Genetic Disorders of the Glomerular Filtration Barrier

Anna S. Li,1,2 Jack F. Ingham,3 and Rachel Lennon1,4

Abstract
The glomerular filtration barrier is a highly specialized capillary wall comprising fenestrated endothelial cells, podocytes, and an intervening basement membrane. In glomerular disease, this barrier loses functional integrity, allowing the passage of macromolecules and cells, and there are associated changes in both cell morphology and the extracellular matrix. Over the past three decades there has been a transformation in our understanding about glomerular disease, fueled by genetic discovery, and this is leading to exciting advances in our knowledge about glomerular biology and pathophysiology. In current clinical practice, a genetic diagnosis already has important implications for management ranging from estimating the risk of disease recurrence post-transplant to the life-changing advances in the treatment of atypical hemolytic uremic syndrome. Improving our understanding about the mechanistic basis of glomerular disease is required for more effective and personalized therapy options. In this review we describe genotype and phenotype correlations for genetic disorders of the glomerular filtration barrier, with a particular emphasis on how these gene defects cluster by both their ontology and patterns of glomerular pathology.

Introduction
Defects in >80 genes have been found to cause disorders of the glomerular filtration barrier, with a rapid rise in gene discovery over the last 10 years (Figure 1). This list continues to expand with the use of next-generation sequencing in large cohorts of patients who have been deeply phenotyped (1–4). Whole-exome and whole-genome sequencing allows rapid screening for both pathogenic and novel variants in affected individuals and their families who lack a genetic diagnosis (5). Furthermore, advances in cell-specific genetic engineering techniques such as Cre-lox recombination (6) and more recent genome-editing approaches with CRISPR-Cas9 (7) have enabled focused in vivo and in vitro modeling of gene function. These approaches can elicit mechanistic details about genetic variants and cellular physiology to establish a causal link from gene to clinical phenotype (8). Using this pipeline from gene discovery to experimental modeling, our understanding of the glomerular filtration barrier in health and disease has been transformed. This review focuses on known human genetic disorders of the filtration barrier by considering the key component parts: podocytes, endothelial cells, and the glomerular basement membrane.

The Glomerular Filtration Barrier
The filtration barrier comprises three layers: podocytes and endothelial cells with an intervening glomerular basement membrane (GBM). Together, this specialized capillary wall allows selective ultrafiltration while retaining circulating cells and plasma proteins. The barrier is both size selective and charge selective, as demonstrated by early studies of transferrin accumulation (9). Glomerular endothelial cells have fenestrae that are 70–100 nm in diameter and covered by an endothelial surface layer consisting largely of glyocalyx that contributes to the charge-selective barrier (10). The GBM is a unique basement membrane formed by secreted products from both endothelial cells and podocytes during glomerulogenesis (11). It is a complex gel-like structure consisting of core basement membrane components, including laminin isoforms, type IV collagen, nidogen, and heparan sulfate proteoglycans, in addition to many more less abundant structural and regulatory components (12). Podocytes are specialized epithelial cells covering the outer aspect of the glomerular capillary. These cells are basally anchored to the GBM through transmembrane receptors such as integrins and dystroglycans (10) and specialized cell-cell junctions known as slit diaphragms interconnect podocytes laterally (10). Podocyte foot processes have an actin-based cytoskeleton connecting basal, lateral, and apical domains via linker proteins to both cell-cell and cell-matrix junctions and thereby convey cues from the extracellular environment (10).

Pathogenic variants in a wide range of genes with functional relevance in glomerular filtration have been identified to date. As a high-level starting point, these genes can be classified according to their location within the three-layered filtration barrier (Figure 2). An alternative representation is demonstrated with enrichment analysis of Gene Ontology cellular compartment annotations for known genes (Figure 3). This analysis demonstrates the importance of the cellular cytoskeleton, cell-cell junctions, and extracellular matrix in genetic disorders of the filtration barrier. In the following sections, we demonstrate how genetic discovery has highlighted particular
The nephrotic syndrome diffuse mesangial sclerosis is a frequent histologic pattern observed in steroid-resistant nephrotic syndrome, characterized by the clinical triad of massive proteinuria, albumin <25 g/L, and edema. Many genetic causes of nephrotic syndrome are resistant to treatment with glucocorticoids, leading to the classification of steroid-resistant nephrotic syndrome. The prognosis for patients with steroid-resistant nephrotic syndrome is poor and they invariably progress to kidney failure. Although kidney biopsy remains an important clinical tool for the histologic diagnosis of nephrotic syndrome, the availability of genetic testing has enabled a further layer of classification. Overall the most frequent histologic pattern observed in steroid-resistant nephrotic syndrome is FSGS, whereas in early-onset steroid-resistant nephrotic syndrome, malignant hypertension, and in later-onset nephrotic syndrome and cause slower progression. Some individuals with PLCE1 variants were responsive to corticosteroids and immunosuppressive therapy. Recently, defects in proteins encoded by PLCE1 and APOL1, also involved in early-onset nephrotic syndrome, have also been found in children with steroid-resistant nephrotic syndrome (15,16).

Enhanced calcium influx appears to be a key factor for mediating podocyte injury and is associated with monogenic causes of steroid-resistant nephrotic syndrome. Transient receptor potential channel C6 (encoded by TRPC6) is a slit diaphragm–associated calcium channel and mechanical stretch sensor. A heterozygous gain-of-function variant enhances TRPC6-mediated calcium signal amplification, resulting in prolonged channel activation. TRPC6 is also associated with angiotensin II–mediated calcium influx and apoptosis, leading to podocyte loss (17). Variants in other genes such as NPHS2, ACTN4, and APOL1 also result in calcium overload and podocyte injury, possibly via TRPC6 hyperactivity (18).

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**Podocyte Genetics**

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**Slit Diaphragm–Related Genes**

*NPHS1* encodes nephrin, a transmembrane protein and a core component of the slit diaphragm. Between adjacent foot processes, nephrin molecules form homo- and heterodimers with its homolog Nep1 forming the slit diaphragm in a zipper-like pattern. Intracellularly, nephrin phosphorylation by the tyrosine kinase Fyn leads to enhanced PI3K/Akt/Rac pathway activation, promoting dynamic modeling of actin cytoskeleton. Nephrin interacts with podocin (encoded by *NPHS2*), an integral membrane protein, and CD2-associated protein (encoded by *CD2AP*), an adapter protein connecting nephrin to the actin cytoskeleton as well as interacting with the PI3K/Akt pathway. Nephrin also interacts with IQ motif–containing GTPase-activating protein 1 (IQGAP1), which in turn interacts with phospholipase Cε1 (encoded by *PLCE1*), a phospholipase generating downstream messengers such as such as inositol 1,4,5-trisphosphate (IP₃) and diacylglycerol. *NPHS1* was identified as the pathogenic gene in congenital nephrotic syndrome of the Finnish type (13). Disease-causing homozygous *NPHS1* variants are common in Finland, affecting approximately 1 in 10,000 children. Two truncating variants (Fin-major and Fin-minor) account for >94% of Finnish cases, demonstrating a founder effect. Outside Finland, classic *NPHS1* variants are rare. Missense variants are associated with a milder FSGS phenotype (14). Homozygous variants in *NPHS2* and *PLCE1* causing steroid-resistant nephrotic syndrome display genotype-phenotype correlation. Different *NPHS2* variants can cause steroid-resistant nephrotic syndrome with variant-specific disease severity and onset from early childhood to early adulthood. Truncating variants in *PLCE1* cause early onset of proteinuria and progression to kidney failure, whereas missense variants are found in later-onset nephrotic syndrome and cause slower progression. Some individuals with *PLCE1* variants were responsive to corticosteroids and immunosuppressive therapy. Recently, defects in proteins encoded by *KIRREL1* and *KIRREL2*, members of the NEPH family that interact with podocin, have also been found in children with steroid-resistant nephrotic syndrome (15,16).

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that maintains the opening of the slit diaphragm through charge repulsion. Autosomal dominant variants in podocalyxin, encoded by \textit{PODXL}, cause adolescence-to-adult-onset steroid-resistant nephrotic syndrome with incomplete disease penetrance (19).

PTPRO encodes a tyrosine phosphatase expressed at the apical membrane of the foot processes. Tyrosine phosphorylation of the slit diaphragm components nephrin and ZO-1 alters their association with other slit diaphragm proteins. Notably, patients harboring PTPRO variants showed partial response to corticosteroid and cyclosporin combination therapy (20).

Cytoskeletal Genes

Podocyte cells are highly differentiated and polarized. Their architecture and morphology is integral to function as part of the glomerular filtration barrier. Healthy podocytes have an arborized shape characterized by multiple branching projections forming the foot processes (21). A hallmark feature of nephrotic syndrome is the loss of podocyte arborization and foot-process effacement, and this is associated with significant cytoskeletal remodeling. The slit diaphragm complex is inextricably connected to the highly dynamic actin cytoskeleton, transducing signals to affect and coordinate podocyte structure and function. Variants in a number of genes encoding modulators and components of the actin cytoskeleton have been identified as the causes of steroid-resistant nephrotic syndrome. Myosin 1E, encoded by \textit{MYO1E}, is an actin-based molecular motor and a key component of the podocyte cytoskeleton that interacts with the slit diaphragm complex. Podocytes expressing defective MYO1E could not efficiently assemble actin cables along new cell-cell junctions (22).

\textit{a}-Actinin-4 is an actin-filament crosslinking protein encoded by \textit{ACTN4}. Pathogenic variants in its actin-binding domain increase its binding affinity, resulting in a stiffened and more brittle actin network and making the podocyte vulnerable to detachment under environmental mechanical stress (23). Inverted formin 2, encoded by \textit{INF2}, nucleates actin filaments and promotes actin elongation, as well as accelerating F-actin depolymerization and filament severing. Variants in \textit{INF2} lead to aberrant regulation of actin turnover and restructuring. INF2 also binds to and is regulated by the Rho GTPase Cdc42. The Rho family GTPases RhoA, Rac1, and Cdc42 signaling pathways are implicated in the pathogenesis of other monogenic variants causing steroid-resistant nephrotic syndrome. Under the stress response, podocytes switch from a RhoA-dependent stationary state to a Cdc42- and Rac1-dependent migratory state. Rho GTPase–activating protein 24, encoded by \textit{ARHGAP24}, activates RhoA, leading to downstream suppression of lamellipodia formation and cell spreading. This function is impaired in autosomal
dominant ARHGAP24 variants because both wild-type and mutated proteins homodimerize and heterodimerize (24). In patients with homozygous ARHGDIA variants, the defective encoded protein Rho GDP dissociation inhibitor α fails to interact with Rac1 and Cdc42, resulting in increased GDP-bound Rac1 and Cdc42 activity. KANK1/2/4 genes encoding kidney ankyrin repeat-containing proteins also harbor pathogenic variants (25). KANK2 interacts with ARHGDIA whereas KANK1 colocalizes with synaptopodin encoded by SYNPO. Synaptopodin is a podocyte-specific, actin-binding protein and is antagonized by TRPC5- and TRPC6-mediated calcium influx. Loss-of-function variants in synaptopodin result in the loss of stress fibers and reduction in RhoA abundance and activity (26). Membrane-associated guanylate kinase inverted 2, encoded by MAGI2, directly binds to the cytosolic tail of nephrin and regulates actin cytoskeleton via RhoA. MAGI2 variants have been found in patients with congenital steroid-resistant nephrotic syndrome (27). Recently, together with DLC1, CDK20, TNS2, ITSN1, and ITSN2, MAGI2 variants were also found to be pathogenic in partial treatment-sensitive nephrotic syndrome. These genes encode a cluster of proteins that either physically or functionally interact to regulate RhoA/Rac1/Cdc42 activation. Interestingly, glucocorticoid treatment abolished the effect of DLC1 or CDK20 knockdown on RhoA activation in vitro (28).

Figure 3. Disease-causing genes are connected in their biological roles. A Gene Ontology enrichment analysis was performed for the 87 genes described in this review. We used clusterProfiler (59), which is an open-source tool useful for highlighting the predominant biologic roles in a collection of genes, and we selected the cellular compartment ontology. This highlights the importance of the podocyte, extracellular matrix, and nucleus.

Transcription Factors and Nuclear and Mitochondrial Genes
Pathogenic variants in transcription factors controlling the development of urogenital system can cause a wide spectrum of systemic syndromes with kidney involvement. WT1 was the first mutated gene discovered in steroid-resistant nephrotic syndrome. Variants in WT1 cause Denys–Drash syndrome and Frasier syndrome associated with urogenital abnormalities, malignant Wilms tumor, and gonadoblastoma. Missense variants affecting the WT1 DNA-binding site are associated with diffuse mesangial sclerosis, early-onset steroid-resistant nephrotic syndrome,
and rapid progression to kidney failure. Risk of Wilms tumor is associated with truncating variants and late-onset steroid-resistant nephrotic syndrome. Intronic variants usually present with isolated childhood-onset steroid-resistant nephrotic syndrome and slower progression of kidney impairment (29). Paired box protein 2, encoded by \( PAX2 \), is another transcription factor with a central role in kidney development. Variants in \( PAX2 \) lead to dysregulation in \( PAX2 \) targets including \( WT1 \), resulting in disrupted podocyte and foot process development (30). \( LMX1B \) encodes LIM homeobox transcription factor 1 which regulates slit diaphragm genes. Variants in \( LMX1B \) cause steroid-resistant nephrotic syndrome in isolation or in association with nail-patella syndrome. Variants in \( MAFB \) encoding MAF bZIP transcription factor B cause adolescence- to adult-onset steroid-resistant nephrotic syndrome in association with Duane retraction syndrome, characterized by impaired horizontal eye movement. Variants in \( E2F3 \), encoding E2F transcription factor, leads to early-onset steroid-resistant nephrotic syndrome and intellectual impairment, mediated by dysregulation of VEGF synthesis.

Pathogenic variants in genes encoding several members of the nuclear pore complexes have been identified, including \( NUP93 \), \( NUP25 \), \( NUP107 \), \( NUP85 \), \( NUP133 \), and \( NUP160 \). Nuclear pore complexes are large macromolecular assemblies in the nuclear envelope which mediate the transport of proteins, RNAs, and RNP particles between the cytoplasm and the nucleus. Of interest, in patients with \( NUP93 \) variants, some had partial response to corticosteroid and cyclosporin treatment (31).

Genetic mutations causing mitochondrial dysfunction may be present in the nuclear or mitochondrial genome. Mutations in mitochondrial gene \( MTTL1 \) causes mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (known as MELAS); diabetes; deafness; and steroid-resistant nephrotic syndrome. Steroid-resistant nephrotic syndrome has also been reported in association
with a case of neuropathy, ataxia, retinitis pigmentosa syndrome (known as NARP) caused by mutation in mitochondrial gene MT-ATP6 (32). Variants in enzymes involved in the coenzyme Q10 (CoQ10) biosynthesis pathway in the mitochondria result in CoQ10 deficiency and may present with abnormalities in multiple systems including encephalopathy, neuromuscular involvement, and nephrotic syndrome. Importantly, early initiation of CoQ10 supplementation has been reported to improve kidney phenotype (33).

**Complex Genetic Associations**

Rather than following the Mendelian mode of inheritance, the APOL1 gene (encoding apolipoprotein L1) displays more complex risk associations with development of FSGS, nephrotic syndrome, and CKD with striking racial disparity. From genome-wide association studies, two independent variants in the APOL1 gene have been found to associate with FSGS and hypertensive kidney failure. These variants are common in populations of African descent but absent in populations of European descent and appear to be positively selected in recent evolution history. Experimentally, the kidney disease–associated ApoL1 variants were able to lyse the parasite *Trypanosoma brucei rhodesiense*, suggesting resistance to infection as the selection pressure (34).

Also based on genome-wide analyses, GPCS encoding glypican 5, a member of the heparin sulfate proteoglycan (HSPG) family, was also identified as a risk gene for nephrotic syndrome and conferred susceptibility to damage in diabetic kidney disease. Glypican 5 was shown to localize to the endothelial cells and podocytes in the human kidney. It is known to play a role in binding growth factors such as fibroblast growth factor 2, which has been implicated as a potential damaging signal in nephrotic syndrome (35).

**Basement Membrane Genes**

Laminin-521 is the major laminin isoform in GBM. It is a cruciform, heterotrimeric glycoprotein composed of the laminin α5, β2, and γ1 chains. During glomerulogenesis, laminin-521 trimers are secreted from podocytes and endothelial cells and polymerize in the extracellular matrix to form lattice-like networks on each edge of the GBM. Laminin also serves as a ligand for cellular receptors such as integrins and kinases, therefore enabling cellular signal transduction and cell-matrix adhesion (47). A homozygous variant in CD151 was detected in three patients with kidney failure. Electron microscopy revealed splitting of the tubular basement membrane along with reticulation and fragmentation of the GBM (48).

**Genes Affecting Endothelial Cell Function**

Dysregulation and overactivation of the alternative complement pathway cause endothelial damage and underlie...
the pathogenesis of atypical hemolytic uremic syndrome (aHUS). Histologically, this disease process is characterized by thrombotic microangiopathy, with glomerular capillary wall thickening, endothelial swelling, and subendothelial accumulation of material. Of all aHUS cases, 50% are associated with genetic abnormalities in factor H, factor I, membrane cofactor protein, thrombomodulin, C3, and factor B. Notably, 3% of patients with aHUS carry more than one mutated complement gene (49).

Noncomplement genes have also been found to harbor variants associated with the development of aHUS, including two genes associated with podocyte pathology and steroid-resistant nephrotic syndrome. Homozygous or compound heterozygous variants in DGKE are linked to 1%–5% of aHUS cases, all presenting at <12 months of age. In endothelial cells, DGKs inactivates diacylglycerols and defective DGKs leads to increased protein kinase C activity and endothelial cell activation. Interestingly, a subset of the children developed nephrotic syndrome 3–5 years after the onset of aHUS, a very rare event not usually seen with other forms of aHUS (50). Finally, variants in INF2, another gene related to steroid-resistant nephrotic syndrome, were found in familial aHUS or post-transplant thrombotic microangiopathy in the presence of common aHUS risk haplotypes (51).

Relative Contribution of Genetic Variants to Disease
Several large cohort studies have identified underlying genetic causes for childhood and early adult–onset steroid-resistant nephrotic syndrome or FSGS in approximately 30% of cases (1–4). Distribution of causative genes and prevalence of monogenic diseases in these cohorts strongly correlated with age of onset. The most frequently mutated genes were NPHS1, NPHS2, WT1, and COL4A3/4/5; a significant but less prominent group of contributors included LAMB2, SMARCA1, PLCE1, INF2, ADCK4, INF2, TRPC6, and COQ2 (1–4). In two of the largest international pediatric cohorts, genetic causes were found in close to 70% of congenital nephrotic syndrome cases (age <3 months), 35%–50% of infantile onset (3–12 months), 21%–25% of early childhood onset (1–6 years), 15%–19% in late childhood onset (6–12 years), and 10%–16% in adolescent onset (13–20 years) cases (1,2). In adults, mutations in COL4A3/4/5 were the commonest genetic abnormalities found in FSGS (55%) (52,53) and in a large heterogeneous CKD cohort (30% of pathogenic variants identified) (42).

Current and Future Therapies
Because defects in the glomerular filtration barrier result in albuminuria, conventional therapy relies on (1) renin-angiotensin-aldosterone system (RAAS) blockade to reduce proteinuria, (2) optimization of kidney disease risk factors such as BP control, and (3) RRT with dialysis or transplantation. In Alport syndrome, early initiation of RAAS blockade delays kidney failure by a median of 13 years (54). In addition, a genetic diagnosis helps to better understand the genotype-phenotype correlation of diseases and to stratify patients for management and prognosis. Detection of a genetic variant known to associate with extrarenal manifestations also prompts screening for these features (Table 1). Because most cases of nephrotic syndrome caused by genetic abnormalities are resistant to glucocorticoid and immunosuppressive therapy, early diagnosis can avoid their unnecessary use. On the other hand, patients with variants in NUP93, PTPRO, PLCe1, DLC1, Dlc1, CDK20, TNS2, ITSN1, ITSN2, and MAGI2 achieved partial remission with glucocorticoid and/or immunosuppression, and this could prompt a future trial of treatment based on patient genotype. Understanding the genetic bases of disease has also yielded effective treatments for CoQ10 deficiency–related nephrotic syndrome and aHUS. Eculizumab, a humanized mAb against C5, has revolutionized the management of aHUS. Treatment with eculizumab is able to control disease activity and preserve kidney function in complement-associated aHUS.

In addition, although patients with steroid-resistant nephrotic syndrome who have a confirmed genetic diagnosis have increased risks of disease progression toward kidney failure, their risks of recurrence after kidney transplant are extremely low compared with those without (30%–50% risk) (1,55,56). Genetic diagnosis is also important in evaluating family members for living kidney donation, especially in cases of complex genetic associations such as APOL1 and complement genes. However, underlying genetic causes have only been identified in approximately 30% of steroid-resistant nephrotic syndrome and 50% of aHUS. Better understanding of the biology of the glomerular filtration barrier and further screening of large population cohorts will undoubtedly increase the yield of genetic testing for reaching a molecular diagnosis.

Much hope has been placed upon gene therapy in genetic disorders. Studies showing feasibility and proof of principle have been undertaken in Alport mice. Incorporating collagen α3εα5(IV) chains after initial assembly via activation by a tetracycline induced transgene-delayed proteinuria (57). This suggests a possible target for genetic rescue in Alport syndrome. In fact, prior research showed a transgene was able to rescue Col4a3−/− mice, which had an Alport phenotype, resulting in normal levels of proteinuria after 6 months of follow-up (58). There remain many hurdles to overcome before this treatment modality could be attempted in a human model, including ethical considerations and vector transport.

Summary
Our ability to reach a molecular diagnosis for children and adults with glomerular disease has been transformed over the past three decades due to genetic discoveries. The expanding list of genetic disorders is also providing important insight into the underlying biology of the glomerular filtration barrier. The ontologic clustering of genes highlights the important role of the podocyte slit diaphragm, the cytoskeleton, and its interaction with the GBM. These may represent the importance of these specialized structures for sensing and responding to mechanical strain from capillary blood flow, because our most effective treatment for these disorders (RAAS blockade) reduces capillary hydrostatic pressure. The endothelial cell genetics highlights the susceptibility of the glomerular endothelium to complement dysregulation and the resolution of these mechanisms has led to highly effective
therapy based on a mechanistic understanding of the underlying disease process. In the decades ahead, further dissection of disease mechanisms should lead to new therapies to preserve native kidney function and prevent progression to kidney failure.

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Table 1. Genetic mutations associated with extrarenal manifestations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated Extrarenal Manifestations</th>
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<tbody>
<tr>
<td>WT1</td>
<td>Denys–Drash syndrome: ambiguous genitalia, Wilms tumor, urogenital abnormalities</td>
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<tr>
<td>LMX1B</td>
<td>Frasier syndrome: ambiguous genitalia, gonadoblastoma</td>
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<tr>
<td>SMARCA1</td>
<td>Nail-patella syndrome: hypoplastic nails, absent patellae, skeletal abnormalities, glaucoma</td>
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<tr>
<td>E2F3</td>
<td>Schimke immuno-osseous dysplasia: short stature, lumbar lordosis, T-cell immunodeficiency, skin</td>
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<tr>
<td></td>
<td>hypopigmentation, cerebral ischemia</td>
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<tr>
<td>NFX1</td>
<td>Mental retardation</td>
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<tr>
<td>PAX2</td>
<td>Heart block</td>
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<tr>
<td>LMNA</td>
<td>Coloboma, hearing impairment</td>
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<td>WDR73</td>
<td>Familial partial lipodyrophy</td>
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<td>KEOPS complex</td>
<td>Galloway-Mowat syndrome: microcephaly, developmental delay, seizures, hiatal hernia, optic atrophy,</td>
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<td></td>
<td>movement disorders, intellectual disability</td>
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<tr>
<td>MAFB</td>
<td>Duane retraction syndrome: eye movement anomaly</td>
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<tr>
<td>MYH9</td>
<td>Epstein syndrome: mild hearing loss, thrombocytopenia with giant platelets</td>
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<tr>
<td>INF2</td>
<td>Charco–Marie–Tooth disease: chronic peripheral motor and sensory neuropathies</td>
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<td>ARHD1A</td>
<td>Seizures, cortical blindness</td>
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<td>KAT2B</td>
<td>Cardiomypathy</td>
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<td>COQ2</td>
<td>Coenzyme Q10 deficiency, progressive encephalomyopathy</td>
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<tr>
<td>COQ6</td>
<td>Coenzyme Q10 deficiency, sensorineural hearing loss</td>
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<tr>
<td>PDSS2</td>
<td>Leigh syndrome: coenzyme Q10 deficiency, hypotonia, seizures, ataxia, deafness, growth retardation</td>
</tr>
<tr>
<td>MTTL1</td>
<td>MELAS syndrome: mitochondrial encephalomyopathy, lactic acidosis, strokelike episodes, diabetes, deafness</td>
</tr>
<tr>
<td>MT-ATP6</td>
<td>NARP syndrome: neuropathy, ataxia, retinitis pigmentosa</td>
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<tr>
<td>SCARB2</td>
<td>Action myoclonus–renal failure syndrome: myoclonus, seizures, tremor, sensorineural hearing loss</td>
</tr>
<tr>
<td>ZMPSTE24</td>
<td>Mandibuloacral dysplasia: mandibular and clavicular hypoplasia, cutaneous atrophy, partial lipodyrophy</td>
</tr>
<tr>
<td>PMM2</td>
<td>Congenital defect of glycosylation</td>
</tr>
<tr>
<td>SPCG1</td>
<td>SPL insufficiency syndrome: fetal hydrops, primary adrenal insufficiency, neurologic deterioration,</td>
</tr>
<tr>
<td></td>
<td>immunodeficiency, acanthosis, endocrine abnormalities</td>
</tr>
<tr>
<td>LAMB2</td>
<td>Pierson syndrome: ocular abnormalities, hypotonia, movement disorder</td>
</tr>
<tr>
<td>COL4A3/4/5</td>
<td>Alport syndrome: sensorineural hearing loss, ocular abnormalities</td>
</tr>
<tr>
<td>ITGA3</td>
<td>Epidermolysis bullosa, interstitial lung disease</td>
</tr>
<tr>
<td>ITGB4</td>
<td>Epidermolysis bullosa, pyloric atresia</td>
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