Strategy for Diagnosis of Neuronal Ceroid Lipofuscinoses

Petra Oliva[1], Thomas P. Mechtler[1], Berthold Streubel[2], David C. Kasper[1]

[1]ARCHIMEDlife GmbH, Vienna, Austria, [2]Medical University of Vienna, Department of Pathology, Vienna, Austria

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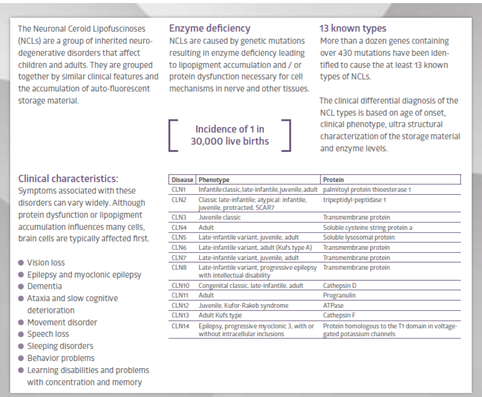
Introduction

The Neuronal Ceroid Lipofuscinoses (NCLs) are a group of inherited neurodegenerative disorders that affect children and adults. They are grouped together by similar clinical features and the accumulation of auto-fluorescent storage material. Enzyme deficiency NCLs are caused by genetic mutations resulting in enzyme deficiency leading to lipopigment accumulation and / or protein dysfunction necessary for cell mechanisms in nerve and other tissues. More than a dozen genes containing over 430 mutations have been identified to cause at least 13 known types of NCLs. The clinical differential diagnosis of the NCL types is based on age of onset, clinical phenotype, ultra-structural characterization of the storage material and enzyme levels. Symptoms associated with these disorders can vary widely. Although protein dysfunction or lipopigment accumulation influences many cells, brain cells are typically affected first. Clinical presentations include vision loss, epilepsy and myoclonic epilepsy, dementia, speech loss, movement disorder, behavior problems and learning disabilities and problems.



The Neuronal Ceroid Lipofuscinoses (NCLs) are a group of inherited neuro-degenerative disorders that affect children and adults. They are grouped together by similar clinical features and the accumulation of auto-fluorescent storage material.

Enzyme deficiency
NCLs are caused by genetic mutations resulting in enzyme deficiency leading to lipopigment accumulation and / or protein dysfunction necessary for cell mechanisms in nerve and other tissues.

Incidence of 1 in 30,000 live births

13 known types
More than a dozen genes containing over 430 mutations have been identified to cause the at least 13 known types of NCLs.

The clinical differential diagnosis of the NCL types is based on age of onset, clinical phenotype, ultra structural characterization of the storage material and enzyme levels.

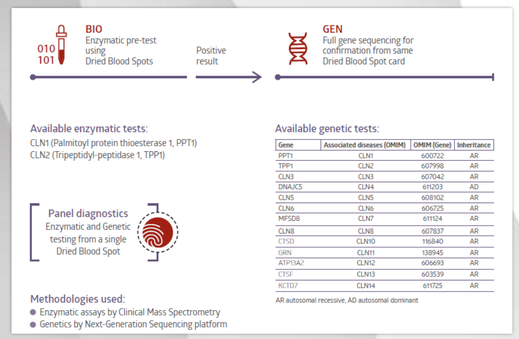
Clinical characteristics:
Symptoms associated with these disorders can vary widely. Although protein dysfunction or lipopigment accumulation influences many cells, brain cells are typically affected first.

- Vision loss
- Epilepsy and myoclonic epilepsy
- Dementia
- Ataxia and slow cognitive deterioration
- Movement disorder
- Speech loss
- Sleeping disorders
- Behavior problems
- Learning disabilities and problems with concentration and memory

Disease	Phenotype	Protein
CLN1	Infantile-classic, late-infantile, juvenile, adult	palmitoyl protein thioesterase 1
CLN2	Classic late-infantile, atypical- infantile, juvenile, protracted, SCAR7	tripeptidyl-peptidase 1
CLN3	Juvenile classic	Transmembrane protein
CLN4	Adult	Soluble cysteine string protein a
CLN5	Late-infantile variant, juvenile, adult	Soluble lysosomal protein
CLN6	Late-infantile variant, adult (Kufs type A)	Transmembrane protein
CLN7	Late-infantile variant, juvenile, adult	Transmembrane protein
CLN8	Late-infantile variant, progressive epilepsy with intellectual disability	Transmembrane protein
CLN10	Congenital classic, late-infantile, adult	Cathepsin D
CLN11	Adult	Progranulin
CLN12	Juvenile, Kufor-Rakeb syndrome	ATPase
CLN13	Adult Kufs type	Cathepsin F
CLN14	Epilepsy, progressive myoclonic 3, with or without intracellular inclusions	Protein homologous to the T1 domain in voltage-gated potassium channels

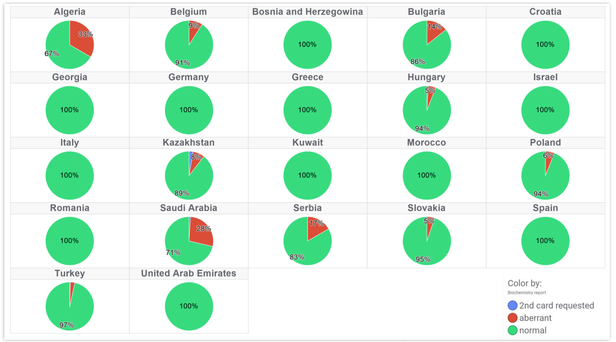
Study Cohort

Our medical laboratory has developed, validated and accredited a novel diagnostic panel for differential diagnosis of NCLs utilizing a single Dried Blood Spot (DBS). Our assay includes testing for NCL1 and NCL2.
Here we are presenting data from a high-risk population screening of over **1,185 cases suspicious of NCL1 and NCL2** by applying our developed diagnostic work-flow, including an MS/MS-based enzyme assay followed by genetic confirmatory testing using Next Generation Sequencing (NGS). We measured enzyme activity for palmitoyl protein thioesterase 1 (PPT1) and tripeptidyl-peptidase 1 (TPP1), followed by confirmatory genetic testing for over 60 cases.



Gene	Associated diseases (OMIM)	OMIM (Gene)	Inheritance
PPT1	CLN1	600722	AR
TPP1	CLN2	607998	AR
CLN3	CLN3	607042	AR
DNAJC5	CLN4	611203	AD
CLN5	CLN5	608102	AR
CLN6	CLN6	606725	AR
MFSD8	CLN7	611124	AR
CLN8	CLN8	607837	AR
CTSD	CLN10	116840	AR
GRN	CLN11	138945	AR
ATP13A2	CLN12	606693	AR
CTSF	CLN13	603539	AR
KCTD7	CLN14	611725	AR

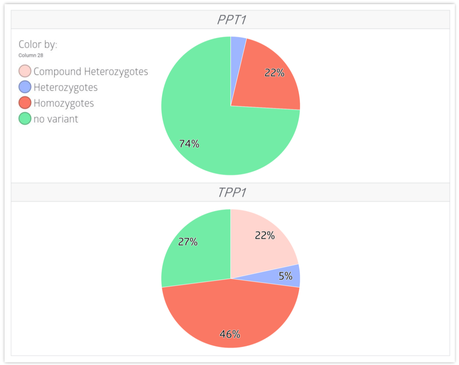
Within this high-risk population screening, samples from **22 countries** were received, notably from Middle East (e.g. Saudi Arabia, Turkey) and Europe.



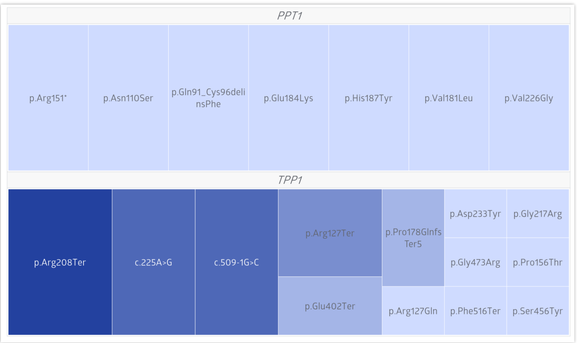
Frequency of gene variants

Gene	Nucleotide change	Amino Acid change	Frequency
PPT1	c.271_287del17insTT	p.Gln91_Cys96delinsPhe	1
	c.329A>G	p.Asn110Ser	1
	c.451C>T	p.Arg151*	1
	c.541G>T	p.Val181Leu	1
	c.550G>A	p.Glu184Lys	1
	c.559C>T	p.His187Tyr	1
	c.677T>G	p.Val226Gly	1
TPP1	c.1204G>T	p.Glu402Ter	2
	c.1367C>A	p.Ser456Tyr	1
	c.1417G>A	p.Gly473Arg	1
	c.1547_1548delTT	p.Phe516Ter	1
	c.225A>G	c.225A>G	4
	c.379C>T	p.Arg127Ter	3
	c.380G>A	p.Arg127Gln	1
	c.466C>A	p.Pro156Thr	1
	c.509-1G>C	c.509-1G>C	4
	c.528delT	p.Pro178GlnfsTer5	2
	c.622C>T	p.Arg208Ter	3
	c.649G>C	p.Gly217Arg	1
	c.697G>T	p.Asp233Tyr	1

44 cases were submitted for **PPT1** genetic confirmation, and **8 patients were diagnosed**. 48 cases were submitted for **TPP1** genetic confirmation with final **diagnosis for 32 patients**.



The list of *PPT1 and TPP1* variants identified is visualized below.
The color and the size of the box represents frequency (bigger box represent more frequent variant).



Conclusion

The presented data underlines the benefit of a fast and reliable diagnostic work-flow for NCLs in suspected individuals.

The study was completed thanks to collaboration and support from BioMarin.

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