopenia	NA	NA

					Prominent veins IBD Inguinal hernia	Mild anemia		
Desplantes, 2014	P77	France	NB	M	ASD Aortic insufficiency Cryptorchidism Prominent veins Umbilical hernia Frontal bossing	ANC 410/μl	IgG 435 mg/dl (332-1160) IgA 32 mg/dl (14-105) IgM 34 (45-190) CD3+ 1891 (2100-6200) CD4 1178 (1300-3400) CD8 682 (620-2000) CD19 651 (720-2600)	NA
Desplantes, 2014	P78	France	NB	F	Tricuspid regurgitation Bilateral RVU Bilateral deafness NA	ANC 400/μl	NA	NA
Desplantes, 2014	P79	France	0.7	F	ASD PH Broad nasal bridge	ANC 700/μl Severe anemia	IgG970 mg/dl (768-1630) IgA 170 mg/dl (68-378) IgM 100 mg/dl (60-230) CD3+ 378 (1200-2000) CD4+ 252 (530-1300) CD8+ 98 (330-920) CD19+ 49 (110-570)	NA
Desplantes, 2014	P80	France	NB	F	ASD Prominent veins	ANC 520/μl Severe thrombocytopenia Mild anemia	NA	NA
Desplantes, 2014	P81	France	4.5	M	ASD Cryptorchidism Prominent veins Delayed puberty	ANC 160/μl Mild anemia	NA	NA
Desplantes, 2014	P82	France	NB	M	Prominent veins Pierre Robin sequence Major intelectual disability	ANC 690/μl Mild thrombocytopenia Mild anemia	IgG1560 mg/dl (420-1090) IgA 55 mg/dl (22-157) IgM 70 mg/dl (45-263) CD3+ 698 (1400-3700) CD4+ 274 (700-2200) CD8+ 332 (490-1300) CD19+ 58 (390-1400)	
Notarangelo, 2014	P83	Italy	13	F	Mitral valve prolapse Inguinal hernia Hypergonadotrophic hypogonadism Frontal bossing	ANC 200/μl Mild anemia Intermittent thrombocytopenia	IgG 1240 mg/dl (231-947) IgA 54 mg/dl (8-74) IgM 79 (26-210)	Global hy Myeloid h Maturatio Paucity of neutrophi

					Retrognathia Prominent superficial venous pattern			
Notarangelo, 2014	P84	Turkey	2	M	Facial dysmorphisms Prominent veins Sensorineural hearing loss Micropenis Coronal hypospadias	ANC 60/μl	IgG 974 mg/dl (462-1710) IgA 64 mg/dl (27-173) IgM 118 mg/dl (62-257)	Delayed g maturatio
Kiykim, 2015	P85	Turkey	19	M	ASD Prominent superficial venous pattern Osteopenia Puberal delay IBD-like Bronchiectasis	ANC 500/μl ALC 400/μl	IgG 2520 mg/dl (913-1884) IgM 89 mg/dl (88-322) IgA 67 mg/dl (139-378) CD4+T cells 124/μl (500-2000) CD8+ T cells 140/μl (200-1200) CD 19+20 cells 20 /μl (64-820) CD16+56 8/μl (100-1200)	Hypercellu marrow, n granulocy
Kiykim, 2015	P86	Turkey	11	F	ASD and PDA Osteoporosis Prominent superficial venous pattern Bronchiectasis	ANC 300/μl ALC 1400/μl	IgG 2000 mg/dl (835-2894) IgM 237 mg/dl (47-484) IgA 56 mg/dl (67-433)	Hypercellu marrow: l granulopo dysplasia lineage.
Kiykim, 2015	P87	Turkey	16	F	Mild mitral valve insufficiency Osteoporosis Pubertal delay Bronchiectasis	ANC 340/μl ALC 1700/μl CD19+20 85/μl (120-740)	IgG 1930 mg/dl (676-2197) IgM 98 mg/dl (75-448) IgA 53 mg/dl (108-447)	Mild dysp granulocy Hyposegr neutrophi hypogran
Mistry, 2017	P88	Great Britain	12	M	Arthritis IBD-like	Cyclic neutropenia Normocytic anemia	Polyclonal increase in IgG and IgM	No defect productio
Bolton, 2019	P89	Great Britain	1.4	M	IBD	Neutropenia ALC 490/μl	IgG 1660 mg/dl (660-1.200)	NA
Case 1 (this report)	P90	México	0.3	M	Low weight Persistent foramen ovale PH	ANC 100-800/μl Intermittent thrombocytopenia ALC 1400 /μl	IgG 398 mg/dl (290-550) IgM 114 mg/dl (30-85)	Hypocellu maturatio myeloid d

					Bilateral hydronephrosis Prominent superficial veins in thorax, abdomen and limbs Hepatomegaly Cryptorchidism Velopalatal insufficiency Bilateral sensorineural hearing loss		IgA 44 mg/dl (30-85)	
Case 2 (this report)	P91	México	15	F	Bilateral sensorineural hearing loss IBD PH Prominent superficial veins Mild tricuspid insufficiency Puberal delay	Intermittent neutropenia, nadir with 400 /µl ALC 1000 /µl	IgG 396 mg/dl (660-1220) IgA mg/dl (56-203) IgM 77 mg/dl (57-162) IgE 36.6 mg/dl	
Case 3 (this report)	P92	México	0.3	F	ASD and PDA Tricuspid insufficiency Prominent superficial veins Bilateral sensorineural hearing loss Severe pulmonary damage PH	ANC 200 /µl ALC 1300 /µl	IgG 2230 mg/dl (240-440) IgA 341 mg/dl 27-86) IgM 77 mg/dl (34-114)	Hypocellu
Case 4 (this report)	P93	México	9	M	Persistent foramen ovale PH Left inguinal hernia. Prominent superficial veins Redundant skin folds in neck	ANC 450-790/µl Intermittent lymphopenia and thrombocytopenia	NA	Cell hypo
Case 5 (this report)	P94	México	2	F	Bilateral conductive hearing loss	ANC 100 /µl Intermittent lymphopenia and thrombocytopenia	IgG 918 mg/dl (340-620) IgA 30.8 mg/dl (33-122) IgM 81 mg/dl (48-143)	Hypocellu

a. Age at diagnosis or follow up

b. F, female; M, male, NA, not available

ASD, atrial septal defect; Hb, hemoglobin; ANC, absolute neutrophil count; ALC, absolute lymphocyte count; Ig, immunoglobulin; G-CSF, granulocyte colony-stimulating factor; PDA, persistent ductus arteriosus; HSCT, hematopoietic stem cell transplantation; PH, pulmonary hypertension; IVIG intravenous gammaglobulin; TMP-SMX, trimethoprim sulfamethoxazole; NB, newborn; IBD, inflammatory bowel disease

Table 2. Genetic information of 94 G6PC3 deficient patients

Author	Individual	Country or ethnicity	Genotype	Protein change	Variant type	Syndromic
Boztug, 2009	P1	Turkey	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Boztug, 2009	P2	Turkey	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Boztug, 2009	P3	Turkey	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Boztug, 2009	P4	Turkey	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Boztug, 2009	P5	Turkey	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Boztug, 2009	P6	Turkey	c. [554TT>C]	p. [Leu185Pro]	Missense, homozygous	Yes
Boztug, 2009	P7	Greece	c. [141C>G]	p. [Tyr47Ter]	Nonsense, homozygous	Yes
Boztug, 2009	P8	Germany	c. [784G>C]	p.[Gly260Arg]	Missense, homozygous	Yes
Boztug, 2009	P9	France	c.[677+1 G>A] + [829C>T]	p. [?] + [Gln277Ter]	Nonsense, comp.het?	Yes
Boztug, 2009	P10	Germany	c. [778G>C]	p. [Gly260Arg]	Missense, homozygous	Yes
Boztug, 2009	P11	Iran	c. [935dupT]	p. [Asn313fs]	Frameshift, homozygous	No
Boztug, 2009	P12	Lebanese	c. [144C>A]	p. [Tyr48Ter]	Nonsense, homozygous	Yes
Eghbali, 2009	P13	Iran	c. [935_936insT]	p.[Asn313fs]	Insertion/Frameshift, homoz.	Yes
Dursun, 2009	P14	Turkish	c.[346A>C]	p.[Met116Val]	Missense, homozygous	Yes
Dursun, 2009	P15	Turkish	c.[346A>C]	p.[Met116Val]	Missense, homozygous	Yes
Arostegui, 2009	P16	Moroccan	c.[257delA]	p.[Glu86fs]	Frameshift, homozygous	Yes
Xia, 2009	P17	USA	NR	NR	NR	No
Xia, 2009	P18	USA	c.[210delC]	p.[170fsTer46]	Frameshift, homozygous	No
McDermott, 2010	P19	USA (Caucasian)	c.[778G>C]	p. [Gly260Arg]	Missense, homozygous	Yes
McDermott, 2010	P20	USA (Caucasian)	c.[778G>C]	p. [Gly260Arg]	Missense, homozygous	Yes
Germeshausen, 2010	P21	Turkish	c.[347T>A]	p. Met116Lys	Missense, homozygous	Yes

Germeshausen, 2010	P22	Caucasian	c.[778G>C]	p.[Gly260Arg]	Missense, homozygous	Yes
Germeshausen, 2010	P23	Caucasian	NR	p.[Arg189Gln]	Missense, homozygous	No
Hayee, 2011	P24	Pakistan	c.[130C>T]	p.[Pro44Ser]	Missense, homozygous	No
Hayee, 2011	P25	Pakistan	c.[190_210del]	p. [Thr64_Ile70del]	Small deletion, homozygous	Yes
Gatti, 2011	P26	Ecuador	c. [765_delAG]	p.[Ser255fs]	Small del/Frameshift, homoz.	Yes
Cullinane, 2011	P27	USA (Caucasian)	c.[986delC]	p.[Thr329ArgfsTer68]	SN del/Frameshift, homoz.	Yes
Banka, 2011	P28	Israel	c.[758G>A]	p.[Arg253His]	Missense, homoz.	Yes
Banka, 2011	P29	Israel	c.[758G>A]	p.[Arg253His]	Missense, homoz.	Yes
Banka, 2011	P30	Israel	c.[758G>A]	p.[Arg253His]	Missense, homoz.	Yes
Banka, 2011	P31	Israel	c.[758G>A]	p.[Arg253His]	Missense, homoz.	Yes
Alizadeh, 2011	P32	Persian	c.[416G>T]	NR	NR	No
Alizadeh, 2011	P33	Persian	c. [935dupT]	p.[Asn313fs]	Dup/Frameshift, homoz.	Yes
Fernandez, 2012	P34	Canada	c. [829C>T]	p.[Gln277Ter]	Nonsense, homozygous	Yes
Smith, 2012	P35	Pakistan	c.[190_210del]	p.[Thr64_Ile70del]	In-frame 21bp deletion, homoz.	Yes
Smith, 2012	P36	Turkey	c.[623T>G]	p.[Leu208Arg]	Missense, homozygous	No
Smith, 2012	P37	Pakistan	c.[130C>T]	p. [Pro44Ser]	Missense, homozygous	No
Smith, 2012	P38	Pakistan	c.[130C>T]	p. [Pro44Ser]	Missense, homozygous	No
Boztug, 2012	P39	Arab	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Boztug, 2012	P40	Hispanic	c.[218+1G>A]	NR	Splice-site intronic, homoz.	Yes
Boztug, 2012	P41	Caucasian	c.[758G>C]	p.[Gly260Arg]	Missense, homoz.	Yes
Boztug, 2012	P42	Caucasian	c.[758G>C]	p p.[Gly260Arg]	Missense , homoz.	Yes
Boztug, 2012	P43	Caucasian	c.[208insC]+ [778G>C]	p.[Ile70fsTer16]+[Gly260Arg]	SN insertion/frameshift + Missense (comp.het)	Yes
Boztug,	P44	Hispanic	c.[766_777delAG]	p.[Ser255fs]	Frameshift, homozygous	Yes

2012						
Boztug, 2012	P45	Hispanic	c.[210delC]+ [348G>A]	p.[Ile70fsTer46] + [Met116Ile]	Frameshift, homozygous	Yes
Boztug, 2012	P46	Caucasian	c.[677+1 G>A]+ [829>T]	p.[?]+[Gln277Ter]	Splice-site intronic + Nonsense, (Comp.het)	Yes
Boztug, 2012	P47	Persian	c.[935dupT]	p. [Asn313fs]	SN dup/Frameshift, homoz.	Yes
Boztug, 2012	P48	Hispanic	c.[210delC]	p.[Phe71fsTer45]	SN del/Frameshift, homoz.	Yes
Boztug, 2012	P49	Hispanic	c. [210delC]	p. [Ile70fsTer4]	SN del/Frameshift, homoz.	Yes
Boztug, 2012	P50	Turkish	c.[779G>A]	p.[Gly260Asp]	Missense, homoz.	Yes
Boztug, 2012	P51	Persian	c.[416G>T]	p. [Ser139Ile]	Missense, homoz.	Yes
Boztug, 2012	P52	Caucasian	c. [482G>A] + [565C>T]	p. [Arg161Gln] + [Arg189Ter]	Missense + Nonsense, comp.het.	Yes
Boztug, 2012	P53	Pakistani	c. [766_777delAG]	p. [Ser255fs]	Small del./Frameshift, homoz.	Yes
Boztug, 2012	P54	White caucasian	c. [131C>T] + [758 G>A]	p. [Pro44Leu]+[Arg253His]	Missense, comp.het.	Yes
Aytekin, 2013	P55	Turkey	c.[461T>C]	p.[Leu154Pro]	Missense, homozygous	Yes
Banka, 2013	P56	Pakistan	c.[130c>T]	p.[Pro44Ser]	Missense, homozygous	No
Banka, 2013	P57	Pakistan	c.[347T>C]	p.[Met116Thr]	Missense, homozygous	No
Banka, 2013	P58	Great Britain	c.[757C>T]+ [1000_1001]	p.[Arg253Cys] + [Met334fs]	Missense + Small del/Frameshift, comp.het.	No
Banka, 2013	P59	Great Britain	c.[757C>T]+ [1000_1001]	p.[Arg253Cys] + [Met334fs]	Missense + Small del/Frameshift, comp.het.	No
Bégin, 2013	P60	Canada	c.[IVS3-1 G>A]+ [G778G>C]	p.[?] + [Gly260Arg]	Splice-site intronic + Missense, comp.het.	Yes
Estévez, 2013	P61	Caucasian	c. [778G>C]	p.[Gly260Arg]	Missense, homozygous	Yes
Alangeri, 2013	P62	Saudi Arabia	c.[974 T>G]	p.[Leu325Arg]	Missense, homozygous	No
Alangeri, 2013	P63	Saudi Arabia	c.[974 T>G]	p.[Leu325Arg]	Missense, homozygous	No
Alangeri, 2013	P64	Saudi Arabia	c.[974 T>G]	p.[Leu325Arg]	Missense, homozygous	No
Alangeri, 2013	P65	Saudi Arabia	c.[974 T>G]	p.[Leu325Arg]	Missense, homozygous	No
Alangeri,	P66	Saudi	c.[974 T>G]	p.[Leu325Arg]	Missense, homozygous	No

2013		Arabia				
Arikoglu, 2014	P67	Turkey	c.[175T>C]	p.[Trp59Arg]	Missense, homozygous	Yes
Kaya, 2014	P68	Turkey	c. [623T>C]	p.[Leu208Arg]	Missense, homozygous	No
Kaya, 2014	P69	Turkey	NR	NR	NR	No
Desplantes, 2014	P70	France	c.[249G>A]	p.[Trp83Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P71	France	c.[249G>A]	p.[Trp83Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P72	France	c.[249G>A]	p.[Trp83Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P73	France	c.[249G>A]	p.[Trp83Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P74	France	c.[249G>A]	p.[Trp83Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P75	France	c.[758G>A]	p.[Arg253His]	Missense, homozygous	Yes
Desplantes, 2014	P76	France	c.[481C > T]	p.[Arg161Ter]	Nonsense, homozygous	yes
Desplantes, 2014	P77	France	c.[778G > C]	p.[Gly260Arg]	Missense, homozygous	Yes
Desplantes, 2014	P78	France	c.[778G > C]	p.[Gly260Arg]	Missense, homozygous	Yes
Desplantes, 2014	P79	France	c.[778G > C]	p.[Gly260Arg]	Missense, homozygous	No
Desplantes, 2014	P80	France	c.[565C > T]	p.[Arg189Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P81	France	c.[565C > T]	p.[Arg189Ter]	Nonsense, homozygous	Yes
Desplantes, 2014	P82	France	c.[565C > T]	p.[Arg189Ter]	Nonsense, homozygous	Yes
Notarangelo, 2014	P83	Italy	c.[144C>A]+ [373_375delAAT]	p.[Tyr48Ter]+[Ile125del]	Nonsense + In-frame del, comp.het.	Yes
Notarangelo, 2014	P84	Turkey	c.[680_684delinsT]	p.[Ser227LeufsTer3]	Indel/Frameshift, homozygous	Yes
Kiykim, 2015	P85	Turkey	c. [535+1G>A]	NR	Splicesite intronic, homozygous	Yes
Kiykim, 2015	P86	Turkey	c. [935dupT]	p. [Asn313fs]	SN dup/frameshift, homoz.	Yes
Kiykim, 2015	P87	Turkey	c. [C394T]	p.[Glu132Ter]	Nonsense, homozygous	Yes
Mistry, 2017	P88	Great Britain	c. [130C>T]	p.[Pro44Ser]	Missense, homozygous	Yes

Bolton, 2019	P89	Great Britain	c.[911dupC]	p.[Gln305fs82Ter]	SN dup/frameshift, homozygous	No
C1 (this report)	P90	México	c.[210delC]	p.[Phe71SerfsTer46]	SN deletion/frameshift, homoz.	Yes
C2 (this report)	P91	México	c.[210delC]	p.[Phe71SerfsTer46]	SN deletion/frameshift, homoz.	Yes
C3 (this report)	P92	México	c.[210delC]	p.[Phe71SerfsTer46]	SN deletion/frameshift, homoz.	Yes
C4 (this report)	P93	México	c.[210del] + c.[481C>T]	p.[Phe71SerfsTer46] + [Arg161Ter]	SN deletion/frameshift + Nonsense (comp.het)	Yes
C5 (this report)	P94	México	c.[210del] + [421del]	p.[Phe71SerfsTer46] + [Trp141GlyfsTer2]	SN deletion/frameshift, comp.het.	No

NR, not reported.

Due to technical limitations, table 3 is only available as a download in the Supplemental Files section.

Figures

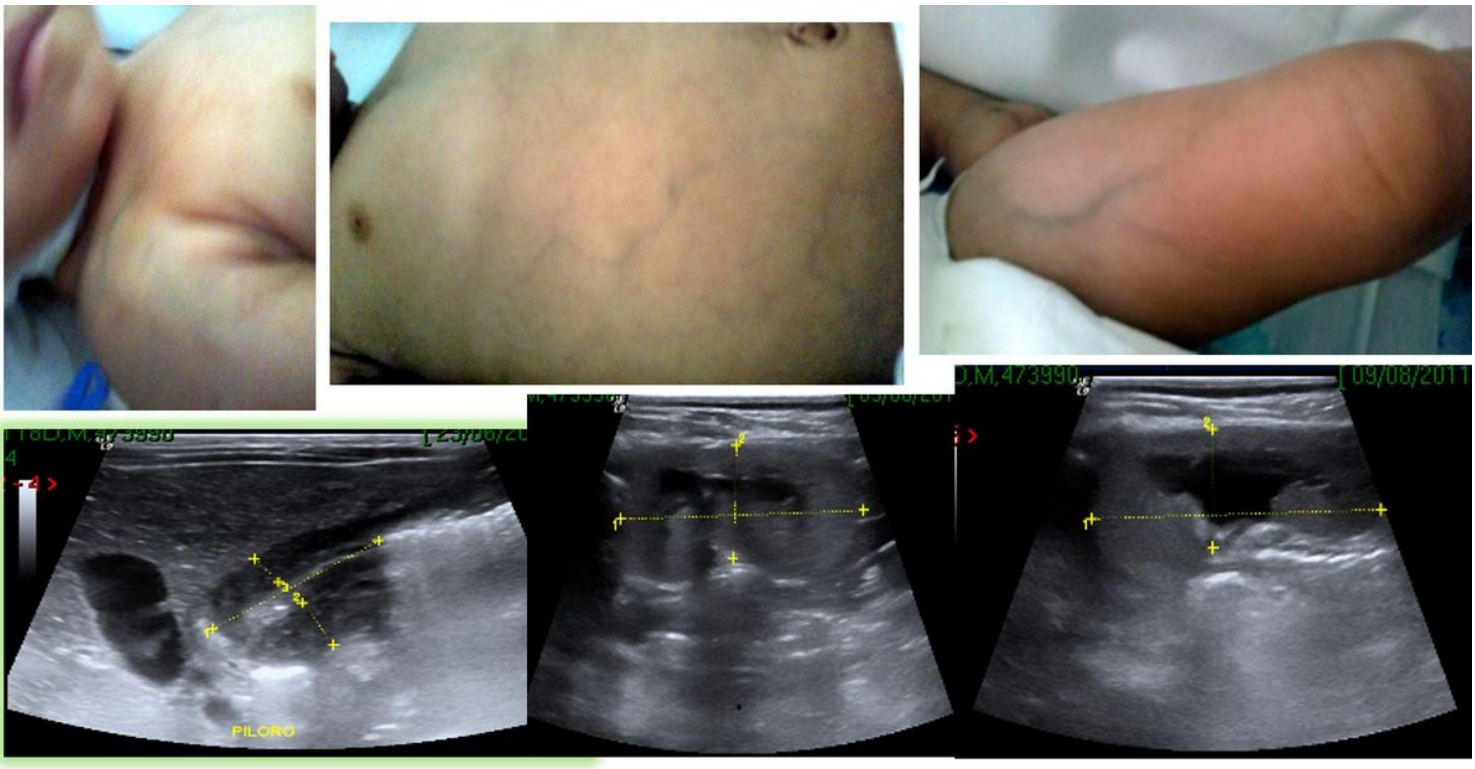

Figure 1

Patient 1 had prominent superficial veins in trunk and limbs (upper panels), pyloric hypertrophy and severe bilateral hydronephrosis grade I and III (lower panels), as well as persistent foramen ovale with bidirectional shunt and pulmonary arterial hypertension, hepatomegaly, cryptorchidia, and bilateral hypoacusis (not shown).

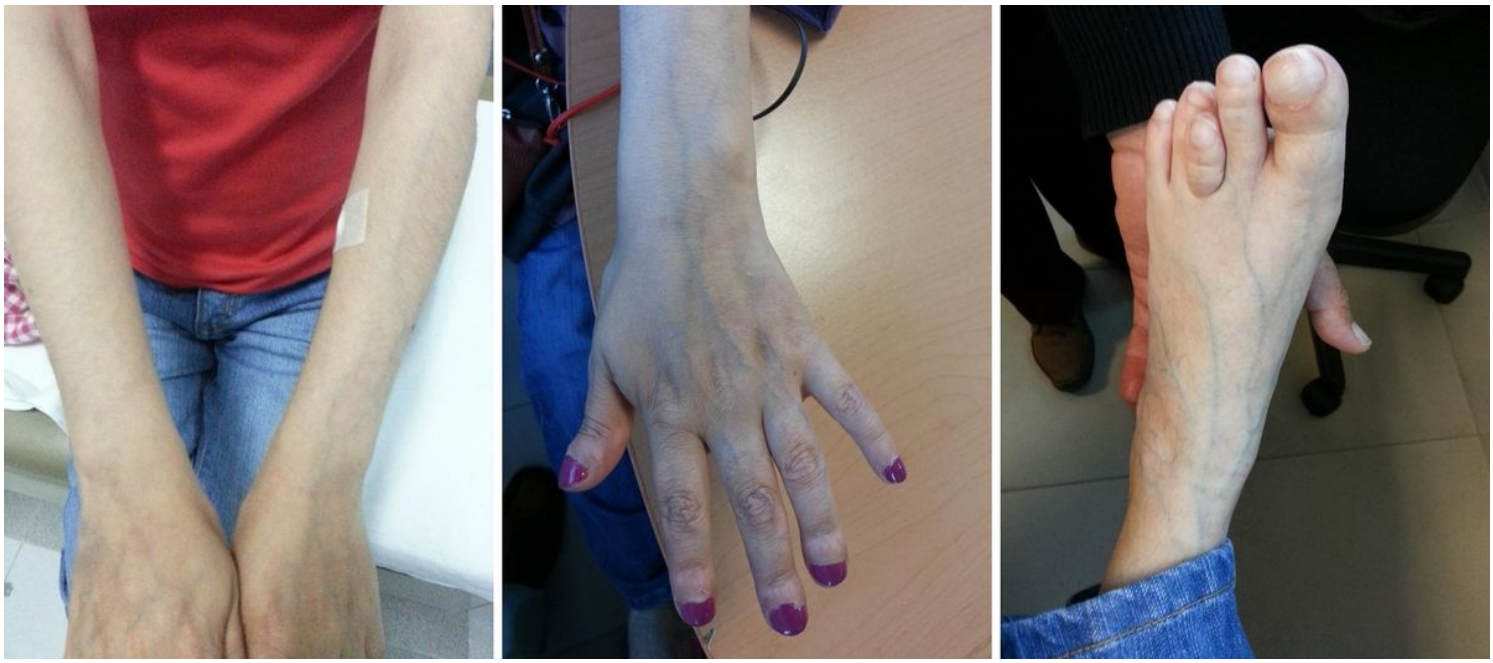

Figure 2

Patient 2 also had prominent superficial veins in limbs, digital clubbing, brachymetatarsia of the third toe, and bilateral hypoacusis.

Supplementary Files

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- Table3.jpg
- G6PC3tablefinal1.docx