Recent advances in understanding the clinical and genetic heterogeneity of Dent’s disease

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Introduction

Dent’s disease 1 (OMIM 300009) is an X-linked proximal tubulopathy [1] first described in 1964 [2], with Fanconi syndrome, a consistent renal abnormality, and low-molecular-weight proteinuria (LMWP) being almost always present. Nephrocalcinosis and renal stone formation occur more frequently in Dent’s disease 1 than in other forms of Fanconi syndrome.

Various features of Dent’s disease 1 predominate in different ethnic groups, and have been noted in earlier reports, resulting in several syndrome names of phenotypically similar disorders. These were referred to as X-linked recessive hypophosphataemic rickets (XLRH), X-linked recessive nephrolithiasis (XRN) and familial idiopathic LMWP in Japanese patients (JILMWP), often referred to as Dent’s Japan disease [3,4]. All of these are now considered phenotypic variants of one unique entity, namely Dent’s disease 1 [5,6].

Clinical features of Dent’s disease 1

Dent’s disease 1 commonly presents in childhood or early adult life with symptoms of LMWP, hypercalciuria and nephrolithiasis/nephrocalcinosis, but less often with renal failure. LMWP is thought to be the only constant feature. However, in one patient, a ClC-5 mutation not associated with LMWP was detected [7]. Female carriers are usually asymptomatic (depending on lyonization) but often show LMWP and, more rarely, hypercalciuria [8,9]. Not all families and patients exhibit the same clinical features, although frequent thorough investigations have been rare. The most complete study is the report of Wrong et al. [1] (Table 1). Not all patients had a decreased glomerular filtration rate (GFR). However, in all tested patients, GFR declined progressively with age. The frequency of reduced tubular phosphate reabsorption is difficult to judge, as decreased GFR has to be taken into account [10]. We calculated the tubular reabsorption from the data of Wrong et al. [1] (Table 1, Figure 1).

Not all patients showed a decrease in phosphate reabsorption. In 14 patients, oral ammonium chloride was given to assess urinary acidification, and in seven patients it was found to be normal. Defective urinary acidification was related to the duration and severity of renal calcification. In four adequately tested children, urinary acidification was normal, thus indicating a secondary defect in the older patients. The cause of rickets in this series could not be adequately investigated [no measurements of parathyroid hormone (PTH) and vitamin D metabolites were available], but rickets was cured by pharmacological doses of vitamin D. In later reports [12], PTH was noted as normal or decreased and 1,25-dihydroxycholecalciferol (1,25-DHC) was elevated. A defect in ClC-5 influences the concentration of 1,25-DHC in an opposing way [13]. It has been hypothesized that 1-α-hydroxylase activity may be higher due to increased luminal PTH, while defective endocytosis leads to decreased availability of the precursor [14]. Hypophosphataemia also augments α-hydroxylase activity. Haematuria in Dent’s disease 1 patients is probably related to nephrocalcinosis/stone formation.
Dent's disease 1 and the CLCN5 gene

The CLCN5 gene, affected by mutations in Dent's disease 1 patients, was first identified in a family carrying a microdeletion [15,16]. The CLCN5 gene, encoding the voltage-gated chloride channel and chloride/proton exchanger (ClC-5) [17,18], spans ~170 kb on chromosome Xp11.23/p11.22, comprises 17 exons and transcription initiates from at least four different start sites (Figure 2). Transcripts (GenBank accession numbers X91906 and BK000969) including the untranslated exon 1a (start site 2) [19] or 1b (start site 4) [16] are spliced to exon 2 containing the start-ATG, whereas a third mRNA (arising from start site 3) comprises a larger exon 1b and retains intron 1 [20].

Two further transcripts (start site 1), due to alternative splicing of exon II, include exons I to IV [21]. Both these transcripts carry the start-ATG in exon III, thereby encoding a longer ClC-5 isoform consisting of 816 amino acids with an additional 70 amino acids at the intracellular amino terminus. Since these two mRNAs maintain the reading frame, the start-methionine of the shorter form (746 amino acids) resides at codon position 71. The longer variant, however, has only been detected at mRNA and not at the protein level [21].

To date, more than 80 distinct CLCN5 mutations, consisting of nonsense, missense, splice site and insertional and deletional mutations, have been reported in patients with Dent's disease 1 [3–5,16,22–45]. These data provide no evidence for a genotype–phenotype correlation, since various mutations were found to be associated with quite different clinical phenotypes ranging from 'classic' Dent's disease 1 to very slight urinary abnormalities, not only in unrelated patients but even within the same family [7]. Also, various groups provided evidence for genetic heterogeneity, in that, patients with typical features of Dent's disease 1, in whom no CLCN5 mutations could be detected, were encountered [21,24,29,39,43].

Dent's disease 2

Recent investigations have revealed that defects in the OCRL1 gene (GenBank accession numbers NM001587 and NM000276) encoding a phosphatidylinositol 4,5-bisphosphate 5-phosphatase [PtdIns(4,5)P2 5-phosphatase; EC 3.1.3.36] are also responsible for a phenotype resembling Dent's disease 1 [46]. In the OMIM database, Dent's disease associated with OCRL1 mutations is now termed Dent's disease 2 (OMIM #300555). Mutations in the OCRL1 gene, located at Xq25 [47], were initially found to cause Lowe syndrome [48], a pleiotropic disease (OMIM 309000), affecting eyes, the nervous system and the kidney. OCRL1 mutations observed in Dent's disease 2 patients comprise insertion/deletion mutations, splice defects and missense mutations, located in various exons (E1: 259–262delTGTT, E7: 436-437insAA, E11: T901G, E14: A1385G) or intron 6 (intervening sequence 6: IVS6-2A>G). Due to frameshifts and premature stop codons, three of these defects were shown to cause absence of OCRL1 protein in Western blot analysis, whereas the two missense mutations give rise to reduced protein levels and diminished PtdIns(4,5)P2 5-phosphatase activity [46]. Interestingly, in Lowe patients, these mutations have not been found to date, whereas mutations leading to a frameshift and/or premature stop codon have frequently been detected [49]. Thus the question remains: why, in these Dent's 2 cases, do the observed mutations not cause cataracts or metabolic acidosis. One obvious possibility is that this subset of patients carries variations in other gene(s) which provides a degree of cerebral and/or ocular protection. It is also worth mentioning that formal neuropsychological testing has not been reported for the majority of classic Dent's 1 patients, and it remains to be determined whether some might have subclinical neuropsychological problems.
Dent’s disease—a polygenic disorder?

Genes other than CLCN5/OCRL1 have been investigated to explain the lack of mutations in patients with a Dent-like phenotype. First, CLCN4, the gene encoding ClC-4 was analysed, since it is located on Xp22.3 and the mutations therein would consequently show an X-linked mode of inheritance. Moreover, ClC-4 (i) is also a member of the ClC-family of voltage-gated chloride channels and chloride/proton exchangers, (ii) gives rise to strong outwardly rectifying anion currents, (iii) exhibits chloride-coupled proton transport activity closely resembling those of ClC-5 [17,18,50], (iv) just as ClC-5, contributes to endosomal acidification by epithelial cells of the renal proximal tubule [51] and (v) could be co-immunoprecipitated with ClC-5, thereby indicating that both these proteins may interact in vivo [51]. As yet, however, no CLCN4 mutations have been found [46,52].

Hoopes et al. [46] also investigated the SLC9A6 gene, located at Xq26.3, which encodes the Na⁺/H⁺ exchanger 6 (NHE6) [53]. This sodium–proton exchanger localizes to early recycling endosomes and is assumed to contribute to the maintenance of the unique acidic pH values of the Golgi and post-Golgi compartments [54]. No SLC9A6 mutation was observed in the 13 patients who met the strict criteria for Dent’s disease [46].

Expression and localization of ClC-5

By Northern analysis CLCN5 mRNA was almost exclusively detected in the kidney [15], but has also been found in aortic and coronary vascular smooth muscle cells and in aortic endothelial cells [55]. The RT–PCR analysis, however, revealed a wider ClC-5 distribution with CLCN5 mRNA expression of the various transcripts also detected in the liver, prostate, placenta, adrenals, leucocytes and the glial cells. Here, some tissues showed specific expression of only some of the transcripts and CLCN5 mRNA was undetectable in the samples from the skin, heart and the hippocampal tissue [21]. However, the role of ClC-5 in extrarenal tissues merits further investigation.

In the kidney, ClC-5 was found to be predominantly expressed in the proximal tubule and α-intercalated cells of the distal nephron [56,57]. In the proximal tubule, ClC-5 mainly locates in intracellular subapical endosomes, where it is thought to participate in the process of endosomal acidification by dissipating the positive endosomal transmembrane voltage gradient generated by the action of the V-type proton ATPase (V-ATPase) [58]. Its presence in the medullary thick ascending limb of the Henle’s loop has also been documented [57]. A small fraction has been localized at the cell surface [50,56]. However, we do not know whether ClC-5 plays a physiological role here, or whether...
Structure and function of CIC-5

Upon heterologous expression, either in *Xenopus* oocytes [50,59] or mammalian cells [50,60], the voltage-gated chloride channel, CIC-5, has been shown to elicit strong outwardly rectifying currents with an anion selectivity profile of nitrate > chloride > bromide > iodide [50]. Recently, it has been shown that CIC5, as CIC4, also shows chloride–proton antiport activity [17,18]. This will be discussed later.

The selective flow of chloride ions is catalysed by a CIC-5 homodimer, with each channel subunit forming its own ion pore [61,62]. X-ray analysis revealed CIC-5 to comprise 18 helices (A–R; Figure 3) which show an internally repeated pattern (helices B–I and J–Q, respectively) forming two roughly repeated halves that span the membrane with opposite (antiparallel) orientations [61]. CIC-5 also harbours two carboxy-terminal intracellular CBS (cystathionine β-synthase) domains that form the so-called Bateman domain [63], an energy-sensing module that binds ATP necessary for the mediation of allostERIC control [64,65]. A proline tyrosine (PY)-like motif (Figure 3), located in the spacer region between the two CBS domains has been shown to be implicated in the internalization and ubiquitination of CIC-5 with mutant CIC-5 displaying a significant increase in surface expression [43,66].

Dysfunction of mutant CIC-5 may be caused by impaired dimerization, altered current kinetics, altered ion selectivity or defective intracellular trafficking. Functional consequences of naturally occurring CLCN5 nonsense and missense mutations were determined by heterologous expression in *Xenopus* oocytes. Here, all the tested nonsense mutations interfered with the CIC-5 function, in that all the recombinant CIC-5 mutants were shown to largely reduce or completely abolish CIC-5 chloride currents [5,29,34,43,67]. Functional properties established for several channels
carrying an amino acid substitution, on the one hand, revealed complete loss of function, whereas other mutant constructs retained up to 50% wild-type activity [4,5,22,23,29,43,50], indicating that type and/or location of a mutation does not predict functional consequences.

Defective trafficking of mutant CIC-5 was also demonstrated in a pig renal tubular cell line [71].

**CICN5 knock-out mice**

Generation of transgenic mice (RZ) with reduced CIC-5 expression [72] or targeted disruption of the CICN5 gene in mouse models revealed phenotypic consequences displaying the characteristic renal tubular defects observed in Dent’s disease 1 [58,73,74]. CIC-5 knock-out (KO) mice exhibited LMWP, glycosuria, aminoaciduria, polyuria and renal phosphate wasting. CIC-5 KO mice generated by different groups also developed hypercalcemia and nephrocalcinosis with progressive renal failure [72, 73] but these features were absent in the KO mice established by Piwon et al. [58]. Moreover, some of these studies indicated that hypercalcemia in the CIC-5 KO mouse—despite elevated levels of 1,25-dihydroxyvitamin D3—is of bone and renal origin [74], rather than caused by increased intestinal calcium absorption [72].

Dysfunction of CIC-5 in endosomes of CIC-5 KO mice furhter improves our understanding of Dent’s disease 1. Here, the internalization of the sodium-proton exchanger NHE3 and the sodium-phosphate cotransporter NaPi-2 was slowed down, indicating an impaired endocytosis from the apical membrane of proximal tubular cells [58]. At a steady state, both these proteins redistributed from the membrane to intracellular vesicles probably due to a rise in luminal PTH concentration. CIC-5 KO mice show greatly reduced abundance of two cell surface receptors, megalin and cubilin, which are involved in the uptake of proteins into the proximal tubular cells [75]. This constitutes a selective loss at the brush border reflecting a trafficking defect of megalin/cubilin.

**Consequences for the acidification of the lysosome**

Along the endocytotic pathway, a successively decreasing pH varying from 6.2 to 4.6 is detected in early endosomes, late endosomes and lysosomes. This acidification is generated and maintained by vacuolar H⁺ATPase, mediating ATP-dependent transport of protons. The movement of H⁺ across membranes results in a net charge translocation, which may be neutralized by a passive influx of counterions such as chloride or by efflux of another cation (proton leakage, K⁺). Sodium entry, mediated by Na⁺/K⁺-ATPase, increases the membrane potential and limits acidification (Figure 4).

Evidence for the role of CIC-5 in the acidification of endosomes is provided by several investigators. Günter et al. [78] demonstrated that endocytic vesicles, isolated from CIC-5 KO mouse kidneys, displayed a slower acidification rate and reached a lower steady-state level of acidification. Marshansky and Vinay [79] showed that vacuolar H⁺ATPase-driven endosomal acidification of the proximal tubules was greatly diminished in the absence of chloride. Sonawane et al. [80] found that endosomal chloride accumulation paralleled acidification in Chinese hamster ovary cells. The pH and chloride concentration in the proximal tubule cell culture from wild-type and CIC-5-deficient mice was measured by Hara-Chikuma et al. [81]: here, acidification and chloride accumulation was impaired in early endosomes but not in the late endosomes and Golgi. Depletion of CIC-5 by the use of antisense RNA resulted in a significant increase of the endosomal pH in Caco-2 cells [51] and it has also been shown that endocytosis in the proximal tubules in wild-type mice but not in KO mice can be inhibited by bafilomycin, an inhibitor of H⁺ATPase [71].

Acidification studies require endosomes which have been carefully isolated and characterized in terms of endosomal markers. Any contamination of the so-called ‘endocytic vesicles’ with other vesicles (Golgi, lysosomes, early vs late endosomes) will result in different acidifications.

**Relation between decreased acidification of the lysosome and the basic defect of CIC-5**

Heterologous expression of wild-type CIC-5 in Xenopus oocytes and Chinese hamster cells yielded outwardly rectifying chloride currents, which were abolished or
markedly reduced by testing the respective mutated CIC-5 observed in Dent’s 1 patients [5]. The Cl− currents however, require 20–40 mV and it is doubtful whether similar voltages can be observed in vivo [17,80].

Two groups of investigators recently demonstrated that CIC-4 and CIC-5 function as voltage-dependent electrogenic chloride/proton exchangers [17,18]. One group used pH sensitive microelectrodes to follow changes in the extracellular pH [17], while the other group measured intracellular pH changes with pH-dependent fluorophores [18]. This antiport would consequently lead to a loss of accumulating protons, constituting an H+ leak which appears contrary to the original proposal that CIC-5 promotes acidification. Hence, Picollo and Pusch [17] speculated that these unfavourable conditions for CIC-5 activation define a brake to limit acidification to a certain degree, namely the one optimal for endosomal function. It is possible that CIC-5 directly acidifies endosomes shortly after budding from the membrane by exchanging cytosolic protons for luminal chloride, which, at that stage, should be similar to the high extracellular concentration [18]. With CIC-5 acting as the exchanger, this might be actually achieved in the absence of V-ATPase. In these early endosomes, inhibition of NHE3 has been shown to disturb acidification and to retard albumin endocytosis, which is consistent with the finding that NHE3 KO mice have tubular proteinuria [82]. The assumption that CIC-channels 3–5 might be involved in the fusion of intracellular organelles is a further, more speculative hypothesis [17] suggesting that the endosome would not mature properly into an acidification-competent state. A clear concept of the role of CIC-5 in intracellular compartments is still lacking.

Consequences for the proximal tubule

Vitamins and iron complexed to carrier proteins as well as several hormones and enzymes bind to megalin and/or cubilin. In the subsequent endocytotic process, ligands are released from the receptors by the low endosomal pH and recycle to the apical membrane [83] (Figure 5). In the CIC-5 KO mice, a selective loss of megalin and cubilin was observed at the brush border [75]. This explains the striking deficiency of urinary megalin detected in Dent’s 1 patients [84].

As demonstrated in the megalin KO mice, deficiency of megalin causes LMWP [83]. In CIC-5 KO mice, not only does an inhibition of apical protein endocytosis of low-molecular-weight proteins occur due to the slowing down of the recycling of megalin and cubilin to the brush border, but there also exists an impaired transfer of endocytic tracers to the lysosomes contributing to an inhibited degradation of internalized β2-microglobulin [75]. As proteinuria in patients with Dent’s disease 1 is frequently >1 g/day, including albumin, CIC-5 will necessarily play a role in the reabsorption of albumin. Defective interaction of CIC-5 with cofilin, a ubiquitously present factor stimulating depolymerization of actin filaments, may contribute to albuminuria in patients with Dent’s disease 1 [85].

Consequences for the reabsorption of peptides/proteins, phosphate, amino acids and glucose

Filtered peptides, normally reabsorbed in the proximal tubule, may have downstream effects on tubular function. The great variety of urinary peptides and proteins in Dent’s disease 1 compared with the normal is impressive [86,87] and includes prolactin, insulin and the chemokine MCP1 [88]. As megalin binds and internalizes angiotensin II, an increased concentration in the distal nephron may be expected with a possible influence on H+ATPase activity [89,90].

The inorganic sodium phosphate cotransporter (NaPi-IIa) accounts for the majority of the renal reabsorption of phosphate. The cotransporter is present in the brush border and retrieved via endocytosis by PTH, leading to lysosomal degradation. No recycling occurs. As megalin is involved in the reabsorption of PTH from the proximal tubular fluid, higher PTH availability was shown to be related to the down-regulation of NaPi-IIa [91]. A PTH-induced retrieval of the cotransporter in the more distal part of the proximal tubule is required to support this hypothesis. Another interfering factor may be a reduced recycling of the parathormone receptor, as demonstrated by proton-pump inhibitors in LLC-PK-1 cells [92].

The impaired reabsorption of amino acids and glucose in the proximal tubular cells is presumably due to the failure to recycle the specific transporters to the apical membrane, as initially assumed by Yamamoto et al. [34]. In this context, the functional role of CIC-5 in the medullary thick ascending limb of the Henle’s loop and the intercalated cells of the collecting tubule is still unclear [93].
Consequences for the medullary thick ascending limb

CIC-5 may play a role in the recycling of transporters present on the apical site of the ascending limb. A decreased presence of these transporters can contribute to the hypercalciuria and defective concentration capacity, as observed in Bartter syndrome [94]. Pham et al. [93] speculate on the possible role of CIC-5 in the exocytosis of Tamm–Horsfall glycoprotein/uromodulin.

Consequences for α-intercalated cells

Using a collecting duct model, Sayer et al. [95] demonstrated that calcium phosphate and calcium oxalate crystals more readily adhere to the CIC-5 KO cells, acting as a nucleus for crystal agglomeration. The authors suppose that the composition of the apical membrane is altered or that a different secretion of molecules regulating crystal adherence may occur and, most recently, they demonstrated in their cell-line a marked increase in plasma membrane annexin A2, a crystal-binding molecule [96]. Moulin et al. [97] found that the expression of the apical H⁺-ATPase was absent in α-type intercalated cells. However, this finding is difficult to reconcile with the normal acidifying capacity observed in about half of Dent’s 1 patients [1].

Consequences for the thyroid gland

Recently, van den Howe et al. [98] reported that the loss of CIC-5 induces euthyroid goiter in the mouse thyroid gland. The authors demonstrated that, contrary to that in the kidney, CIC-5 is not critical for apical endocytosis in the thyroid gland. Instead, its inactivation leads to a delayed apical iodide efflux, associated with a down-regulation of pendrin expression. Additional studies are required to resolve the precise mechanism of this novel CIC-5 function and the interaction with pendrin and to explain why Dent’s 1 patients do not obviously develop a goiter.

Consequences for the intestine

CIC-5 is present in the small intestine and colon of rats in the early endosomes associated with H⁺-ATPase, where its role remains to be defined [99].

Possible treatments for Dent’s diseases

Thiazide therapy has proven effectiveness in correcting hypercalciuria [100,101]. Reports of renal histopathological findings are limited and will depend on the stage of disease progression. Findings from a small number of patients revealed some normal glomeruli, though many glomeruli show periglomerular fibrosis and others were partially or completely hyalinized. Interstitial fibrosis was marked with diffuse as well as focal chronic inflammatory changes [1]. These observations suggest abnormal production of growth factors, cytokines and chemokines inducing interstitial fibrosis. Future therapy should be aimed at the restriction of the production/effect of these factors. Recent studies in CIC-5 KO mice give some reason for optimism [102] in that high citrate diet preserved renal function and delayed the progression of renal disease, despite the fact that interstitial fibrosis was not completely prevented. Based on these findings, early pre-symptomatic treatment with thiazides must be recommended. Thiazide treatment can also be controlled by measuring calciuria.

In order to slow down the progression of renal insufficiency and to achieve a nephroprotective effect as well as antihypertensive medication, the use of an angiotensin-converting enzyme inhibitor might be useful, as observed in patients with cystinosis [103].

Genetic counselling in families, affected with either Dent’s disease type 1 or 2, is recommended not only to confirm the correct diagnosis and corresponding medical benefits for the patients, but also if possible, to identify those individuals by carrier screening who may be at risk for affected offspring. Yet women may manifest recessive X-linked disorders like the Dent’s diseases, despite being heterozygous for the mutation due to a non-random pattern of X inactivation.

Phenotypic overlap in Dent’s disease 1, Dent’s disease 2 and Lowe syndrome

Genetic counselling becomes more complex in Dent’s diseases with evidence of genetic heterogeneity as outlined by Hoopes et al. [39,46]. In their series with 32 patients meeting the criteria of Dent’s disease, mutations in CLCN5 and OCRL1 were observed in 60 and 15% of these patients, respectively, indicating at least one additional gene responsible for this phenotype in the remaining patients.

These findings raise several questions: contrary to Lowe syndrome, where cataracts are uniformly present, none of the Dent’s 2 patients, even harbouring an OCRL-1 mutation resulting in the complete absence of PtdIns(4,5)P₂ 5-phosphatase, showed this lens defect [46]. Renal tubular acidosis (RTA), a prominent feature and often severe in Lowe syndrome [48] has not been observed in any of the Dent’s 2 cases discovered to date [46]. Instead, RTA has been found in a Dent’s 1 family with CLCN5 defect [27]. Mental retardation is a further characteristic feature in Lowe syndrome, and mild mental retardation was present in three of the five Dent’s 2 patients [46]. This observation has clinical implications and should prompt the treating physicians to a careful examination of the mental developmental status in patients with a Dent-like phenotype without the characteristic features (cataracts and RTA) of Lowe syndrome.

Why some patients positive for OCRL1 mutations solely present with the isolated renal phenotype of
Dent’s disease 1 [46] is a further question that remains to be elucidated. As with the features of Fanconi syndrome, there is a considerable similarity between these diseases. The features suggesting the diagnosis of X-linked Dent’s disease provide no clue in order to qualify for either CLCN5 or OCRL1 analysis: both forms of Dent’s disease, as well as Lowe syndrome, are characterized by an impaired proximal tubular function associated with LMWP, aminoaciduria, phosphaturia and glycosuria, and a renal failure is often observed [1,104,105]. Hypercalciuria and nephrocalcinosis/nephrolithiasis are common features in both forms of Dent’s disease but have also been observed in some Lowe patients [106]. Mild elevations in serum muscle enzymes have often been found in Lowe patients [104] and a 1.1–2.0-fold elevated level above the upper limit of the normal was also observed in two patients with Dent’s disease 2 [46].

Urinary megalin is greatly diminished in both Dent’s and Lowe patients [107]. Since this protein receptor resides on the apical surface and in the endosomes of proximal tubular cells, disturbed apical membrane recycling should represent a defect common to both conditions. Given the phenotypic variability observed in either CIC-5-dependent Dent’s 1 or OCRL1-attributable Lowe disease, a variable expression of a combination of abnormalities detected in these disorders should also be expected in patients with Dent’s disease 2 due to OCRL1 mutations.

Conflict of interest statement. None declared.

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2708 M. Ludwig


Clinical and genetic heterogeneity of Dent’s disease


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