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# An overview of Dent disease

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Dent disease is a rare inherited kidney tubulopathy caused by mutations in either the *CLCN5* (Dent disease 1) or *OCRL1* (Dent disease 2) genes, and which is often underdiagnosed in practice. A diagnosis is clinically suspected in patients with low-molecular-weight proteinuria, hypercalciuria, and one of the following: hematuria, nephrolithiasis, nephrocalcinosis, hypophosphatemia, or chronic kidney disease. Inheritance is X-linked recessive, meaning, these symptoms are generally only found in males; female carriers may have mild phenotypes. Genetic testing is only a method to confirm the diagnosis, approximately 25% to 35% of patients have neither the *CLCN5* nor *OCRL1* pathogenic variants (Dent disease 3), making diagnosis more challenging. The genotype-phenotype correlations are not evident with the limited clinical data available. As with many other genetic diseases, the management of patients with Dent disease concentrates on symptom relief rather than any causative process. The current treatments are mainly supportive to reduce hypercalciuria and prevent nephrolithiasis. Chronic kidney disease progresses to end-stage between the ages of the third to fifth decades in 30% to 80% of affected males. In this review, we aimed to summarize the literature on Dent disease and reveal the clinical characteristics and molecular basis of Korean patients with Dent disease.

**Keywords:** Dent disease; Genetic diseases, X-Linked; Proteinuria

## Introduction

Dent disease is a rare X-linked inherited kidney disorder whose most manifestations result from proximal tubule dysfunction [1]. It classically presents as low-molecular-weight (LMW) proteinuria, hypercalciuria, nephrolithiasis or nephrocalcinosis, and progressive kidney insufficiency [1-3]. The condition was first recognized in 1964 by Dent and Friedman in two unrelated young males with renal rickets stemming from injury of the kidney tubule [2]. About 30 years later, Wrong et al. [1] studied 25 patients from five different families and reported the disorder as a familial form of renal Fanconi syndrome. They termed the condition "Dent disease" and suggested that it was inherited in an X-linked pattern. Shortly, the disease-associated gene was identified and fully characterized [4] and is now described as an X-linked recessive kidney disease caused by pathogenic gene variants.

The accurate incidence of Dent disease is unknown [5] and the wide variability of clinical symptoms, along with the absence of family history, makes diagnosis difficult. In addition, its rarity means that clinicians have a relatively restricted understanding of Dent disease, which can lead to misdiagnosis and inappropriate intervention. LMW proteinuria is one of the major features of disease presentation, essentially universally present in all affected males, and is also present in carrier females to a lesser degree. By contrast, other phenotypic symptoms of Dent disease can vary according to the ethnicity of the patient. Typical symptoms of Dent disease tend to manifest in

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early youth and can proceed to end-stage kidney disease between the ages of the third and fifth decades [5,6]. Despite the limited clinical data, there are differences in the clinical features and molecular basis of Dent disease patients in different ethnicities [7-10]. In this review, we aimed to summarize the literature on Dent disease and to reveal the clinical features and molecular basis of Dent disease in Korean patients.

## Genetics

Two gene variants have been identified up to now [11]. Dent disease 1 is named for patients with mutations in the chloride channel-gated 5 (*CLCN5*) gene and comprises approximately 50% to 60% of patients with clinical diagnosis [4,11]. A further 15% to 20% of cases are resulted in mutations in inositol polyphosphate-5-phosphatase (*OCRL1*) and are recognized as Dent disease 2 [12]. Genetic heterogeneity caused by yet-to-be-identified genetic variants is supposed to be liable for the residual cases, which are classified as Dent disease 3 [13].

## Dent disease 1 and *CLCN5* mutations

The first disease-associated gene found to be linked to Dent disease was *CLCN5* on the X chromosome (Xp11.22) (Fig. 1). *CLCN5* encodes chloride channel-5 (CLC-5) antiporter, which is mainly located in the renal and intestinal epithelia. It is primarily presented in the proximal tubule and intercalated cells [14] and is essential for the uptake of LMW proteins through receptor-mediated endocytosis in the proximal tubule [15]. With the loss of CLC-5 function, the endocytosis of the kidney proximal tubule epithelial cells is suppressed, and the carbohydrates, amino acids, and hormones cannot be reabsorbed, causing LMW proteinuria [16]. More than 250 different pathologic variants of *CLCN5* have been identified [17,18]. The reported mutations are missense (35%) or frameshift (31%), nonsense (16%), splice site (10%), and large deletions (4%) [17]. The spectrum of pathogenic variants in patients with Dent disease 1 is very diverse, while the type of pathogenic variants does not look like reliably predicts long-term prognosis or disease outcome [17].

## Dent disease 2 and *OCRL1* mutations

The second disease-associated gene to be linked as responsible for Dent disease was the *OCRL1* gene [12], which maps on the long arm of the X chromosome (Xq25) and is also known to cause Lowe syndrome (Fig. 1) [19]. Interestingly, some *OCRL1* mutations cause the Lowe syndrome, and others cause the isolated renal phenotype of Dent disease. *OCRL1* encodes a lipid phosphatase that hydrolyzes phosphatidylinositol 4,5-bisphosphate [20], which acts as an intracellular messenger for membrane trafficking and cytoskeleton shapes and functions [21]. A study of zebrafish showed that the absence of *OCRL1* leads to impaired endocytosis [22], similar to what is seen in cases of CLC-5 depletion. All *OCRL1* genetic variants revealed in Dent disease are distributed in the 5' half of the gene, in exons 1–15, while pathogenic variants for Lowe syndrome are mainly distributed in exons 8–23 [5,20,23]. Thus far, more than 140 pathogenic variants in the *OCRL* gene that cause Dent disease 2 have been reported [7].

## Clinical phenotype

The clinical phenotype of Dent disease reflects a dysfunction in proximal tubular solute reabsorption. LMW proteinuria is the

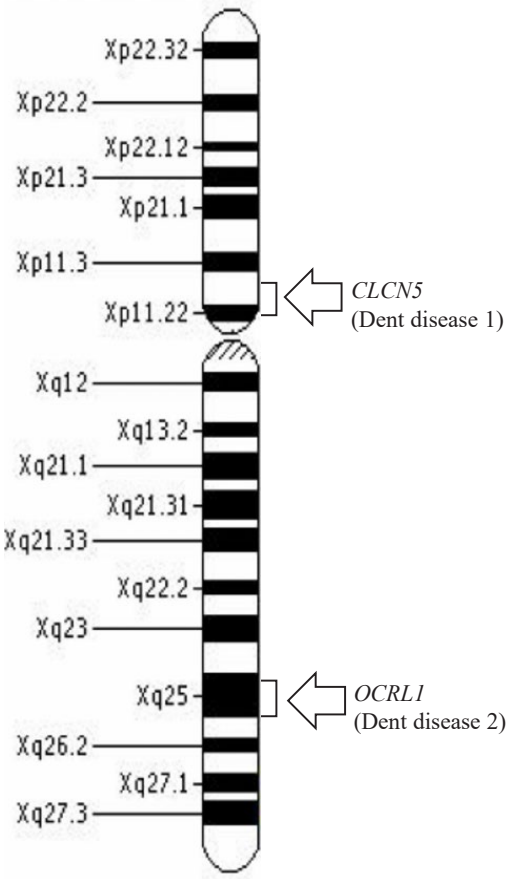


**Fig. 1.** Genes and loci for Dent disease.

most consistent symptom of Dent disease and is essentially universally present in all affected males and carrier females to a lesser degree. It occurs in infancy before any other evidence of kidney dysfunction [1]; it can also be an isolated finding in adults [24]. Protein excretion typically occurs at a rate of 1–2 g/day, with LMW proteins accounting for 50% to 70% of the total urine protein [20]. Proteinuria in Dent disease reflects a defect in the reabsorption of filtered urine proteins rather than the damage of the glomerulus or tubule [1]. It begins in early childhood and worsens with age [10]. Approximately 50% of patients have proteinuria in the nephrotic range. However, serum albumin levels tend to be normal, so these patients do not typically develop nephrotic syndrome [25].

Along with LMW proteinuria, hypercalciuria is highly prevalent and is reported in more than 80% of patients with Dent disease [9-11]. However, symptoms are often intermittent and some patients may be asymptomatic [26]. The degree of hypercalciuria is higher in children compared with adults [6], but it also tends to decrease along with the decrease of the glomerular filtration rate (GFR) [10]. Although the hypercalciuria mechanism is undetermined in Dent disease, it has been ascribed to the vitamin $D_3$ synthesis stimulation by inappropriately high parathyroid hormone levels in the proximal tubule, with consecutive stimulation of calcium absorption in the intestine [6,18,27].

Nephrocalcinosis may come from hypercalciuria, as the degree of hypercalciuria in Dent disease is in approximately 75% of male patients with Dent disease 1 and 40% with Dent disease 2 [28]. Nephrocalcinosis manifests frequently during adolescence and sometimes during early childhood, although the existence and severity of nephrocalcinosis do not always agree with the risk of developing chronic kidney disease (CKD) [6]. Approximately 30% to 50% of male patients ultimately develop kidney stones despite the considerable interfamilial and intrafamilial variability [6,10]. Nephrolithiasis seems to result from the association of hypercalciuria and a defect in the handling of calcium oxalate phosphate crystals in the medullary collecting duct [10,29]. An estimated 50% of female carriers have hypercalciuria, although nephrolithiasis is rare [5].

Kidney function declines progressively, and the GFR generally declines at a rate of 1.0–1.6 mL/min/1.73 $m^2$ per year [10]. This will lead to end-stage kidney disease, which will occur in two-thirds of patients. However, this can vary, and some patients can reach an advanced age with only modest or even minor renal impairment [1]. In the most aggressive cases, GFR declines measurably in late childhood and may reach end-stage in a patient's early twenties; however, more typically, progression to end-stage kidney failure occurs when a patient is in their 40s or 50s [6,30]. The mechanism of kidney failure is not well understood.

In addition to the main clinical features, other symptoms of proximal tubular dysfunction such as, aminoaciduria, phosphaturia/hypophosphatemia, kaliuresis/hypokalemia, and glycosuria may also be present at varying frequencies [31]. Some patients with Dent disease 2 have also presented with non-renal symptoms such as mild intellectual impairment [2], hypotonia, cataracts, and growth defects [5,26], and these symptoms are likely to be milder than those who have Lowe syndrome.

## Diagnosis

In the absence of other known causes of proximal tubular dysfunction, Dent disease should be suspected in patients who present with the following criteria [11]: (1) LMW proteinuria (elevation of urinary excretion of β2-microglobulin and/or retinol-binding protein at least 5-fold above the upper limit of normality); (2) hypercalciuria (>4 mg/kg in a 24-hour collection or >0.25 mg calcium per mg creatinine on a spot sample); and (3) at least one of the following: nephrocalcinosis, nephrolithiasis, hematuria, hypophosphatemia, or CKD [5]. A family history indicating an X chromosome-linked inheritance of one or more of the clinical symptoms discussed above supports the diagnosis, with pathogenic variants recognition in either *CLCN5* or *OCRL1* confirming disease. However, not all affected patients have a pathogenic variant in one of these two genes, and some patients with confirmed pathogenic variants in *CLCN5* or *OCRL1* will not fulfill all three of the above clinical criteria. Therefore, while the identification of pathogenic variants in genes can confirm the diagnosis of Dent disease in someone with suggestive clinical symptoms, a negative genetic test cannot rule out a diagnosis.

## Treatment

As with many other genetic diseases, the treatment of Dent disease focuses on symptom relief rather than a causative process [26]. Although the evidence to support the effectiveness of most of the current therapies is poor, current treatments of Dent disease are aimed at decreasing the levels of hypercalciuria and its complications and slowing the CKD progression



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[31]. Treatment of hypercalciuria mainly consists of a low-sodium diet and thiazide diuretics, the use of which has not been evaluated in randomized controlled trials. However, it has been shown to significantly reduce urinary calcium excretion in the short term [32] despite it also being related to significant adverse effects, such as hypovolemia and hypokalemia, related to primary tubulopathy [33]. Thus, thiazide diuretics in Dent disease should be used with caution and only with recurrent stone formation. Similarly, the management of rickets with vitamin D should proceed with caution since it can accrete hypercalciuria and therefore, only be indicated for patients with symptomatic bone disorder [20]. Angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are widely used drugs for the treatment of proteinuria [25,34]. Even though ACEI and ARB should not theoretically be effective against tubular proteinuria, they have nonetheless been shown to reduce proteinuria in patients with Dent disease [9,10]. Blanchard et al. [10] suggest that the existence of histological glomerular injury and/or heavy proteinuria might provide grounds for the treatment of ACEI and ARB. However, the long-term outcomes of ACEI and ARB were not studied in detail.

## Korean patients with Dent disease

According to the data of a multicenter study for the Korean Society of Pediatric Nephrology, a total of 55 male patients who had genetically confirmed Dent disease were collected from 2002 to 2021 in Korea (unpublished). The data sharing is permitted by the co-authors. The patients' median age at clinical diagnosis was 8.1 years, and the initial symptoms leading to a diagnosis of Dent disease were proteinuria (91%), hematuria (5%), family screening (3.6%), nephrocalcinosis (1.8%), growth retardation (1.8%), and polyuria (1.8%). In total, 49 of the 55 patients carried pathogenic variants of the *CLCN5* gene (Dent disease 1), and the remaining six patients showed pathogenic variants of the *OCRL1* gene (Dent disease 2) which is similar to the

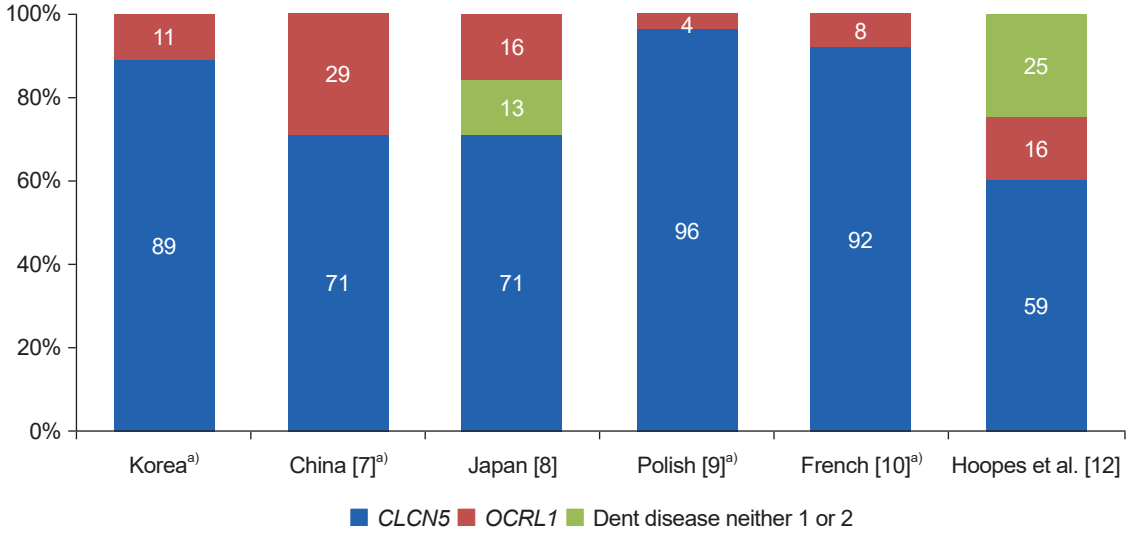


**Fig. 2.** Genetic heterogeneity in Dent disease. [a)]Only patients with a molecular diagnosis of Dent disease were included in the analysis.

**Table 1.** Frequency of clinical presentations in the global literature

| Global literature | Low-molecular-weight proteinuria | Hypercalciuria | Nephrocalcinosis | Nephrolithiasis | Chronic kidney disease |
|---|---|---|---|---|---|
| Korea | 100 (55/55) | 43.4 (23/53) | 29.6 (16/54) | 5.45 (3/55) | 5.66 (3/53) |
| China [7] | 100 (32/32) | 65.6 (21/32) | 43.8 (14/32) | 9.38 (3/32) | 12.5 (4/32) |
| Japan [8] | 100 (61/61) | 46.3 (25/54) | 37.7 (20/53) | - | 7.55 (4/53) |
| Poland [9] | 100 (15/15) | 86.4 (19/22) | 56.5 (13/23) | 13.0 (3/23) | - |
| France [10] | 100 (93/93) | 92.0 (81/88) | 42.3 (44/104) | 32.4 (24/74) | - |
| Claverie-Martin et al. [20] | 100 | 89 | 76 | - | 42 |

Values are presented as percent (number/number).

Polish and French studies (Fig. 2) [7-10,12]. All patients had LMW proteinuria, although hypercalciuria and nephrocalcinosis/nephrolithiasis were found in 43.4% and 34.5% of the patients, respectively. Hypercalciuria is a less constant presentation owing to the difference in definitions or various presentations of clinical features depending on the legions [7-10,20]. The clinical phenotypes in Korean patients with Dent disease do not differ significantly from the occurrence of various clinical symptoms in Asia patients with Dent disease (Table 1). However, the occurrence of hypercalciuria, nephrocalcinosis, nephrolithiasis, and CKD is higher in Europe and America than in Korean patients with Dent disease [7-10,20]. The estimated GFR (eGFR) at diagnosis and eGFR at an average follow-up of 7 years are comparable (106 mL/min/1.73 $m^2$ vs. 108 mL/min/1.73 $m^2$). The annual eGFR decline rate is similar to the previous report [10], with an annual decline in eGFR of 1.1 mL/min/1.73 $m^2$. Initial therapy consisted of thiazides in five patients, ACEI and ARB in 25 patients, and potassium citrate in four patients. At the last follow-up, three patients took thiazide, 10 patients took ACEI/ARB, and three patients took potassium citrate.

## Conclusions

Dent disease is an uncommon X-linked recessive kidney disease that is often underdiagnosed. Although the identification of genetic pathogenic variants can support the diagnosis of Dent disease, not all affected patients have a pathogenic genetic variant. Clinicians should suspect Dent disease in male patients with LMW proteinuria or with idiopathic nephrocalcinosis, nephrolithiasis, or CKD.

## Conflicts of interest

Eun Mi Yang is an editorial board member of the journal but was not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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## Author contributions

All the work was done by EMY and SHC.

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