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Rare Inherited Diseases Among Hemodialysis Patients

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Additional information is available at the end of the chapter

1. Introduction

Several diseases can be observed in patients submitted to hemodialysis treatment. Besides all variants of renal failure, hypertension and diabetes are the most common disorders that can be observed among these patients.

On the other hand, diagnosis of rare inherited diseases is more difficult and often done too late, because knowledge about them is limited, included among medical staff. It is estimated that 6-8% of the population in general will lead to some kind of rare disease and about 80% of that have a genetic background.

Although this is an extensive theme, the goal of this chapter is describe briefly two group of rare inherited conditions observed in patients submitted to hemodialysis: (1) tubular and (2) glomerular diseases. The major clinical features, genetic and molecular aspects and the management of the patient will be presented in the next pages.

2. Tubular diseases

2.1. Polycystic Kidney Diseases (PKD)

Up to 10-15% of the patients in hemodialysis can present cystic kidneys and different diseases with several phenotypes should be considerate in these situations. The autosomal dominant (ADPKD) and recessive (ARPKD) polycystic kidney diseases are the most important examples of these clinical conditions.

Approximately 50% of patients with ADPKD progress to End Stage Renal Disease (ESRD). In most cases, regular clinical monitoring is essential and the adoption of a method of renal replacement therapy (RRT - hemodialysis, peritoneal dialysis or transplantation) becomes indispensable in the treatment.

Reference	Year	Etnicity	% ADPKD
Iglesias *et al.*	1983	Euro-descendant	2.75
Gabow	1993	Euro-descendant	8-10
Sesso *et al.*	1994	Euro-descendant	3
Higashira *et al.*	1998	Asian	2.5
Glassberg *et al.*	1998	Caucasian	10
Hwang *et al.*	2000	Asian	3.2
Nunes *et al.*	2008	Euro-descendant	7.5
Harris < Torres	2009	Euro-descendant	4.4

Table 1. Percentage of ADPKD among hemodialysis patients.

Although an apparent 100% penetrance, is considered to ADPKD heterogeneous genetic viewpoint, caused by mutations in one of two genes known to be associated with the disease: PKD1 (polycystic kidney disease 1), located in chromosome 16p13.3 and PKD2 (polycystic kidney disease 2), mapped on 4q21. Most cases (80-85%) results from mutations in PKD1, causing ADPKD type 1 ADPKD1. In the remaining patients (15-20%) mutations are identified in PKD2 and give rise to ADPKD type 2 ADPKD2.

The PKD1 gene encompasses 46 exons distributed over a genomic segment of about 52kb to produce a 14.2 kb mRNA and associated with an open reading frame of approximately 12.9 kb. The PKD1 gene encoding polycystin-1 (PC1), an integral membrane glycoprotein of 4303 amino acids. The PC1 has a large extracellular amino-terminal portion with approximately 3000 amino acids, 11 transmembrane domains and a short intracellular carboxy-terminal portion. The extracellular portion has a complex combination of fields, apparently involved in protein-protein and protein-carbohydrate bindings. This group comprises many domains types, like 16 copies of a repeat of 80 amino acids to similar regions of immunoglobulin domains PKD, a signal sequence segments of the leucine-rich repeats, a domain WSC, lectin-binding domains of type-C and LDL-A plus a field REJ (receptor for egg jelly) domain and a GPS domain.

PKD2 gene, in turn, expresses a 5.4 kb mRNA which encodes a polypeptide of 968 amino acids, polycustin-2 (PC2). The PC2 has six transmembrane domains and the two tails, amino and carboxy terminals, are intracytoplasmic.

Furthermore, PC2 shows homology with the last six transmembrane domains of PC1. Together, the polycystins form a subfamily to the part TRP channels (transient receptor poten-

tial). The PC2 works also as a channel of non-selective cation permeable to Ca^{++}, whose activity is regulated by PC1. Note also the presence of a field EF hand in the carboxy-terminus of PC2, involved in binding to Ca^{++}.

Of clinical point of view, although both forms are similar in their phenotypes, the greater severity ADPKD1 shows that ADPKD2, and the median age at diagnosis and progression to ESRD are lower. In addition, the patient is more likely to ADPKD1 hypertension, hematuria and urinary tract infections. The early development of a greater number of cysts in patients with ADPKD1 explain the fact seems to be virtually thus more serious than ADPKD2, since there seems no difference between these two forms on the rate of formation and/or cystic expansion. In terms of phenotype, ADPKD presents a great variability between different families and between members of one family. Cases of infants born to families living with ADPKD, with signs of established disease are good examples of this variability.

Several studies agree that this model of two events, also known as 'second hit', might explain the heterogeneous and focal mechanism of cyst formation of ADPKD kidney and liver. This process, which can be applied to both forms of genetic disease (ADPKD1 and ADPKD2) has the first blow the germline mutation inherited from one parent and all present in the patient's renal tubular cells, while the second event is represented by a somatic mutation in allele previously normal gene.

In addition to the genetic *locus* involved in the disease, the position of intragenic germline mutation and the nature of some mutations may account for the variation clinical interfamily, but cannot explain how a germline mutation subjects with common phenotype can significantly different. The specific type of this mutation does not appear to correlate with the phenotype of a decisive manner, but mutations located at the 5' portion of the PKD1 gene have been associated with progression to ESRD earlier than other positioned at the 3' portion of the same gene. Furthermore, the presence aneurysm also was more prevalent in patients with mutations in the 5' PKD1.

Recently, some studies in animal models are supporting the hypothesis that there is still a 'third hit' involved in the evolution of ADPKD. According to this hypothesis, the genetic basis associated events to accelerate cystogenesis in adult kidney may contribute to the clinical variability of ADPKD and its prognosis. Experiments carried out in animal models of ischemia/reperfusion demonstrated that the ischemic insult can be considered as additional blow to the formation of kidney cysts.

In fact, comparative observations between identical twins and siblings show that the regular course of renal disease is heterogeneous even among individuals with similar genetic heritage. Another important aspect is the fact that mechanisms of different nature, can influence the rate of somatic mutations on renal tubular epithelial cells, can potentially interfere with the severity of renal phenotype, also contributing to the observed variability in ADPKD.

Family history is essential for the diagnosis of ADPKD. For preparation of the interview should be alert to family history of cystic disease, with or without renal impairment. By presenting a pattern of dominant inheritance, are expected to be found members of ADPKD patients in all generations. However, the occurrence of new cases should be con-

sidered in those genealogies where prior registration is not found in polycystic kidney disease or kidney disease.

In the absence of a family history, which occur about 10% of all cases, the presumptive diagnosis may be done with evidence of bilateral renal cysts, according to criteria recently standardized by Pei *et al.* (2009). The adoption of more specific criteria relating to age of the patient increased the predictive value of diagnostic imaging. Furthermore, the inclusion of genetic tests, such as genetic linkage studies or direct DNA sequencing also allowed the identification of new cases with more accuracy and robustness. Besides that, the existence of one or more of the following criteria should also be considered: bilateral enlargement of the kidneys, hepatic, pancreatic or spleen cysts, brain aneurysm, cyst arachnoid alone in the pineal gland and diverticulitis.

The imaging examination is also essential for the diagnosis. In this sense, ultrasonography (US) is very useful in the diagnosis and can detect cysts from 1.0 to 1.5 cm. The presence of liver or pancreatic cysts helps confirm the diagnosis. The US diagnostic criteria include the number of cysts for each kidney and age of patients, as described in Table 2. In terms of sensitivity, computed tomography (CT) is the imaging test that can detect cysts from 0.5 cm. However, this test is not as the first choice is to use radiation or by having a higher cost. Finally, magnetic resonance imaging (MRI) is considered a more accurate tool than the US and must be requested in cases in which the distinction between carcinoma and renal cysts becomes necessary. The MRI examination allows detection of cysts from 0.3 cm in diameter and is able to assess more accurately the size of the kidneys.

Age	Diagnostic criteria for Inclusion
15-39 years	3 or more cysts unilaterally or bilaterally
40-59 years	2 or more cysts in each kidney
≥ 60 years	4 or more cysts in each kidney
	Diagnostic Criteria for Exclusion
≥ 40 years	Less than 2 cysts

Table 2. Diagnostic criteria for ADPKD.

The goal of treatment for patients with ADPKD is to preserve renal function and blood pressure control. In this context it is important to reduce progression to chronic kidney disease and monitor the risk of rupture of intracranial aneurysms and subarachnoid hemorrhage. Another important practice is to guide the patient to avoid sporting activities in which there is possibility of trauma in the lower back or abdominal in felt to minimize the risk of rupture of the cysts.

In normotensive patients with normal renal function annual US tests and renal function must be regular, keeping intervals not exceeding 12 months between assessments. For the control of blood pressure, angiotensin I to angiotensin converting (ACE), or receptor An-

tagonists of angiotensin II (ATII) are the drugs of choice, as the system renin-angiotensin system plays a central role in the pathophysiology of hypertension in this clinical situation.

Inhibition of vasopressin receptor also occupies a significant challenge as a therapeutic agent for ADPKD, since the increase of these receptors may directly contribute to increase the concentration of cAMP and interact with many other proteins associated with cyst formation. Studies with drugs specific to this scenario are underway and their results may help in clinical management soon.

Abdominal pain is managed with analgesics and rest. Avoid nonsteroidal anti-inflammatory effect due to the nephrotoxic potential of these drugs. When the cysts become infected patients should be hospitalized and monitored. It is recommended in this situation, administer antibiotics able to penetrate the cyst, such as ciprofloxacin, clindamycin, chloramphenicol and trimethoprim-sulfamethoxazole.

Surgical intervention may be needed in the following cases: *(1)* Pain: Acute pain can be caused by intracystic hemorrhage or renal obstruction, either by clot or lithiasis. Decompression of cyst is effective in relieving pain in approximately 60-80% of cases. One option is the percutaneous drainage followed by instillation of sclerosing substance. Another possibility is the decortication of cysts by laparotomy. *(2)* Cysts infected: non-responsive to conventional antibiotic therapy. *(3)* Nephrectomy: cysts suitable for high volume (> 35cm), recurrent infections, uncontrolled hypertension and possibility of malignancy. *(4)* Massive polycystic liver disease: when liver cysts, due to the large volume, preclude the patient adequate nutrition or cause severe abdominal discomfort.

2.2. Bartter's Syndrome (BS)

Bartter syndrome (BS) was so named after Dr. Frederic Bartter, in collaboration with Dr. Pacita Pronove, describes the first case in 1960. BS is a rare inherited defect in the thick ascending limb of the loop of Henle. Hypokalemia (low potassium levels), alkalosis (increased of blood pH) and normal to low blood pressure and elevated plasma renin and aldosterone are the major features of this disorder. There are two types of BS: neonatal (NBS) and classic (CBS). A closely associated disorder, Gitelman's syndrome (described below) is milder than both subtypes of Bartter's syndrome.

NBS are observed between 24 and 30 weeks of gestation with polyhydramnios (excess amniotic fluid) in 90% of cases. In first time after birth, the newborn presents polyuria (excess of urine production) and polydipsia (excessive thirst). Life-threatening dehydration may result if the infant does not receive adequate fluids. About 85% of infants dispose of hypercalciuria (excess of calcium in the urine) and nephrocalcinosis (excess of calcium in the kidneys), which may lead to kidney stones. In rare occasions, the infant may progress to renal failure.

Patients with CBS may have symptoms in the first two years of life, but they are usually diagnosed at school age or later. Like infants with the neonatal subtype, patients with CBS also have polyuria, polydipsia, and a tendency to dehydration, but normal or just slightly increased urinary calcium excretion without the tendency to develop kidney stones. These

patients also have vomiting and growth retardation. Kidney function is also normal if the disease is treated, but occasionally patients proceed to ESRD.

Numerous causes of this syndrome probably exist. Diagnostic pointers include high urinary potassium and chloride despite low serum values, increased plasma renin, hyperplasia of the juxtaglomerular apparatus on renal biopsy, and careful exclusion of diuretic abuse. Excess production of renal prostaglandins is often found. Magnesium wasting may also occur.

The differential diagnosis should be made to avoid mistake with other identical symptoms like those observed in patients that use furosemide, for example. Although the major clinical findings characteristic of BS are hypokalemia, metabolic alkalosis, and normal to low blood pressure, these findings may also be caused by chronic vomiting, abuse of diuretic medications and magnesium and calcium deficiencies. These conditions should be available in all BS suspects.

Different mutations are associated to BS pathophysiology. These mutations are related to genes that encoding proteins with ions transporter role across renal cells in nephron, mainly in thick ascending limb.

BS type	Common name	Mutated gene	Deficiency
1	Neonatal Batter's Syndrome	SLC12A2 (NKCC2)	Na-K-2Cl symporter
2	Neonatal Batter's Syndrome	ROMK/KCNJ1	Thick ascending limb K^+ channel
3	Classic Batter's Syndrome	CLCNKB	Cl^- channel
4	BS with sensorineural deafness	BSND	Cl^- channel accessory subunit
5	BS associated with autosomal dominant hypocalcemia	CASR	Calcium-sensing receptor (activating mutation)

Table 3. Major characteristics of different types of BS.

In addition to hemodialysis the BS patient can received specific treatment to avoid the potassium loss. Spironolactone and potassium supplements can be required. Besides that, an increased sodium diet also can be associated. In specific cases, angiotensin-converting enzyme (ACE) inhibitors and nonsteroidal anti-inflammatory drugs can also be used, mainly in NBS patients.

In terms of prognostic, the limitation of knowledge about BS hampers any extrapolation on this field. In any case, early diagnosis remains the best predictor of successful treatment. For example, in CBS patients, the early treatment of electrolyte imbalances promotes good responses and patients tend to have few developmental failures.

2.3. Gitelman's Syndrome (GS)

Gitelman's syndrome (GS) was discovered in 1966 by Dr. Hillel Gitelman. It was discovered that some patients with BS showed a different myriad of symptoms. GS is also a renal salt

wasting disorder but the defective tubule is in the thiazide-sensitive Na-Cl cotransporter in the distal convoluted tubule (DCT). Both disorders are associated with hypokalemia, renal potassium wasting, activation of the renin-angiotensin-aldosterone axis, and normal blood pressure. Unlike patients with Bartter's, patients with Gitelman's syndrome have hypomagnesemia, increased urinary magnesium and decreased calcium excretion.

GS is characterized by a milder and later clinical presentation. Often, this disorder is diagnosed in asymptomatic adults who present with unexplained hypokalemia. Pediatric cases typically present in the school age period with fatigue, muscle weakness, and symptoms of neuromuscular irritability. Growth retardation and polyuria-polydipsia are not prominant features of GS. Joint pain secondary to chondrocalcinosis has been described in this subset of patients and attributed to the hypomagnesemia.

Diagnosis of GS is distinguished by high plasma renin activity with normal aldosterone secretion rates, normal urinary prostaglandin excretion, hypocalciuria and usually marked hypomagnesemia.

Gitelman's is more common than Bartter's but is still a rare disorder. There is no racial predisposition for either BS or GS and both are inherited as autosomal recessive syndromes. Besides that, there is no gender preference and GS is often not easily diagnosed until adolescence or early adulthood.

The exact pathogenic mechanism of hypocalciuria and hypomagnesemia in GS is unclear. However, know that GS is an autosomal recessive kidney disorder caused by loss of function mutations of the thiazide sensitive sodium-chloride symporter (also known as NCC, NCCT or TSC) located in the distal convoluted tubule. This failure is associated to inactivating mutations in the *SLC12A3* gene. Until the distinct genetic and molecular bases of these disorders were identified Gitelman's syndrome was formerly considered a subset of Bartter's syndrome.

GS presents a great variability among patients. These phenotypic variations can be associated to genetic background and express specifics amino acid changes in the TSC mutated protein, which normally reabsorbs about 7% of the filtered NaCl load. This failure function cause defective Na and Cl reabsorption in the DCT.

Treatments to GS can be combine magnesium and potassium supplementation in association to spironolactone, amilioride and triamterene.

3. Glomerular diseases

3.1. Fabry Disease (FD)

Fabry disease (FD) is a lysosomal storage disorder caused by the deficient α-galactosidase A (α-gal A) activity. Fabry nephropathy typically progresses throughout the fifth decade to ESRD requiring hemodialysis and/or kidney transplantation. Except for ESRD development, a milder phenotype "renal variant" type is characterized with low plasma α-gal A activity.

FD low prevalence expresses the importance of this investigation among ESRD patients without known cause. Routine screening of male hemodialysis patients would enable earlier identification of other family members who might benefit from specific clinical treatment. The analysis of other epidemiological characteristics of regular FD could be used for the screening and detection of other kindred who might benefit from specific therapy as well as their offspring.

FD beginning in childhood, common symptoms include chronic or intermittent numbness; burning, tingling pain that can occur daily, usually in the fingers and feet; episodic pain that is incapacitating and may be brought on by stress, exercise, or temperature changes; recurring fever with elevated erythrocyte sedimentation rate; angiokeratomas that may appear in adolescence and increase as an adult; opacity of the corneal lens; inability to perspire; severe abdominal pain; and an intolerance to temperature (heat or cold) and exercise. The condition then progresses in adulthood to include renal, cardiovascular, cerebrovascular, and pulmonary complications that may lead to ESRD, stroke, myocardial infarction, breathing problems and obstructions, and more.

FD is a rare inborn error with a recessive X-linkage inherited pattern. The estimated FD incidence is between 1:40,000 and 1:117,000 in general population. The prevalence of end stage FD males on dialysis was estimated between 0.22% and 1.2% in several populations.

The enzymatic defect in FD results from the deficient activity of the α-galactosidase A (α-gal A), a lysosomal hydrolase encoded by a gene (*GLA*) localized to Xq22. The *GLA* gene is 12 kb long and consists of 7 exons encoding 429 amino acids including a 31-amino acid signal peptide. The mature form of α-gal A is a homodimeric glycoprotein with molecular weight of ~46kDa synthesized from that point on cleavage of the signal peptides with ~50kDa.

In FD this leads to progressive intracellular accumulation of glycosphingolipids, mainly in the form of globotriaosylceramide (Gb-3), in many cells, particularly in renal epithelial cells, endothelial cells, pericytes, vascular smooth muscle cells, cardiomyocytes, and neurons of the autonomic nervous system.

The genetic defect occurs in all cell types, but involvement differs greatly among different organs and cell types. This heterogeneity likely reflects different rates of sphingolipid metabolism. Thus the minimum threshold requirement for α-gal A activity to prevent Gb-3 accumulation varies across cell types due to the type and amount of substrates that are recycled by the different cells.

Clinical onset of the disease typically occurs during childhood or adolescence with recurrent episodes of severe pain in the extremities, characteristic cutaneous lesions know as angiokeratomas and a distinctive but asymptomatic corneal dystrophy. Proteinuria and chronic renal disease occur with increasing age. Severe renal impairment leads to hypertension and uremia. Without dialysis, transplantation or enzyme replacement therapy (ERT), progressive renal failure is the main cause of death in the 4th decade of life in most hemizygous males with FD. However, a number of variants with residual α-gal A activity with late-onset manifestations primarily limited to the heart or kidney have been described.

The 'classical phenotype' includes the pain and paresthesias in extremities, diffused angiokeratoma and hypohidrosis during childhood or adolescence, and also corneal opacities and renal failure. Fabry nephropathy typically progresses throughout the fifth decade of life to ESRD requiring hemodialysis and/or kidney transplantation. In view of this fact, hemodialysis patients represent an important target group for FD screening. Death usually occurs due to renal failure, cardiac or cerebrovascular disease. In addition, milder variants with residual α-gal A activity have been described. The cardiac and renal variants present with either late-onset manifestations primarily limited to the heart or kidney. The 'renal variant', a milder FD phenotype, can present late-onset manifestations primarily limited to the kidney.

While in an epidemiological point of view FD occurrence is low, on the other hand the FD diagnosis is very important for detection of family members. In view of this fact, dialysis patients represent an important target group for FD screening because they permit to identify FD patients and therefore others carriers among your family members. Each screened confirmed patient could allow early diagnosis of others related subjects, who can get treatment before or in the earlier symptoms manifestations. In these terms, FD screening among ESRD patients consists of an important tool for detection of FD patients and it could be followed by FD screening between family members of the index case. Both pedigree and population screening studies have been described and it can be carried out in subpopulations thought to be at higher risk of disease than the general population.

FD patients with proteinuria or CRI should have aggressive treatment of hypertension is present and should probably be treated preferentially with angiotensin antagonist therapy; the latter recommendation is based on theoretical considerations, as definitely proof of efficacy has not been obtained yet.

Two different recombination α-galactosidase-A preparations are in use for treating FD. One enzyme is produced by Chinese hamster ovary (CHO) cells with classic recombinant technology (agalsidase β, Fabrazyme – Genzyme Corporation), and the other enzyme is produced by cultured human skin fibroblast with an activated promoter of the α-gal A gene (Agalsidase α, Replagal – Shire Human Genetics Therapies). Both recombinant enzymes are quite comparable in properties and differ only alightly in glycan composition. The two enzyme preparations have independently been examined in clinical investigations. Although both enzyme therapies were found to result in the desired Gb-3 from endothelium, the clinical effects are not robust as anticipated. In some patients, stabilization of renal function and improvement in cardiac hypertrophy occurs upon therapy.

3.2. Alport's Syndrome (AS)

Alport syndrome (AS) or hereditary nephritis was first identified in a British family by Dr. Cecil Alport in 1927. It is a genetic disorder characterized by glomerulonephritis, ESRD and hearing loss. AS can also affect the eyes (lenticonus). Hematuria is almost always found in this condition.

This disorder is caused by mutations in COL4A3, COL4A4 and COL4A5 genes and/or in collagen biosynthesis genes. Mutations in any of these genes prevent the proper production

or assembly of the type IV collagen network, which is an important structural component of basement membranes in the kidney, inner ear and eye. Basement membranes are thin, sheet-like structures that separate and support cells in many tissues. When mutations prevent the formation of type IV collagen fibers, the basement membranes of the kidneys are not able to filter waste products from the blood and create urine normally, allowing blood and protein into the urine.

The abnormalities of type IV collagen in kidney basement membranes cause gradual scarring of the kidneys, eventually leading to kidney failure in many people with the disease. Progression of the disease leads to basement membrane thickening and gives a "basket-weave" appearance from splitting of the *lamina densa*. Single molecule computational studies of type IV collagen molecules have shown changes in the structure and nanomechanical behavior of mutated molecules, notably leading to a bent molecular shape with kinks.

AS can have different inheritance patterns that are dependent on the genetic mutation. The pattern most common is X-linked, due to mutations in the COL4A5 gene. Mutations in both copies of the COL4A3 or COL4A4 genes, located on chromosome 2, confer an autosomal recessive pattern to mutation bearer. On the other hand, in rare situations (about 5%), some patients can have clinical features associated to AS autosomal dominant transmission. In these specific cases, renal failure tends to occur slowly.

The diagnosis of AS can be made according following observations:

1. family history of nephritis of unexplained hematuria in a first degree relative of the index case or in a male relative linked through any numbers of females;

2. persistent hematuria without evidence of another possibly inherited nephropathy such as thin Glomerular Basement Membrane (GBM) disease, polycystic kidney disease or IgA nephropathy;

3. bilateral sensorineural hearing loss in the 2000 to 8000Hz range. The hearing loss develops gradually, is not present in early infancy and commonly presents before the age of 30 years;

4. Mutation in one of the genes associated to disease (COL4A3, COL4A4 or COL4A5);

5. immunohistochemical evidence of complete or partial lack of the Alport epitope in glomerular, or epidermal basement membranes, or both;

6. widespread GBM ultrastructural abnormalities, in particular thickening, thinning and splitting;

7. ocular lesions including anterior lenticonus, posterior subcapsular cataract, posterior polymorphous dystrophy and retinal flecks;

8. gradual progression to ESRD in the index case of at least two family members;

9. macrothrombocytopenia or granulocytic inclusions, similar to the May-Hegglin anomaly and

10. diffuse leiomyomatosis of esophagus or female genitalia, or both.

Do not have a specific treatment to AS. In this case, treatments are symptomatic and patients are advised on how to manage the complications of kidney failure and the proteinuria that develops is often treated with ACE inhibitors, although they are not always used simply for the elevated blood pressure.

4. Conclusions

Many aspects can be considered in analysis of rare inherited diseases. In this chapter, we described only five different rare inherited disorders possible to observe among hemodialysis patients. However, is important to comment that other diseases with few population frequencies should be analyzed in patients with uncommon signals. Besides that, infection diseases and drugs dependent diseases also should be investigate in some cases. Genetic and molecular analysis also can be a relevant tool to use in situations of rare clinical presentations. A multidisciplinary approach, including the nephrologists and the geneticists besides others professionals, is the most important strategy to investigate any rare inherited disorder. For these specific uncommon conditions, the linkage between clinical and research staffs can be improve the diagnosis strategy.

Acknowledgments

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