Poster P214

Analysis of *NPC1* Genotypes: Findings From the US Arimoclomol Expanded Access Program for Niemann-Pick Disease Type C

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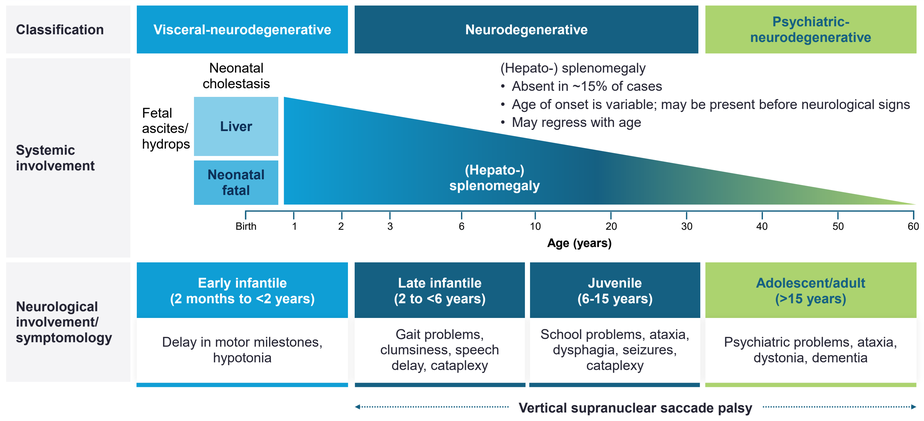
BACKGROUND

- Niemann-Pick disease Type C (NPC) is an ultrarare, progressive, neurodegenerative lysosomal disease with heterogeneous clinical presentation. NPC is caused by disease-associated variants in *NPC1* or *NPC2* genes.[1] Many patients with NPC harbor novel, private variants in *NPC1*, seen only once in that person or family. [2]
- Arimoclomol is the first US Food and Drug Administration (FDA)-approved treatment for NPC in combination with miglustat.[3]
- Here we present demographic and genotypic data from a US Expanded Access Program (EAP; NCT04316637) cohort of patients with NPC who were not eligible to enroll in clinical trials.[4]

Figure 1. Clinical Manifestations by Age of Disease Onset



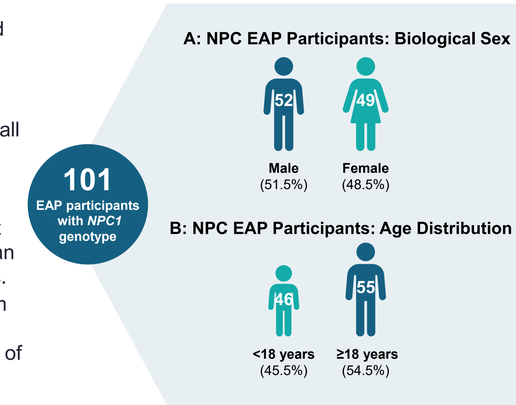
- **NPC:** Presents variably with neonatal jaundice, hepatosplenomegaly, developmental delay, eye movement issues (vertical supranuclear gaze palsy [VSGP]), clumsiness (ataxia), slurred speech (dysarthria), muscle stiffness (dystonia), cognitive decline, and in some cases psychiatric presentations. Seizures, cataplexy (sudden loss of muscle tone), and hearing loss may also be present.
- **Key diagnostic steps:** Blood tests for oxysterols (oxidized cholesterol), fibroblast cell analysis (filipin staining to assess cholesterol buildup in lysosomes), and importantly, genetic testing of *NPC1* and *NPC2* are used to confirm the biochemical genetic diagnosis of NPC.

METHODS

Figure 2. US Arimoclomol EAP (NCT04316637)

Description and Methods

- Fourteen sites in the US enrolled 110* participants into the EAP.
- All data were handled per the Health Insurance Portability and Accountability Act (HIPAA), with all documentation and samples anonymized to ensure confidentiality. Written informed consent was obtained from adult participants; parent/legal guardian consent was obtained for minors.
- Genotype analyses sourced from historical patient records were available for 101 participants, all of whom had ≥1 variant in *NPC1*.

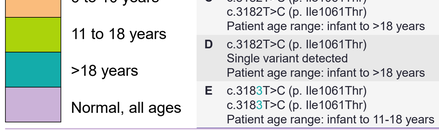


*109 were treated and consented to real-world data (RWD) collection; updated from the abstract.

RESULTS

Figure 3. Wide Variety of *NPC1* Genotypes and Variants Observed in Participants of the US Arimoclomol EAP

A. Overview of *NPC1* Genotypes and Variants

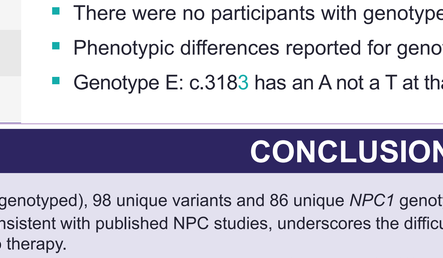


Eleven novel *NPC1* variants observed not previously reported in ClinVar

Two most common *NPC1* variants: **c.3182T>C, p.Ile1061Thr** (n=28, 28.6%) and **c.3019C>G, p.Pro1007Ala** (n=16, 16.3%)

Two most common genotypes observed: **c.3019C>G, p.Pro1007Ala, homozygous**; **c.3182T>C, p.Ile1061Thr, homozygous**

B. *NPC1* Genotypes by Functional Consequence*



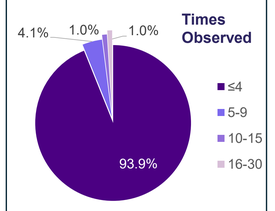
US EAP genotypes most commonly reported a missense variant for each *NPC1* allele (2 missense) or ≥1 functional null

*Updated from the abstract.

Figure 4. US EAP Unique *NPC1* Variants (n=189): Recurrences by Times Observed, Type, and Consequence

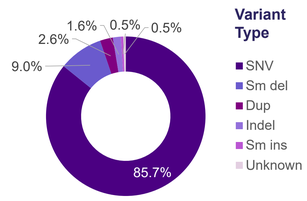
***NPC1* Unique Variant Recurrences by*:**

A. Times Observed



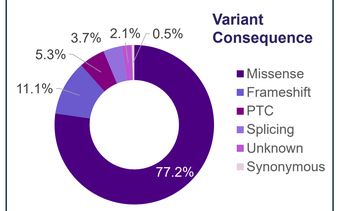
- >90% of variants observed ≤4 times

B. Variant Type



- SNV was the most common variant type

C. Variant Consequence



- Missense was the most common variant consequence

*Updated from the abstract.
Dup, duplicate; indel, insertion deletion; PTC, premature termination codon; sm del, small deletion; sm ins, small insertion; SNV, single-nucleotide variant.

Table 1. US Arimoclomol EAP *NPC1* Variants Observed (n=98)

	NPC1 Variant	Protein Change		*NPC1* Variant	Protein Change
1	c.180G>T	p.Gln60His	33	c.1843C>T	p.Arg615Cys
2	c.201_203del	p.Phe68del	34	c.1901A>T	p.Tyr634Phe
3*	c.238_243delCTTCAG	p.Leu80_Gln81del	35	c.1947+5G>C	p.?
4	c.302T>G	p.Phe101Cys	36	c.1990G>A	p.Val664Met
5	c.337T>C	p.Cys113Arg	37	c.2050C>T	p.Leu684Phe
6	c.423_424dup	p.Lys142Argfs	38	c.2071C>G	p.Pro691Ala
7	c.451_452del	p.Ser151fs	39	c.2072C>A	p.Pro691Gln
8	c.466A>G	p.Met156Val	40	c.2072C>T	p.Pro691Leu
9	c.530G>A	p.Cys177Tyr	41	c.2196dupT	p.Pro733Serfs
10	c.688_693del	p.Ser230_Val231del	42	c.2201G>T	p.Ser734Ile
11	c.743G>T	p.Gly248Val	43	c.2228C>T	p.Thr743Ile
12	c.761C>A	p.Pro254Gln	44	c.2365C>G	p.Arg789Gly
13	c.813_815delCAT	p.Ile271del	45	c.2365C>T	p.Arg789Cys
14	c.1201C>A	p.Pro401Thr	46	c.2524T>C	p.Phe842Leu
15	c.1210C>T	p.Arg404Trp	47	c.2621A>T	p.Asp874Val
16	c.1211G>A	p.Arg404Gln	48	c.2683G>T	p.Glu895Ter
17	c.1219C>T	p.Gly407Ter	49	c.2761C>T	p.Gln921Ter
18*	c.1226T>C	p.Ile409Thr	50	c.2764C>T	p.Gln922Ter
19	c.1301C>T	p.Pro434Leu	51	c.2780C>G	p.Ala927Gly
20	c.1312C>T	p.Gln438Ter	52*	c.2792_2793del	p.Asn931fs
21	c.1412C>T	p.Pro471Leu	53	c.2798C>T	p.Thr933Ile
22	c.1421C>T	p.Pro474Leu	54	c.2800C>T	p.Arg934Ter
23	c.1436G>A	p.Cys479Tyr	55	c.2819C>T	p.Ser940Leu
24	c.1550T>A	p.Val517Glu	56	c.2848G>A	p.Val950Met
25	c.1552C>T	p.Arg518Trp	57	c.2861C>T	p.Ser954Leu
26	c.1553G>A	p.Arg518Gln	58	c.2872C>T	p.Arg958Ter
27*	c.1554-1009G>A	p.?	59	c.2903A>G	p.Asn968Ser
28	c.1554-13A>G	p.?	60*	c.2912-27A>T	p.?
29*	c.1586T>A	p.Leu529His	61	c.2932C>T	p.Arg978Cys
30	c.1627C>T (written c.1621C>T)	p.Pro543Ser	62	c.2942C>T	p.Pro981Leu
31	c.1747T>G	p.Trp583Gly	63	c.2956G>A	p.Gly986Ser
32	c.1819C>T	p.Arg607Ter			

	NPC1 Variant	Protein Change		*NPC1* Variant	Protein Change
64#	c.2958G>A should be c.2958C>A but that is a silent change	This could be c.2957G>A p.Gly986Asp or c.2956G>A p.Gly986Ser	89	c.3557G>A	p.Arg1186His
65	c.2972_2973del	p.Gln991fs	90	c.3570_3573dup	p.Ala1192fs
66	c.2974G>C or c.2974G>A	p.Gly992Arg	91	c.3591+1G>A	p.?
67	c.2974G>T	p.Gly992Trp	92	c.3591+2dup	p.?
68*	c.3001A>C	p.Met1001Leu	93	c.3611_3614del	p.Ile1204fs
69	c.3011 C>T	p.Ser1004Leu	94	c.3662T>C	p.Phe1221Ser
70	c.3019C>G	p.Pro1007Ala	95	c.3742_3745del	p.Leu1248fs
71	c.3044G>T	p.Gly1015Val	96*	c.3754+3A>C	p.?
72	c.3100G>C	p.Glyc1034Arg	97*	c.3812_3813del	p.Glu1271fs
73	c.3107C>T	p.Thr1036Met	98	Splice site variant	p.?
74	c.3134T>C	p.Leu1045Pro			
75	c.3135dupG	p.Gln1046fs			
76	c.3182T>C	p.Ile1061Thr			
77	c.3183T>C (3183 has an A not T and a change from A to C would be silent.	So should be either c.3182T>C (p.Ile1061Thr) or 3183A>G which is p.Ile1061Met			
78*	c.3250T>C	p.Phe1084Leu			
79	c.3259T>C	p.Phe1087Leu			
80	c.3265G>A	p.Glu1089Lys			
81#	c.3282T>C This likely should be c.3182T>C	p.Ile1061Thr (if c.3182T>C)			
82	c.3294dup	p.Ile1099fs			
83*	c.3410_3411insA	p.Val1137fs			
84	c.3426G>A	p.Met1142Ile			
85	c.3451G>A	p.Ala1151Thr			
86	c.3467A>G	p.Asn1156Ser			
87	c.3493G>A	p.Val1165Met			
88	c.3500T>G	p.Phe1167Cys			

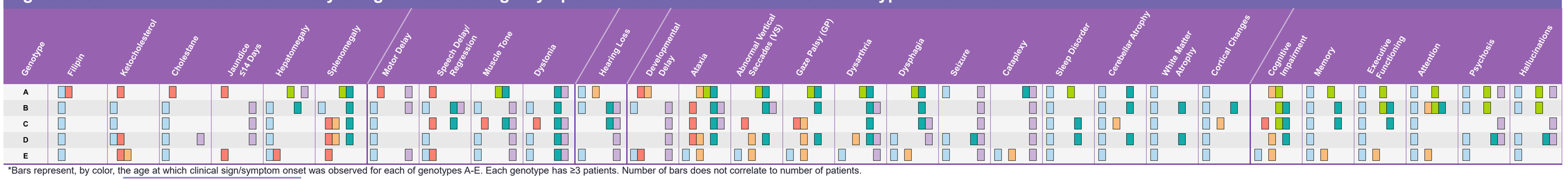
Variant observed # of times: Red ≥20×; Purple =15-19×; Teal font: Variant reporting discrepancy or variant imputed from single entry; ***Novel variant not found in ClinVar at data cut.**

Table 2. US Arimoclomol EAP Novel Variants

NPC1 Variant	Protein Change
c.238_243delCTTCAG	p.Leu80_Gln81del
c.1226T>C	p.Ile409Thr
c.1554-1009G>A	p.?
c.1586 T>A	p.Leu529His
c.2792_2793del	p.Asn931fs
c.2912-27A>T	p.?
c.3001A>C	p.Met1001Leu
c.3250T>C	p.Phe1084Leu
c.3410_3411insA	p.Val1137fs
c.3754+3A>C	p.?
c.3812_3813del	p.Glu1271fs

Novel variants (n=11*) not found in ClinVar at time of data cut. Two variants# originally classified as novel are likely data entry errors as the nucleotides reported are not correct for those positions.

Figure 5. US Arimoclomol EAP Summary of Age of Clinical Sign/Symptom Onset for 5 Common *NPC1* Genotypes Observed*



*Bars represent, by color, the age at which clinical sign/symptom onset was observed for each of genotypes A-E. Each genotype has ≥3 patients. Number of bars does not correlate to number of patients.

LEGEND

- No data
- ≤5 years
- 6 to 10 years
- 11 to 18 years
- >18 years
- Normal, all ages

5 Common Genotypes

A	c.3019C>G, p.Pro1007Ala c.3182T>C, (p.Ile1061Thr) Patient age range: infant to >18 years
B	c.3019C>G, p.Pro1007Ala c.3019C>G, p.Pro1007Ala Patient age range: infant to >18 years
C	c.3182T>C (p. Ile1061Thr) c.3182T>C (p. Ile1061Thr) Patient age range: infant to >18 years
D	c.3182T>C (p. Ile1061Thr) Single variant detected Patient age range: infant to >18 years
E	c.3183T>C (p. Ile1061Thr) c.3183T>C (p. Ile1061Thr) Patient age range: infant to 11-18 years

- Clinical signs/symptoms/biochemical data were in general provided as medical history prior to treatment with arimoclomol.
- Splenomegaly and ataxia were the 2 most common clinical signs reported in all age groups.
- There were no participants with genotype B (homozygous c.3019C>G, p.Pro1007Ala) with reported jaundice and few with reported splenomegaly; participants of this genotype reported later-onset neurological signs.
- Phenotypic differences reported for genotypes highlight that phenotypic expression is likely highly variable for *NPC1* genotypes; siblings with the same genotype had some variability in phenotype (data on file).
- Genotype E: c.3183 has an A not a T at that position; a change from A to C would be silent. Genotype E may in fact be c.3182T>C (p.Ile1061Thr), the same as genotype E.

CONCLUSIONS

- In the US arimoclomol EAP NPC patient cohort (n=101 genotyped), 98 unique variants and 86 unique *NPC1* genotypes were observed; 11 novel *NPC1* variants not reported previously in ClinVar were identified.
- The diversity of *NPC1* gene variants and genotypes, consistent with published NPC studies, underscores the difficulty of establishing clear genotype-phenotype correlations and may limit the utility of genotype-based approaches for predicting the clinical response to therapy.
- Patients in the US EAP had access to and most received arimoclomol treatment irrespective of genotype (99%).
- These findings highlight the importance of reporting genotype-phenotype data to support future newborn screening and newborn sequencing initiatives.

REFERENCES

1. Geberhiwot T, et al. *Orphanet J Rare Dis*. 2018;13(1):50. 2. Vanier MT. *Orphanet J Rare Dis*. 2010;5:16. 3. Miplyffa. Prescribing information. Zevra Therapeutics, Inc; 2025. 4. ClinicalTrials.gov identifier: NCT04316637. Updated August 16, 2024. Accessed February 25, 2026. https://clinicaltrials.gov/study/NCT04316637.

CONFLICT OF INTEREST STATEMENT

HS, RO, LH, and CD are employees at Zevra Therapeutics. NM was a contractor at Zevra Therapeutics at the time of the project.

ACKNOWLEDGMENTS

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