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Review

The characteristics and biological significance of *NPC2*: Mutation and disease

Yanan Xu[a,1], Qian Zhang[a,1], Liang Tan[b,1], Xubiao Xie[b,**], Yong Zhao[a,c,*]

[a] State Key Laboratory of Membrane Biology, Institute of Zoology, Chinese Academy of Sciences, University of Chinese Academy of Sciences, Beijing, China
[b] Department of Urological Organ Transplantation, The Second Xiangya Hospital, Central South University, Changsha, China
[c] Institute for Stem Cell and Regeneration, Chinese Academy of Sciences, China

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ABSTRACT

Niemann–Pick C disease (NPC) is a rare autosomal recessive disorder characterized by severe neurodegeneration of central nervous system. Linkage studies in multiplex NPC families and genetic complementation research revealed two disease genes, *NPC1 and NPC2,* both of which are important transporters for cholesterol trafficking. NPC2 executes cholesterol-transport function through protein-protein interaction with NPC1 as well as through protein-membrane interaction directly with membrane of late endosome and lysosome. In addition, NPC2 may play many other roles as indicated by its widely expressing pattern in different cells and presenting in numerous secretory fluids, although it biological significance is less studied today. About 50 clinical cases have been reported documenting over twenty different mutations of *NPC2* in NPC patients so far. In this review, we will mainly summarize the molecular characteristics and biological significance of NPC2, highlighting its vital roles in NPC disease.

1. Introduction

Niemann-Pick type C (NPC) disease is a rare neurovisceral disorder characterized by neurodegeneration in the central nervous system and progressive hepatosplenomegaly. In the early 1980s, a vital discovery of a problem in cellular cholesterol handling in fibroblasts of NPC patients [1–3] led to the development of reliable diagnostic tests [4,5]. Abnormalities of intracellular translocation could be attributed to a block of egress of low density lipoprotein (LDL)-derived (exogenous) cholesterol from lysosomes [3]. In the early 1990s, linkage studies in NPC families first led to assess chromosome 18q11 to NPC disease [6], and to a gene named NPC1 later on. In a first study using genetic complementation by cell hybridization, all cell lines belonged to this gene locus [7]. A further study using the same technique found that a family did not complement with the main group of NPC [8]. More families belonging to this minor group of NPC patients were discovered later on, which was confirmed by linkage analysis [9]. This secondary gene was named as to *NPC2* subsequently. Interestingly, *NPC2* gene was identified by proteomics [10], on the basis of lysosomal proteins binding to mannose-6-phosphate, which was different with positional cloning of *NPC1*. Both of these two gene products (NPC1 and NPC2) are localized primarily in the late endosomal and lysosomal compartments [10,11], and both are involved in the egress of cholesterol from these organelles and cellular cholesterol homeostasis. While a large number of studies have been devoted to the NPC1 protein, a few of data on the NPC2 protein have been published so far. In the present review, we will mainly discuss the structure and important biological functions of NPC2, as well as its roles in the occurrence and development of NPC disease.

2. Molecular and biochemical characteristics of NPC2

At the end of the twentieth century, several studies were devoted into identifying the secondary NPC disease gene, then the group of Peter Lobel finally identified *HE1* as the *NPC2* gene. The *HE1/NPC2* gene, renamed as *NPC2*, is 13.5 kb long and composed of five exons which is located on the long (q) arm of chromosome 14 at position 24.3 in humans [10,12,13] (Fig. 1).

Before identifying *HE1* gene as *NPC2*, researchers had reported HE1 first as a major secretory protein in the human epididymis which is a

* Corresponding author at: Transplantation Biology Research Division, State Key Laboratory of Membrane Biology, Institute of Zoology, Chinese Academy of Sciences, Beichen West Road 1-5, Chaoyang District, Beijing, 100101, China.
** Corresponding author.
E-mail addresses: xiexubiao@csu.edu.cn (X. Xie), zhaoy@ioz.ac.cn (Y. Zhao).
[1] Equal contribution as the first authors.

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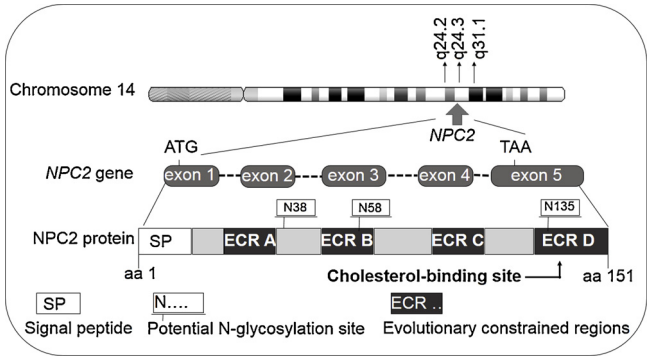

Fig. 1. Schematic representation of the NPC2 gene and protein.
NPC2 is located on the long (q) arm of chromosome 14 at position 24.3 with 13.5 kb length and five exons. The NPC2 protein is a small soluble 151-amino-acid glycoprotein containing a 19-amino-acid signal peptide, heterogeneity of the N-glycosylation may contribute to their different isoforms with different molecular mass (19–23 kDa) observed. Four identified evolutionary constrained regions (ECRs) A, B, C and D show greatest contribution cholesterol binding.

small soluble 151-amino-acid glycoprotein containing a 19-amino-acid signal peptide [14] (Fig. 1). Different isoforms with different molecular mass (19–23 kDa) were observed by Western blot in several normal cells reflecting heterogeneity of the N-glycosylation [10,13,15–17]. Analysis of vertebrate proteins related to NPC2 identified four evolutionary constrained regions (ECRs) A, B, C and D show greatest contribution cholesterol binding [18] (Fig. 1). Three other members of the MD-2-related lipid recognition domain family, ganglioside monosialic 2 (GM2) activator protein (GM2-AP) [19] as well as the dust mite allergens Der f2 and Der p2 [20,21] were found to be identical to NPC2.

The structure of bovine NPC2 has an Ig-like β-sandwich fold consisting of seven β-strands arranged in two β-sheets, related by a 30° rotation [22], whereas high-resolution structure of human NPC2 protein has not be resolved. Structural basis of sterol binding by NPC2 protein has been reported, which indicates that the physiologically relevant ligands bound by NPC2 are likely to be dictated by the specific subcellular repertoire of sterols available for binding rather than by stringent selectivity of the binding cavity [23].

As mentioned above, NPC2 was delivered to lysosomes (LY) via the mannose-6-phosphate receptor signal after translation and modification, and was secreted and N58 is crucial for this transport [10,16]. Apart from being found in epididymis, which lead to its postulated role in sperm formation, NPC2 protein has been detected in several different tissues or secretory fluids such as milk, bile, and plasma indicating its more global functions [10,24,25]. By using immunofluorescence microscopy, the intracellular localization of NPC2 protein has been studied. NPC2 is present in the LY of both cholesterol-depleted and cholesterol-replenished cells, unlike NPC1 protein, which is recruited to the late endosomes (LE) only upon uptake of low-density lipoproteins [26].

3. The intracellular cholesterol-transport functions of NPC2

Cholesterol is an essential structural component of all animal cell membranes and serves as a precursor for numerous biologically active molecules such as steroid hormones, bile acid and vitamin D, many of which serve as ligands for transcription factors. It is important that Intracellular cholesterol is under precise regulation [27]. The main sorting station for cholesterol within the cell is the LE, an intermediate stage in the endosomal-LY trafficking pathway, and NPC1 and NPC2 are key players that initiate the sorting process with function as a tag team duo [28]. NPC1, an integral membrane protein on the limiting membrane of LE/LY, is known that it can accept cholesterol from NPC2 and then mediate cholesterol transport from LE/LY to endoplasmic reticulum and plasma membrane, which has been deeply studied and nicely reviewed [28–31] (Fig. 2).

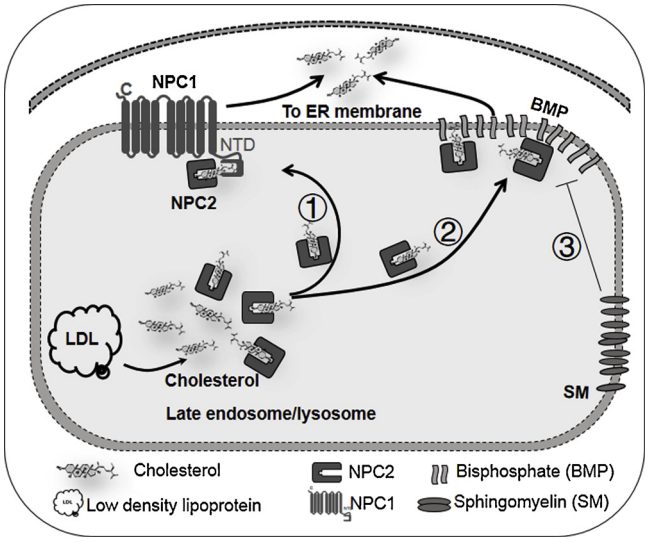

Fig. 2. Intracellular cholesterol-transport functions of NPC2.
Unesterified cholesterol is released by acid lipase from LDL in LE/LY and is bonded by NPC2. Then cholesterol-binding NPC2 continues to transport cholesterol through handing to NPC1 or interaction with membrane. BMP and SM on membrane of LE/LY regulate cholesterol transport by NPC2. ① Cholesterol transport through protein-protein interaction. Cholesterol binds NPC2 with its isooctyl chain and then interacts with NPC1-NTD via its hydroxyl group; ② Cholesterol transport through protein-membrane interaction; ③ NPC2 interacts specifically with BMP but not SM.

Cholesterol-binding is the most widely recognized function of NPC2. In 1999, researchers reported cholesterol-binding activity of the purified NPC2 porcine homolog [12]. Later on, murine NPC2-myc-his protein from stably expressing CHO cells was purified and showed to be functional with high cholesterol-binding affinity, and only a small amount of NPC2 protein added to *NPC2* deficient cells can stimulate the movement of a greater number of cholesterol molecules [18]. Human NPC2 protein was shown to bind cholesterol with high affinity at neutral and acidic pH simultaneously [22]. And point mutants that disrupt cholesterol-bind ability failed to rescue *NPC2* deficiency cells, which provided new evidence that cholesterol binding is essential for the function of the NPC2 protein [18].

NPC disease is caused by mutations of either *NPC1* or *NPC2* and exerts an identical etiology with indistinguishable symptoms, suggesting that they were integral to cholesterol transport out of the LE/LY. Wild-type *NPC2* efficiently rescued the abnormal cholesterol accumulation in *NPC2*-deficient cells, but other three point mutations with normal cholesterol-binding activity failed to rescue this phenotype in *NPC2*-deficient cells [18], which indicates that NPC2 may have additional biological functions other than cholesterol-binding or other important functional domains of NPC2 are required. Infante et al. first proposed that NPC1 and NPC2 function as the cellular “tag team duo” to transport cholesterol within LE to effect egress through the limiting bilayer of the LE [30]. By producing mutant forms of NPC2 and NPC1 (NTD, N-terminal domain, luminal domain, contains several conserved cysteine residues), researchers revealed that NPC2 binds to NPC1 (NTD), displacing the helices and allowing direct transfer of cholesterol into the binding pocket of NPC1(NTD) without passing cholesterol through the water phase [31] (Fig. 2). A quantum mechanics/molecular mechanics (QM/MM) study of conformational changes in cholesterol in the NPC1 and NPC2 binding pockets revealed that cholesterol isomerization in the NPC2 binding pocket, either before or after docking, may ensure an efficient transfer of cholesterol to NPC1 [32]. Intensive study of structure of NPC2-NPC1-NTD interaction revealed that NPC2 binds directly to the secondary lumenal domain of NPC1 protein [33], and some of the key residues of NPC2 and NPC1 in this process were

uncovered [34]. These studies have also been complemented by another two computational investigations focused on the cholesterol transfer process between the N-terminal domain of NPC1 and NPC2 and sterol-binding to NPC2 [35,36].

It has been reported that ATP-binding cassette transporter (ABCA1) can bypass mutations in *NPC1* to mobilize cholesterol either directly or indirectly from the lysosomal membrane. However the expression of ABCA1 cannot rescue the deficiency of cholesterol output from the lysosomal lumen in *NPC2* mutation cells [37], indicating a more irreplaceable role of NPC2 in the progress of intracellular cholesterol transport. The in vitro methods using the endogenous tryptophan fluorescence of NPC2 demonstrated the potential cholesterol transport function of NPC2 [38]. Two hypothetical mechanisms come forward to explain NPC2-mediated cholesterol transport, aqueous diffusion transfer mechanism and collisional mechanism [18,38,39]. NPC2 exerts the strongest transport ability at acidic pH, which is consistent with its localization in the acidic LE/LY compartment. LE/LY manifest a multivesicular appearance due to the presence of a unique anionic phospholipid called bis (monoacylglycero) phosphate (BMP), also known as lysobisphosphatidic acid (LBPA), while sphingomyelin (SM) represents the most abundant sphingolipid of the intraluminal vesicles where sphingolipid degradation takes place [40–42]. The regulatory mechanisms of NPC2-membrane interactions have been reported, showing that when binding to a membrane, NPC2 interacts specifically with BMP, which modulates its efficiency in cholesterol transport and SM strongly inhibits cholesterol transfer by NPC2 [23,38,41,42] (Fig. 2). As for NPC2-mambrane interaction mechanisms, recent research reveals that NPC2 favorably binds to the charged membranes, while BMP and SM modulated two competitively favorable NPC2-mambran interaction orientations to promote or hinder NPC2-dependent cholesterol transport, respectively [43].

Mouse models for both of the NPC1 and NPC2 disease are available, and these mice show various pathological progressions in manners very similar to those of the human NPC disease [44,45]. Moreover, comparative analysis of *NPC1* or *NPC2* knockout mice and double knockout mice showed a high consistency or identity in terms of disease onset and progression, pathology, neuronal storage, and biochemistry of lipid accumulation, providing genetic evidence that the NPC1 and NPC2 proteins function in concert to facilitate the intracellular transport of lipids from the lysosome to other cellular sites [45].

4. Intracellular and extracellular functions of NPC2

Apart from cholesterol binding and transportation, NPC2 likely plays other roles on the basis of available data. In 2016, a clinical cohort study reported that *NPC2* might serve as an accurate single-gene mRNA biomarker for tuberculosis (TB) disease/infection with microarray-based approaches (sensitivity: 82–100%; specificity: 94–97%) [46]. There is research showing that some Drosophila NPC2 proteins and possibly some other insect myeloid differentiation factor 2-related Lipid-recognition family (ML family) proteins may function as co-receptors or pattern recognition receptors (PRRs) for different ligands to modulate innate immune signal pathways [47]. This research demonstrated that recombinant NPC2 bound to LPS and lipid A as well as peptidoglycan and lipoteichoic acid. Over-expression of NPC2 activated diptericin promoter reporter in S2 cells stimulated by peptidoglycan [47]. Thus, NPC2 may be closely involved in innate immunity, which needs to be further clarified.

As mentioned above, NPC2 protein has been detected in several secretory fluids such as milk, bile, epididymis and plasma [10,24,25], indicating there may be extracellular functions which have not been discovered to date. NPC2 is secreted in different glycol-forms by different tissues of human male reproductive tract. Recent study reported that the seminal plasma of the male boar semen with highest freezability had higher concentrations of the NPC2 of 19 kDa protein, which was reduced by incubating with highest freezability spermatozoa [48]. NPC2 is secreted from the liver into bile and plasma, where it may have a functional role in cholesterol transport in normal and disease conditions [25]. A murine study demonstrated that NPC2 is a positive regulator of biliary cholesterol secretion via stimulation of ABCG5/G8-mediated cholesterol transport in mice, which was further supported by the correlation between levels of NPC2 protein and cholesterol in human bile [49]. In a mouse model, study results showed that NPC2 can be secreted from tumor cells and taken up by macrophage-lineage cells (IMCs) to restrain IMCs recruitment to the tumor microenvironment by suppressing secretion of the CCR1 ligand CC chemokine 6 (CCL6), at least in part, by facilitating its lysosomal degradation [50].

5. The involvement of NPC2 in diseases

NPC is an autosomal recessive disorder that exhibits marked lipid accumulation in the LE/LY compartments of disease cells. *NPC1* and *NPC2* are two clearly identified genes responsible for this disease to date. Approximately 95% of NPC cases are caused by genetic mutations in the *NPC1* gene, while another about 5% are caused by mutations in the *NPC2* gene [51,52]. It seems to be indistinguishable between the biochemical phenotypes of *NPC1* or *NPC2* mutants.

Structural analysis and expression studies of artificial mutants have elucidated many of the precise function of NPC2 protein, but studies dissecting the biological behavior in vivo rely on the exploration of natural naturally occurring mutations. About 50 clinical cases have been reported that there are many different mutations of *NPC2* so far. Nevertheless, all of those reported cases nicely highlighted mutation sites of *NPC2*, which were summarized in detail here (Table 1 and Fig. 3). Though the global contribution of NPC disease has rarely been calculated, more patients originating from North Africa, Italy and Turkey have been described with *NPC2* mutations, which was briefly discussed in recent clinical guidelines on NPC disease [53].

Some of case reports presented the involvement of the severe lung dysfunction that usually lead to death at about 6 months of age, before the onset of neurological symptoms and usually accompanied with hepatosplenomegaly [8,54–59]. Accordingly, there were other studies showing that NPC2 patients have a higher prevalence pulmonary involvement than NPC1 patients [9,13,55,56]. Because of the accumulation especially in the viscera, such as liver, spleens and lungs, and in the central nervous system of unesterified cholesterol and other lipids [60,61], affected patients are mainly characterized by neurological dysfunction and liver damage [62,63]. Neurological dysfunction causes many identifiable symptoms including vertical supranuclear ophthalmoplegia, cataplexy, dysarthria, dysphagia, seizures, speaking and swallowing difficulty and dementia. Moreover, all of these differ greatly between patients in terms of age-at-onset, clinical presentation, disease severity and course of the neurodegeneration [64].

Importantly, researchers have figured out some of the genotype-phenotype correlations in NPC patients with NPC2 mutations. More than half of reported mutations are very severe ones (frame shift, stop codon, mutation of the initiation codon, large deletion encompassing both exons 2 and 3…), including p.M1L, p.M1l, p.L9fs, p.E20X, p.E118X and so on, which often result in early disease onset with a short lifespan [9,13,55,65–67]. However, some of the missense mutations, e.g. C47F, C93F, C99R or S67P, were shown to lead to a functionally very deficient protein, retained in the endoplasmic reticulum [65,68]. Patients with two very severe alleles who survived more than one year almost invariably showed a severe early infantile neurological phenotype. On the other hand, IVS2 + 5G > A [13], V39 M [69] and P120S [65] have been associated with juvenile or adolescent/adult neurological forms. Especially, patients with a homozygous P120S mutation, as a missense mutation in the cholesterol-binding ECR D domain, also had a juvenile neurological onset form of disease [65,70]. The impact on cholesterol binding activity of P120S was further demonstrated by the group of Goldstein and Brown [31]. Further and deep-going identification of patients with NPC2 and their specific

Table 1
A summary of the reported mutations of *NPC2* in patients.

No	NPC2 Mutation	Nucleotide Changes	Locations	References
1	p.M1l	c. 3 G > C	Exon 1	[66]
2	p.M1L	c.1 A > T	Exon 1	[67]
3	p.L9fs	c.27delG	Exon 1	[54,85]
4	p.E20X	c. 58 G > T	Exon 1	[8,10,13,54,65,85,86]
5*	p.Y55X	?	Exon 1	[65]
6	IVS1 + 2T > C	c.82 + 2T > C	Intron 1	[65]
7	p.V39M	c. 115 G > A	Exon 2	[69,86]
8	p.Q45X	c. 133C > T	Exon 2	[68]
9	p.C47F	c. 140 G > T	Exon 2	[86]
10	p.C47X	c. 141C > A	Exon 2	[68]
11	IVS2 + 5G > A	c.190 + 5G > A	Intron 2	[13,66]
12	p.S67P	c. 199 T > C	Exon 3	[13]
13	p.C93F	c. 278 G > T	Exon 3	[86]
14	p.C99R	c. 295 T > C	Exon 3	[68]
15	p.N111fs	c.331delA	Exon 3	[10]
16	p.N111K	c.333 T > G	Exon 3	[87]
17	p.E118X	c. 352 G > T	Exon 3	[55,85]
18	p.P120S	c. 358C > T	Exon 3	[65,70]
19	IVS 3 + 6 T > G	c.363 + 6T > G	Intron 3	[88]
20	p.Q136fs	c.408-409delAA	Exon 4	[58]
21	p.V145E	c. 434 T > A	Exon 4	[89]
22	p.Q146X	c. 436C > T	Exon 4	[65,70]
23**	\	\	Exon 2 + Exon 3	[90]

5*: No specific nucleotide change was documented in original reference.
23**: Deletion of two exon 2 and exon 3 in the *NPC2* gene.

molecular change of NPC2 proteins are important because of their considerably suggestive roles in developing the better diagnosis and treatment approach.

Therapeutic options for NPC disease are quite limited. In January of 2009, miglustat was approved by the European Medicines Agency for use in treatment of neurological symptoms in patients with NPC disease, which is the only one approved treatment so far. However, there is no published reports about the effect in NPC2 patients. Unlike NPC1, since NPC2 protein is secreted and can be recaptured by other cells, NPC2 is theoretically amenable to correction by hematopoietic stem cell transplantation. However, only one patient so far survived transplantation and the result indicated hematopoietic stem cell transplantation could be considered for patients with this mutation as long as performed early in the course of the disease [71].

Recently, accumulating evidence indicates that cyclodextrins, as a cholesterol sequestering agent, can mobilize cholesterol from LE/LY of NPC-deficient cells depending on bulk-phase endocytosis [72–74] or clathrin-mediated endocytosis of cyclodextrins into LE/LY [75]. Treatment of NPC mice with the cholesterol sequestering agent cyclodextrins, the derivative is 2-hydroxy-propyl-beta-cyclodextrin, significantly improves the neurodegeneration and increases in lifespan of those mice are encouraging [76–79]. Reported clinical cases using 2-hydroxy-propyl-beta-cyclodextrin for compassionate use in NPC disease suggested that efficacy may be partial and dependent on the early administration of the drug, the severity of the disease, and interpersonal variability, which was accurately re-analyzed and reviewed by Megias-Vericat et al. [80]. Researchers are still working on the effectiveness of cyclodextrins as a therapeutic agent [81,82].

Moreover, gene therapy seems to be a potential option for the treatment of NPC disease, which can be provided as a one-time treatment, with the prospect of lifelong beneficial effects. Recent published studies in the NPC1 and NPC2 disease mouse models demonstrated that neonatal intravenous delivery of adeno-associated virus expressing *NPC1* or *NPC2* gene lead to an increase in survival and favorable prognosis [83,84].

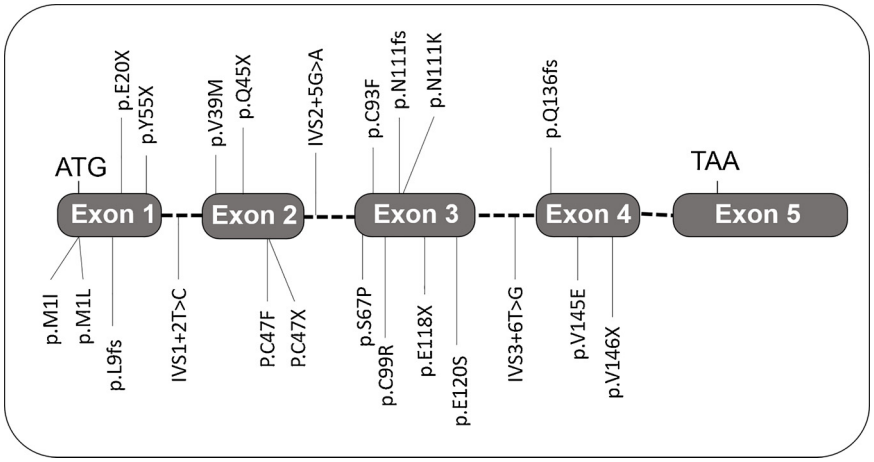

Fig. 3. All reported mutations of *NPC2*.
The known and reviewed mutations of NPC2 are shown on schematic view of the gene.

6. Conclusions

NPC2 acts as an intracellular cholesterol-transport protein working in the acidic environment of LE/LY. Besides intracellular cholesterol-transport function, NPC2 might play other intracellular and extracellular biological roles, indicated by its wide expression in different cells and being detected in numerous secretory fluids. Homozygous mutations in *NPC2* genes cause NPC type 2 disease and about 50 clinical cases have been reported documenting over twenty different mutations so far. As the overall biological functions of NPC2, especially its extracellular biological roles, haven't been clarified, further studies are urgently needed. The good news is that some of the genotype-phenotype correlations have been determined and this may help to improve the effectiveness of earlier diagnosis and clinical treatments. The severest challenge is that the therapeutic options for NPC disease are quite limited and breakthroughs are needed.

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