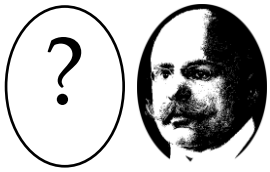
Pfrieger's Digest



Issue 14
May – August 2025

Niemann-Pick Diseases

Summaries of latest research advances related to Niemann-Pick diseases, acid sphingomyelinase deficiency (ASMD) and Niemann-Pick type C disease (NPCD), based on selected peer-reviewed publications in scientific journals.

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Dear Readers.
Welcome to the **fourteenth** issue covering May 1st 2025 to August 31st 2025. The corresponding links for the PubMed queries are:
- for **NPCD**:

((niemann-pick c OR niemann-pick type C OR niemann-pick type C1 OR niemann-pick type c2 OR npc1 OR npc2) AND (("2025/05/01"[Date - Publication] : "2025/08/31"[Date - Publication])))) NOT (("2020/01/01"[Date - Publication] : "2025/04/30"[Date - Publication]))

- for **ASMD**:

((niemann-pick AND ("type a" OR "type B" OR "type A/B") OR smpd1 OR asmase OR acid sphingomyelinase) AND (("2025/05/01"[Date - Publication] : "2025/08/31"[Date - Publication])))) NOT (("2020/01/01"[Date - Publication] : "2025/04/30"[Date - Publication]))

During this period, **69** (NPCD) and **28** (ASMD) articles were published in scientific journals including **9** (NPCD) and **3** (ASMD) reviews. **Three** articles appears in both queries. Note that English versions of the Digest are accessible through the open science archive HAL!

Please note: 1) My selection of articles is subjective. 2) I comment only peer-reviewed original articles, and neither preprints nor review articles nor case studies describing single patients. 3) I only include articles that I can read from start to end. 4) I try to ensure correctness of statements, but I cannot guarantee this. 5) Errors of any kind are not excluded. 6) My judgements and interpretations are subjective and reflect my personal opinion, they do not claim any validity. 7) I apologize for any errors in grammar, punctuation and orthography, and for any wrong, quirky or otherwise weird expressions. 8) This text is my translation of my original German version, which was written by myself thanks to my own natural and naturally limited intelligence without any help from an artificial one. 9) Feel free to distribute this issue, as long as there are no changes to the text or layout. 10) Translations to other

languages are welcome, as long as my authorship and the original version are mentioned. 11) The digest does not indicate sources of funding for published studies. This information can be found in a dedicated section of each publication. 12) English versions are freely available from the open science archive HAL, issues 2-6 will be uploaded. 13) I thank the German Niemann-Pick Selbsthilfegruppe e.V. and NPSuisse for support and all others who kindly host the Digest on their websites or distribute it otherwise.
13) Feedback (praise, criticism, giftcards) welcome to: fw-pfrieger@gmx.de.

Patients (NPCD)

PMID:40525490 Farmer et al. Convergent Validity of the Fine Motor, Speech, and Cognitive Domains of the 5-Domain Niemann-Pick Disease Type C Clinical Severity Scale. J Child Neurol. 2025 Jun 17:8830738251346348.

Let's start with severity scales, a truly important topic. They are supposed to measure the severity of the disease in a patient based on different domains. They should indicate how the disease advances in patients, and – very important – whether and how a therapy works (see issues 4, 6, 10 and 12). There are different scales, for example the "scale for the assessment and rating of ataxia" (SARA), the whopping 17 domain NPC clinical severity scale (NPC-CSS-17) and slimmed down NPC-CSS versions. Now, attention please! These scales are scoring systems, a bit similar to (numeric) school grades. To put it in mathematical terms, they are discrete instead of continuous. Each score is assigned based on predefined specific criteria. Example: fine motor control 0: normal voluntary movement, 2: mildly impaired, etc. up to 5: severely impaired. The points from different domains are added. So, for five domains and five points per domain, this results in a scale of 0 (very good) to 25 (very bad). The million dollar question is obviously how well these scoring systems reflect the "real" state of a patient. The scoring has a touch of subjectivity. Moreover, the scores are averaged in clinical studies. This leads to funny decimal points (those numbers behind the point) of unknown importance ("improvement from 4.3 to 3.8" what does that mean? See also next article!). Well, similar questions arise in the school environment. The present, indeed important work aimed at the five domain NPC-CSS with a large dataset from the NIH and Rush University Medical Center in Chicago (USA). Previous studies had looked at the utility of the scale. Here, the NPC-CSS scores for cognition, speech and fine motor control were compared to results of independent standard tests. For example, fine motor control was measured among others with the 9 hole peg test which delivers a continuous measure, the time until the task is done. In total, data from 128 patients were analysed. Not every patient did every test, some patients could repeat certain tests, for some domains (fine motor control and speech) heavily impaired

patients could not be taken into account, also age-adapted tests had to be used. The study shows that the NPC-CSS scores in the three domains agree on average (!) relatively well with the results from standard tests, at least in specific ranges. Looking at the cognition values (there's a figure in the paper) reveals that intelligence measured by standard tests vary much more widely among patients compared to the coarse NPC-CSS scoring system. And there are overlaps: patients with similar IQ values according to standard tests got distinct NPC-CSS scores for cognition. Well, no system is perfect. NPCD like other phenomena (school!) cannot be fully grasped by scoring systems.

PMID:40520915	Mengel et al. Efficacy results from a 12-month double-blind randomized trial of arimoclomol for treatment of Niemann-Pick disease type C (NPC): Presenting a rescored 4-domain NPC Clinical Severity Scale. Mol Genet Metab Rep. 2025 May 28;43:101233. doi: 10.1016/j.ymgmr.2025.101233.
PMID:40663813	Mengel et al. Long-term efficacy and safety of arimoclomol in Niemann-Pick disease type C: Final results of the phase 2/3 NPC-002 48-month open-label extension trial. Mol Genet Metab. 2025 Aug;145(4):109189. doi: 10.1016/j.ymgme.2025.109189. Epub 2025 Jul 7.

This is about arimoclomol, which has been rebabtized to marketing-friendly Miplyffa, and the results of clinical studies. The first publication shows what happens after 12 months treatment with the drug or placebo (see issue 4 and 5) using the Pippi Longstocking strategy ("I make the world as I like it"; cited from the German version of the title song). No, just kidding, it's not as bad. The data were re-analysed: cognition was removed from the five domain scale (see also next paper!), because the results are not comparable due to different test conditions and ages of patients. In addition, the scale measuring swallowing was smoothened. Now, the results look better (see issue 5). With arimoclomol (and miglustat) it's getting worse more slowly than with placebo. Does it stop getting worse? A first response gives the second publication with results from 29 patients who completed the followup study (*open label extension*). The outcome measure were the five- and four-domain scales mentioned above. The results – based on mean (!) values across all participants – can be summarized as follows: Switching from placebo to arimoclomol showed a positive effect, namely with respect to swallowing. In the long-term the diseases progressed, but seemingly slower compared to values from

untreated patients from previous studies. Red flag: This is based on mean values. How did the scores in the different domains change in individual patients?

PMID:40513057 Patterson et al. Disease-Modifying, Neuroprotective Effect of N-Acetyl-l-Leucine in Adult and Pediatric Patients With Niemann-Pick Disease Type C. Neurology. 2025 Jul;105(1):e213589. doi: 10.1212/WNL.0000000000213589. Epub 2025 Jun 13.

We stay with the topic and come to n-acetyl-l-leucine (NALL), marketing-friendly levacetylleucine or – even better – AQNEURSA (see issues 4, 5, 10 and 11). Patterson and colleagues report the latest results of a second Intrabio-sponsored study. As reminder, in the first study (issue 11) patients older than 4 years received either for 3 months placebo and then for 3 months NALL or the other way around, so, first NALL and then placebo. In the second follow-up study all those who wanted received NALL, in total 49 patients of which 41 also took miglustat. What was measured? Three scales were used (see previous articles): the 5 and a 15 domain NPC-CSS and SARA. The results are promising, at least when looking at the mean values (!) across all participants (see above): treatment with NALL slowed down disease progression, and eventually led to improvements. Since this follow-up study did not have a placebo group, published values from previous studies were used for comparison. Once again, how did the values in the different domains change in indivudal patients. By the way, a brief comment concerning a percentage numbers game. Those who do not like numbers, just skip the following. The paper states with NALL its getting 18% better than without (baseline). What does that mean? Well, here somewhat arbitrarily an annual worsening by +1.5 points in the 5 domain NPC-CSS in untreated patients is taken as 100%. The value is from a previous study (Mengel et al., 2020; s. issue 4). Then, the -0.27 points change with NALL (so decrease = better!) is considerer an improvement by 18% (0.27 divided by 1.5 times 100). That sounds like something, but what does it mean *realiter*?

PMID:40701909 Gascón-Bayarri et al. Efficacy and safety of efavirenz in Niemann-Pick disease type C. Neurotherapeutics. 2025 Jul 22:e00706. doi: 10.1016/j.neurot.2025.e00706.

And another clinical study, this one's from Spain, and it's about efavirenz (s. issue 10) and its effect in patients with adolescent/adult form. Sixteen patients older than 14 years participated, all received the drug, there was no placebo control. The focus was on cognition, since the target of efavirenz, the enzyme Cyp46, is mainly active in nerve

cells. There, it's supposed to serve as overflow trap helping to get rid of superfluous cholesterol. Drug efficacy was measured in three domains, dementia, language and executive function by a large battery of tests before and at different intervals during treatment. Overall, all patients reacted positively, no worsening in two of the three domains tested during the 52 weeks period. Well, obviously it's a matter of definition, what is considered positive. A closer look at the results reveals a more mixed picture. Positive changes in some but not all tests showed those patients whose onset of symptoms was not too long ago. The authors suggest a threshold of 12 years. So, once more, the earlier the treatment the better!

PMID:40866990 Karimzadeh et al. Clinical characteristics and treatment outcomes in patients with Niemann-Pick disease type C (NP-C): a cross-sectional study. Orphanet J Rare Dis. 2025 Aug 27;20(1):459. doi: 10.1186/s13023-025-03897-9.

This study provides an overview over 58 iranian patients that were treated between 2013 and 2024 in a Teheran hospital, and reports effects of miglustat treatment. With respect to the latter, nothing new. However, the cohort consists of many young patients, the average age at symptom onset was 3.35 years. The colleagues also used a scale to measure the effects of miglustat, but again a different one. This was about categories (worse, stable, better) and percentages, so for example swallowing at the beginning 5 (9.6% of all) patients, after treatment stable in 3 (5,8%) and worse in 2 (3.8) patients. Another variation on the theme.

Patients (ASMD)

PMID:40420295 Villeneuve et al. Advanced strategies for detecting acid sphingomyelinase deficiency type B with attenuated phenotypes. Orphanet J Rare Dis. 2025 May 26;20(1):252. doi: 10.1186/s13023-025-03746-9.

Back to dusty bins and patient files, they can be very useful, notably, when they are available in a database. The work shows that ASMD patients can be found retrospectively. How? Just take electronic files of maaaaaaaaaaaaaaaany people (around 60,000), who were admitted to the university hospital in Toulouse (France) beween 2012 and 2023, filter the data by specific criteria, let experts check them, et voilá.

PMID:40717061 Eskes et al. Exploring Exhaled Breath Analysis in Adults With Chronic Visceral Acid Sphingomyelinase Deficiency to Identify Potential Biomarkers of Pulmonary Involvement. J Inherit Metab Dis. 2025 Jul;48(4):e70039.

Here new and exciting stuff from the Netherlands. It's about breathing problems, biomarkers and a surprising approach. Impaired lung function is a big issue that severely impairs the quality of life of ASMD (and NPCD) patients, and on the other hand, it is clearly understudied. The authors analysed the exhaled breath of ASMD patients to detect possible biomarkers. The idea *per se* is not new, this has been studied in other diseases, notably lung cancer, but it's never been done for ASMD (nor for NPCD). Highly welcome pioneering work! The study comprised 15 patients and 34 "control exhalers". The exhaled breath was analysed thoroughly together with established blood biomarkers. Lung function and structure were examined, the latter by MRI scans. The study identified three substances, short carbon chain molecules with strange names 2-hydroperoxyhexane, 6-heptyn-2-one and 4-pentenyl acetate that are characteristic for the exhaled breath of ASMD patients and that correlate with other markers and the state of the lungs. Where these molecules come from is unclear. A possible source is lipid oxidation, possibly in the lung tissue. As icing/cherry on the cake, the study also delivers a damage score for the lung based on MRI scans. To be followed up, maybe also for NPCD.

PMID:40806768 Van Baelen et al. High-Resolution Mass Spectrometry Method for Targeted Screening and Monitoring of Fabry, Gaucher and ASMD Using Dried Blood Spots and Capitainers: Impact of Sample Matrix on Measurement Results. Int J Mol Sci. 2025 Aug 7;26(15):7641.

This is about three known biomarkers for three diseases including *lysosphingomyelin* and ASMD. The authors validate an improved method to accurately measure the concentrations of the markers in dried blood spots. Those are important for newborn screening.

PMID:40810828 Youssef et al. Outcome of enzyme replacement therapy for hematological and visceral manifestations in children with acid sphingomyelinase deficiency: a single center experience in upper Egypt. Mol Cell Pediatr. 2025 Aug 14;12(1):11. doi: 10.1186/s40348-025-00199-9.

An important study about the effects of olipudase comes from a hospital in Asyut in upper Egypt. Ok, there are many studies already. True! But not with pediatric patients (2–6 years, five with type A/B so chronic neurovisceral and five with type B, so chronic visceral). The results after twelve months of treatment with olipudase are clear, the treatment works based on positive changes in different measures such as weight, hemoglobin, platelets, cholesterol, liver and spleen size, bone density. Two patients with decreased lung function showed considerable improvement.

Animal models (NPCD)

PMID:40869913 Servín-Muñoz Gene Expression Profile of the Cerebral Cortex of Niemann-Pick Disease Type C Mutant Mice. Genes (Basel). 2025 Jul 24;16(8):865.

Here, another socalled gene-expression study, a favourite topic (issues 2, 5, 6, 9, 13). As reminder, one aims to know which cellular processes are affected by NPCD, switched off, switched on, or disturbed otherwise. A popular approach aims to study the pattern of gene expression, and indirectly of protein production. Which proteins and thus processes are up or downregulated by the disease in cell xyz. This can be addressed in different ways, the present work took the easiest and most cost efficient. The authors studied how the gene expression pattern in the cortex of mice with normal and mutant NPC1 differs. The animal model named *imagine* was introduced in 2017 by Gomez-Grau and colleagues. The mice carry a variant that was found in a Spanish patient, they produce very little to no NPC1 protein. The study shows, as many before, genes that are up- and downregulated indicating disease-linked changes in this or that process. However, the approach used does not show what happens in which cell (neuron, glia etc.). This would require much more demading single cell analyses that have also been done previously though with different mouse models and brain regions (see e.g. issues 2 and 9).

PMID:40847051 Yamada et al. Inability of α-cyclodextrins to accommodate cholesterol potentially underlies their lack of efficacy and ototoxicity in Niemann-Pick disease type C treatment. Sci Rep. 2025 Aug 22;15(1):30857. doi: 10.1038/s41598-025-15599-0.

Alpha, beta, gamma, there are the three and many more, but in the context of cyclodextrin we only hear of beta. Why's that? Japanese colleagues took a closer look. Beta- and gamma-cyclo work in cell and mouse models, but not alpha, simply because it's cup size is too small for cholesterol – and whatever else fits in and causes damage.

Animal models (ASMD)

PMID:40543381 Kell et al. Secondary accumulation of lyso-platelet activating factors in lysosomal storage diseases. Mol Genet Metab. 2025 Aug;145(4):109180. doi: 10.1016/j.ymgme.2025.109180. Epub 2025 Jun 17.

Topic biomarker, precisely *lyso-platelet activating factors* (Lyso-PAFs). These are special fat molecules that popped up in the context of NPCD as secondary storage material, secondary because they have nothing to do with the protein that is broken (so for example NPC1, issue 11 or ASM). The study shows that the content of Lyso-PAFs is enhanced in brain tissue of ASM-deficient mice, the older the more. And it shows that Lyso-PAFs accumulate in animal models and human samples from other lysosomal diseases, including Sandhoff and GM1 gangliosidosis. This is probably not surprising, these diseases have probably more in common than we realize.

PMID:40609755 Naya-Forcano et al. Sphingomyelin-induced glucocorticoid receptor alterations lead to impaired presynaptic plasticity in acid sphingomyelinase deficient neurons. Neurobiol Dis. 2025 Sep;213:107016.

This work may lay a new track to a better understanding of neurologic symptoms in ASMD and their treatment, a truly neglected topic. It's about glucocorticoid, or, if this sounds strange, cortisol. These are natural steroid hormones. They are made from cholesterol and they exert many functions throughout the body including the brain. A pharmacologically exploited function is inhibition of inflammation and pain reduction. Just to illustrate: PubMed lists 90,000 articles related to this group of hormones. Glucocorticoids are formed in adrenal glands and bind to specific proteins, receptors, in their target cells which then control expression of cell-specific gene. In addition, there

are genome-independent effects. The glucocorticoid concentration waxes and wanes with the day/night cycle, and it skyrockets during stress. The Ledesma group studied glucocorticoids in the brains of ASM-deficient mice, and found lower concentrations of receptors, notably at synapsen, possibly due to accumulation of sphingomyeline. The synapses transmitted electric activity differently. Can this be repaired? Yes, in cell cultures by treatment with cortisol. The observations support positive effects of glucocorticoids in ASM-deficient mice that the group reported in 2014.

Cell-based Models (NPCD)

PMID:40768564 — Pirone et al. Drug-Induced Reversible Lysosomal Changes Tracked in Live Cells by Holo-Tomographic Flow Cytometry. ACS Nano. 2025 Aug 19;19(32):29601-29615. doi: 10.1021/acsnano.5c08530. Epub 2025 Aug 6.

This article almost slipped through. It's about an interesting new optical method to separate cells with defective NPC1 from healthy ones, label-free! so without any staining. Stains are always ugly in one way or another (Bolognese sauce on white shirts!). Often, like with filipin, you have to kill cells before you can stain them. The new approach is based on smart illumination of cells and intense image data munging.

PMID:40565243 — Parente et al. (2025) Exploration of Bromodomain Proteins as Drug Targets for Niemann-Pick Type C Disease. Int J Mol Sci. 2025 Jun 16;26(12):5769.

"New kid on the block!" This article written by the Digest author delivers first evidence for a new therapeutic approach based on experiments with those notorious patient-derived fibroblasts. This is about inhibition of socalled Bromodomain and Extraterminal Domain (or BET) Proteins. Attention, biology! These proteins recognize patterns on histones (histone acetylation, for fans), and cling to them. Histones on the other hand are a sort of bobbins that wind and unwind the DNA thread. Where the BET proteins cling to, the genomic information cannot be read. BET inhibitors prevent the clawing and enable the production of specific proteins. Ok, the whole thing is more complex and still not well understood. The study shows that inhibition of BET proteins kickstarts NPC1 production and reverts some pathologic changes in cells including cholesterol accumulation. Btw, publication of this article has taken one year, four journals did not want to publish the story. "Stay tuned, there's more to come!"

PMID:40516874 Wang et al. Itraconazole and posaconazole, inhibitors of NPC1 sterol transport, act as pharmacological chaperones after washout. J Biol Chem. 2025 Jul;301(7):110370. doi: 10.1016/j.jbc.2025.110370. Epub 2025 Jun 16.

On with drug candidates, now itraconazole and posaconazole. They should have been mentioned previously. *Mea culpa*! The terrible names aren't an excuse. Both are used to treat fungal infections. Earlier studies showed that these drugs also bind to NPC1 protein. Thereby, they help pathogenic variants to fold correctly and to escape merciless degradation by the quality control system. Great! But, the drugs also inhibit the function of NPC1. Bummer! The new work shows in skin fibroblasts from patients that a pulsed treatment with either drug (add-remove-add-remove...) has positive effects: it reduces cholesterol accumulation and gets NPC1 protein to its workplace. Whether this works in NPCD animal models and in patients remains remains to be seen.

PMID:40603986 Wüstner et al. Dynamic mode decomposition for analysis and prediction of metabolic oscillations from time-lapse imaging of cellular autofluorescence. Sci Rep. 2025 Jul 2;15(1):23489.

Everybody knows, sometimes it goes up, somestimes down and so on. This can be wonderful or terrible depending on the situation. Also cells show ups and downs, for example with respect to energy metabolism, in technical mumbo-jumbo: it oscillates, even minute by minute. Healthy cells probably swing differently than sick cells. The question is can they be discerned simply based on the ups and downs of energy metabolism. So far, so easy. The work from Denmark addresses this question using – "thin-ice warning!" – very complex methods. Quote from the biophysics lecture: "If you do not understand it, just get used to it!". Ok! So, here's the answer and a brief summary: one can, at least in bakers yeast. The authors developed a procedure (no details, keywords for freaks are *dynamic mode decomposition*, *time delay embedding, machine learning* and the good old time lapse imaging) that allows to distinguish yeast cells with or without NPC1 or NPC2 based on time-dependent changes in the metabolite concentration. No, hocus pocus, simply advanced data analysis! The gripping question is whether the approach works in other cell types and in tissues.

PMID:40554661 Lin et al. An Integrated Platform for High-Throughput Extraction and Mass Spectrometry-Based Quantification of Cholesterol and Sphingosine. Anal Chem. 2025 Jul 15;97(27):14177-14188. doi: 10.1021/acs.analchem.4c06628. Epub 2025 Jun 24.

Measuring the cholesterol content should be easy, one may think! But it depends, where, how exactly and how fast. The present work from the NIH in Maryland introduces an automated *high-throughput* system that allows to measure within two hours the cholesterol content in socalled 384-well plates. They contain 384 caves, where cells dwell. These allow to test numerous conditions (for example drug candidates) for their effect on the cellular content of cholesterol.

PMID:40436106 Igarashi et al. Neurogenin 2-induced central neurons generated from NPC patient-derived iPSC display attenuated neurite outgrowth while accumulating cholesterol. Biochim Biophys Acta Mol Cell Biol Lipids. 2025 Aug;1870(6):159639. doi: 10.1016/j.bbalip.2025.159639. Epub 2025 May 26.

New model, new joy – and possibly trouble. This is about nerve cells that are generated from human induced pluripotent stem cells. This trendy model is exciting for different reasons, it's human, easy to manipulate, and scalable to yield large quantities. The field develops at the speed of light. The colleagues from Japan generated, as others bevor (issue 6), nerve cells from skin fibroblasts of healthy donors and NPCD patients and characterized them. They used a sort of turbo method that was originally introduced in 2013. It generates within two weeks nerve cell-resembling things in the plastic dish, older methods took much longer. There were differences between sick and health cells, treatment with miglustat reduced cholesterol accumulation – this had not been seen previously –, and a drug screen exposed at least two new drug candidates (lacosamide and phenelzine). The work shows that the model leaves its infancy, but there are stepping stones ahead: A deficit of all previous studies is that they rarely measure what is really important for nerve cells, their synaptic activity.

Cell-based Models (ASMD and NPCD)

PMID:40427492 Guerra et al. c-Abl/TFEB Pathway Activation as a Common Pathogenic Mechanism in Lysosomal Storage Diseases: Therapeutic Potential of c-Abl Inhibitors. Antioxidants (Basel). 2025 May 20;14(5):611. doi: 10.3390/antiox14050611.

The work by the Zanlungo team from Chile follows up on their previous observations (s. Issue 3) that inhibition of ABL1 (a.k.a. c/Abl) cranks up lysosome production and reduces cholesterol accumulation in NPCD. The new results show positive effects also in pharmacologic cell culture models of ASMD and Gaucher disease following treatment with imatinib, neurotinib oder vitamin E.

Miscellaneous

PMID: 40333988 Appu et al. Niemann Pick C1 mistargeting disrupts lysosomal cholesterol homeostasis contributing to neurodegeneration in a Batten disease model. Sci Adv. 2025 May 9;11(19):eadr5703. doi: 10.1126/sciadv.adr5703. Epub 2025 May 7.

A gripping story, but its about something else, and about palmitoylation. No, palmitoylation is not an animator-cheered on activity under palm trees of holiday clubs! One by one: neuronal ceroid lipofuscinoses (a.k.a. Batten disease) are a diverse set of lysosomal storage diseases. A terrible form, socalled CNL1 or infantile CNL, is provoked by defects in an enzyme that reverts the above mentioned palmitoylation. Palmitoylation means that a fatty acid, mostly palmitic acid (palm oil!), is added to protein X. This process ensures that protein x gets from its place of birth to its place of function. There, protein x has to be liberated from the fatty acid, so it can function. This is done by the above mentioned enzyme with the wonderful name *palmitoyl-protein thioesterase-1* or PPT1. The work shows that in CNL1, so PPT1 broken, also NPC1 cannot get to its place of work due to the defective depalmitoylation. In fact, it gets lost and odyssees to the plasma membrane. So, CNL1 is some kind of combination of NPCD and probably other diseases, since other so far unknown proteins cannot get to their workplace either. So what? Well, defects in de-palmitoylation of NPC1 may provoke or contribute to NPCD!

PMID: 40870568	Lin et al. Functional Analysis of NPC2 in Alarm Pheromone Recognition by the Red Imported Fire Ant, Solenopsis invicta (Formicidae: Solenopsis). Insects. 2025 Jul 25;16(8):766. doi: 10.3390/insects16080766.
PMID: 40780340	Rao et al. Niemann-Pick type C2 protein PpseNPC2-1 binding volatile nerolidol mediates prey localization of the pond wolf spider Pardosa pseudoannulata. Int J Biol Macromol. 2025 Sep;322(Pt 1):146675. doi: 10.1016/j.ijbiomac.2025.146675. Epub 2025 Aug 6.

Back to the topic pests, insects, but from two directions. Evidently, what is called a pest is variable, but the first study is about a real problem bug, the red fire ant, an invasive species from South America that causes major havoc around the world. Chinese colleagues found that these ants require Npc2 protein to "smell" the alarm signal spread by their fellow ants. Npc2 binds the signal with the alarming name *2-ethyl-3,6-dimethylptrazine* (EDMP). The second study is about the wandering wolf spider *Pardosa pseudoannulata*, which is used in industrial agriculture to eliminate plant-eating (herbivorous) insects. The scientists show that the spider needs Npc2 to find its prey. The story goes roughly like this: some plants that are infested by pests produce *nerolidol*. The stuff is "smelled" by the spider thanks to Npc2. Thereby the spider finds the plant and its prey. Npc2 seems to bind all sorts of stuff, at least in insects. Did the protein become more specialized during evolution ending up binding solely cholesterol in mammals?