Product Description
SALSA® MLPA® Probemix P470-A1 NCL

To be used with the MLPA General Protocol.

Version A1
For complete product history see page 8.

Catalogue numbers:
- **P470-025R:** SALSA MLPA Probemix P470 NCL, 25 reactions.
- **P470-050R:** SALSA MLPA Probemix P470 NCL, 50 reactions.
- **P470-100R:** SALSA MLPA Probemix P470 NCL, 100 reactions.

To be used in combination with a SALSA MLPA reagent kit and Coffalyser.Net data analysis software. MLPA reagent kits are either provided with FAM or Cy5.0 dye-labelled PCR primer, suitable for Applied Biosystems and Beckman/SCIEX capillary sequencers, respectively (see www.mrcholland.com).

Certificate of Analysis
Information regarding storage conditions, quality tests, and a sample electropherogram from the current sales lot is available at www.mrcholland.com.

Precautions and warnings
For professional use only. Always consult the most recent product description AND the MLPA General Protocol before use: www.mrcholland.com. It is the responsibility of the user to be aware of the latest scientific knowledge of the application before drawing any conclusions from findings generated with this product.

General information
The SALSA MLPA Probemix P470 NCL is a **research use only (RUO)** assay for the detection of deletions or duplications in the *PPT1*, *TPP1*, *CLN3*, *CLN6*, and *CLN8* genes, which are associated with Neuronal Ceroid Lipofuscinoses (NCLs).

NCLs are a heterogeneous group of inherited neurodegenerative disorders with autosomal recessive inheritance. They are characterised by the accumulation of autofluorescent hydrophobic material in the cytoplasm of neurons and other cell types. NCLs are divided in several subtypes, based on age of onset, clinical course and structure of the storage material. Some of the clinical features are visual impairment, progressive myoclonic epilepsy and cognitive decline leading to progressive neurodegeneration and premature death.

Three typical forms, the infantile (INCL), late-infantile (LINCL), and juvenile (JNCL), are among the most common childhood-onset neurodegenerative disorders. They result from mutations in the genes *PPT1* (CLN1 locus), *TPP1* (CLN2 locus), and *CLN3*, respectively. The most common known deletion is a 1.02-kb deletion in *CLN3*, causing JNCL (also known as Batten disease). The International Batten Disease Consortium (1995) demonstrated that 73% of Batten disease cases are caused by this 1.02-kb deletion covering exons 7 and 8 of *CLN3*. In Finland, 90% of patients with Batten disease carry the 1.02-kb deletion (Järvelä et al., 1996). Other *CLN* genes, like *CLN6* and *CLN8*, have also been identified to cause a (more rare) form of NCL.

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1428/.

This SALSA MLPA probemix is not CE/FDA registered for use in diagnostic procedures. Purchase of this product includes a limited license for research purposes.

Gene structure and transcript variants:
Entrez Gene shows transcript variants of each gene: http://www.ncbi.nlm.nih.gov/sites/entrez?db=gene
For NM_ mRNA reference sequences: http://www.ncbi.nlm.nih.gov/sites/entrez?db=nucleotide
Locus Reference Genomic (LRG) database: http://www.lrg-sequence.org/

Exon numbering
The *PPT1*, *TPP1*, *CLN3*, *CLN6*, and *CLN8* exon numbering used in this P470-A1 NCL product description is the exon numbering from the LRG_690, LRG_830, LRG_689, LRG_832, and LRG_691 sequences, respectively. The exon numbering of the NM_ sequence that was used for determining a probe's ligation site does not always correspond to the exon numbering obtained from the LRG sequences. As changes to the databases can occur after release of this product description, the NM_ sequence and exon numbering may not be up-to-date.

Probemix content
The SALSA MLPA Probemix P470-A1 NCL contains 50 MLPA probes with amplification products between 121 and 502 nucleotides (nt). This includes nine probes for the *PPT1* gene, 12 probes for the *TPP1* gene, 16 probes for the *CLN3* gene, and two probes for the *CLN6* and *CLN8* genes. In addition, nine reference probes are included that detect autosomal chromosomal locations. Complete probe sequences and the identity of the genes detected by the reference probes are available online (www.mrcholland.com).

This probemix contains nine quality control fragments generating amplification products between 64 and 105 nt: four DNA Quantity fragments (Q-fragments), two DNA Denaturation fragments (D-fragments), one Benchmark fragment, and one chromosome X and one chromosome Y-specific fragment (see table below). More information on how to interpret observations on these control fragments can be found in the MLPA General Protocol and online at www.mrcholland.com.

Length (nt)	Name
64-70-76-82	Q-fragments (only visible with <100 ng sample DNA)
88-96	D-fragments (low signal indicates incomplete denaturation)
92	Benchmark fragment
100	X-fragment (X chromosome specific)
105	Y-fragment (Y chromosome specific)

MLPA technique
The principles of the MLPA technique (Schouten et al. 2002) are described in the MLPA General Protocol (www.mrcholland.com).

MLPA technique validation
Internal validation of the MLPA technique using 16 DNA samples from healthy individuals is required, in particular when using MLPA for the first time, or when changing the sample handling procedure, DNA extraction method or instruments used. This validation experiment should result in a standard deviation ≤0.10 for all probes over the experiment.

Required specimens
Extracted DNA free from impurities known to affect MLPA reactions. For more information please refer to the section on DNA sample treatment found in the MLPA General Protocol.

Reference samples
A sufficient number (≥3) of reference samples should be included in each MLPA experiment for data normalisation. All samples tested, including reference DNA samples, should be derived from the same tissue type, handled using the same procedure, and prepared using the same DNA extraction method when possible. Reference samples should be derived from different unrelated individuals who are from families without a history of Neuronal Ceroid Lipofuscinoses. More information regarding the selection and use of reference samples can be found in the MLPA General Protocol (www.mrcholland.com).

Positive control DNA samples
MRC Holland cannot provide positive DNA samples. Inclusion of a positive sample in each experiment is recommended. Coriell Institute (https://catalog.coriell.org) and Leibniz Institute DSMZ (https://www.dsmz.de/) have diverse collections of biological resources which may be used as positive control DNA samples in your MLPA experiments. Sample ID numbers NA05875, NA20381, and NA03184 from

the Coriell Institute have been tested with this P470-A1 probemix at MRC Holland and can be used as positive control samples to detect heterozygous deletion of the complete *CLN3* gene, heterozygous deletion of exon 7-8 of the *CLN3* gene, and heterozygous duplication of the complete *CLN6* gene, respectively. The quality of cell lines can change; therefore samples should be validated before use.

Sample name	Source	Chromosomal position (hg18) of copy number alteration*	Altered target genes in P470-A1	Expected copy number alteration
NA05875	Coriell Institute	16p11.2	*CLN3*	Heterozygous deletion (4.8 Mb) that includes the complete *CLN3* gene.
NA20381	Coriell Institute	16p11.2	*CLN3*	Heterozygous *CLN3* exon 7-8 deletion.
NA03184	Coriell Institute	15q23	*CLN6*	Heterozygous duplication (82 Mb) that includes the complete *CLN6* gene.

* Indicated chromosomal bands (hg18) accommodate genes targeted by MLPA probes, however, the whole extent of copy number alteration (CNA) present in this cell line cannot be determined by this P470-A1 NCL probemix.

Data analysis

Coffalyser.Net software should be used for data analysis in combination with the appropriate lot-specific MLPA Coffalyser sheet. For both, the latest version should be used. Coffalyser.Net software is freely downloadable at www.mrcholland.com. Use of other non-proprietary software may lead to inconclusive or false results. For more details on MLPA quality control and data analysis, including normalisation, see the Coffalyser.Net Reference Manual.

Interpretation of results

The standard deviation of each individual probe over all the reference samples should be ≤0.10 and the final ratio (FR) of each individual reference probe in the patient samples should be between 0.80 and 1.20. When these criteria are fulfilled, the following cut-off values for the FR of the probes can be used to interpret MLPA results for autosomal chromosomes or pseudo-autosomal regions:

Copy number status	Final ratio (FR)
Normal	0.80 < FR < 1.20
Homozygous deletion	FR = 0
Heterozygous deletion	0.40 < FR < 0.65
Heterozygous duplication	1.30 < FR < 1.65
Heterozygous triplication/homozygous duplication	1.75 < FR < 2.15
Ambiguous copy number	All other values

Note: The term “dosage quotient”, used in older product description versions, has been replaced by “final ratio” to become consistent with the terminology of the Coffalyser.Net software. (Calculations, cut-offs and interpretation remain unchanged.) Please note that the Coffalyser.Net software also shows arbitrary borders as part of the statistical analysis of results obtained in an experiment. As such, arbitrary borders are different from the final ratio cut-off values shown here above.

- Arranging probes according to chromosomal location facilitates interpretation of the results and may reveal more subtle changes such as those observed in mosaic cases. Analysis of parental samples may be necessary for correct interpretation of complex results.
- False positive results: Please note that abnormalities detected by a single probe (or multiple consecutive probes) still have a considerable chance of being a false positive result. Sequence changes (e.g. SNVs, point mutations) in the target sequence detected by a probe can be one cause. Incomplete DNA denaturation (e.g. due to salt contamination) can also lead to a decreased probe signal, in particular for probes located in or near a GC-rich region or in or near the *TPP1* and *CLN8* genes. The use of an additional purification step or an alternative DNA extraction method may resolve such cases. Additionally,

contamination of DNA samples with cDNA or PCR amplicons of individual exons can lead to an increased probe signal (Varga et al. 2012). Analysis of an independently collected secondary DNA sample can exclude these kinds of contamination artefacts.

- Normal copy number variation in healthy individuals is described in the database of genomic variants: http://dgv.tcag.ca/dgv/app/home. Users should always consult the latest update of the database and scientific literature when interpreting their findings.
- Not all abnormalities detected by MLPA are pathogenic. In some genes, intragenic deletions are known that result in very mild or no disease (as described for *DMD* by Schwartz et al. 2007). For many genes, more than one transcript variant exists. Copy number changes of exons that are not present in all transcript variants may not have clinical significance. Duplications that include the first or last exon of a gene (e.g. exons 1-3) might not result in inactivation of that gene copy.
- Copy number changes detected by reference probes or flanking probes are unlikely to have any relation to the condition tested for.
- False results can be obtained if one or more peaks are off-scale. For example, a duplication of one or more exons can be obscured when peaks are off-scale, resulting in a false negative result. The risk on off-scale peaks is higher when probemixes are used that contain a relatively low number of probes. Coffalyser.Net software warns for off-scale peaks while other software does not. If one or more peaks are off-scale, rerun the PCR products using either: a lower injection voltage or a shorter injection time, or a reduced amount of sample by diluting PCR products.

Limitations of the procedure

- In most populations, the major cause of genetic defects in the *PPT1*, *TPP1*, *CLN3*, *CLN6*, and *CLN8* genes are small (point) mutations, none of which will be detected by using SALSA MLPA Probemix P470 NCL.
- MLPA cannot detect any changes that lie outside the target sequence of the probes and will not detect copy number neutral inversions or translocations. Even when MLPA did not detect any aberrations, the possibility remains that biological changes in that gene or chromosomal region *do* exist but remain undetected.
- Sequence changes (e.g. SNVs, point mutations) in the target sequence detected by a probe can cause false positive results. Mutations/SNVs (even when >20 nt from the probe ligation site) can reduce the probe signal by preventing ligation of the probe oligonucleotides or by destabilising the binding of a probe oligonucleotide to the sample DNA.

Confirmation of results

Copy number changes detected by only a single probe always require confirmation by another method. An apparent deletion detected by a single probe can be due to e.g. a mutation/polymorphism that prevents ligation or destabilises the binding of probe oligonucleotides to the DNA sample. Sequence analysis can establish whether mutations or polymorphisms are present in the probe target sequence. The finding of a heterozygous mutation or polymorphism indicates that two different alleles of the sequence are present in the sample DNA and that a false positive MLPA result was obtained.

Copy number changes detected by more than one consecutive probe should be confirmed by another independent technique such as long range PCR, qPCR, array CGH or Southern blotting, whenever possible. Deletions/duplications of more than 50 kb in length can often be confirmed by FISH.

NCL gene variant database

https://www.ucl.ac.uk/ncl-disease. We strongly encourage users to deposit positive results in the NCL Database of the University College London (UCL). Recommendations for the nomenclature to describe deletions/duplications of one or more exons can be found on http://varnomen.hgvs.org/.

Please report copy number changes detected by the reference probes, false positive results due to SNVs and unusual results (e.g., a duplication of *PPT1* exons 5 and 7 but not exon 6) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P470-A1 NCL

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]				
		Reference	*PPT1*	*TPP1*	*CLN3*	*CLN6/CLN8*
64-105	Control fragments – see table in probemix content section for more information					
121	Reference probe 19616-L27455	4p				
126	Reference probe 18709-L21698	5q				
131 +	**CLN3 probe** 20789-L29152				**Exon 7**	
136	**CLN3 probe** S1119-L28982				**Exon 4**	
144	**CLN3 probe** 20788-L28801				**Exon 12**	
148	**PPT1 probe** 20811-L29153		**Exon 9**			
154 «	**TPP1 probe** 20818-L28831			**Exon 4**		
160	Reference probe 10694-L26069	6p				
166	**PPT1 probe** 20813-L28826		**Exon 3**			
172	**CLN3 probe** 20919-L29090				**Exon 15**	
178	**CLN3 probe** 20801-L28993				**Exon 6**	
184 «	**TPP1 probe** 20827-L28994			**Exon 6**		
190	**CLN3 probe** 20797-L28995				**Exon 9**	
196	**PPT1 probe** 20806-L28819		**Exon 6**			
202 «	**TPP1 probe** 20815-L28828			**Exon 10**		
208	Reference probe 18847-L24371	3p				
214	**CLN3 probe** 20798-L28811				**Exon 3**	
220 «	**TPP1 probe** 20821-L28834			**Exon 1**		
226 «	**CLN8 probe** 20804-L28817					**Exon 2**
232	**PPT1 probe** 20812-L28825		**Exon 4**			
238 +	**CLN3 probe** 20799-L28812				**Exon 7**	
245	**PPT1 probe** 20808-L28821		**Exon 7**			
251	**PPT1 probe** 20810-L28823		**Exon 2**			
257	**PPT1 probe** 20809-L28989		**Exon 8**			
264 «	**TPP1 probe** 20825-L28838			**Exon 3**		
274	**CLN3 probe** 20787-L28800				**Exon 10**	
283	Reference probe 11140-L11824	13q				
292 +	**CLN3 probe** 20800-L28813				**Exon 8**	
301	**PPT1 probe** 20814-L28827		**Exon 1**			
310 «	**TPP1 probe** 20823-L28836			**Exon 9**		
319	**CLN6 probe** 20803-L28816					**Exon 2**
328	Reference probe 08576-L08577	17q				
337	**CLN6 probe** 20802-L28815					**Exon 4**
344	**CLN3 probe** 20786-L28799				**Exon 14**	
355	**CLN3 probe** 20790-L28803				**Exon 1a**	
364 «	**TPP1 probe** 20820-L28833			**Exon 7**		
373	**PPT1 probe** 20807-L28820		**Exon 5**			
384	**CLN3 probe** 20794-L28807				**Exon 5**	
391 «	**TPP1 probe** 20826-L28839			**Exon 12**		
400	**CLN3 probe** 20795-L28808				**Exon 2**	
409 «	**TPP1 probe** 20824-L28837			**Exon 2**		
418	Reference probe 07924-L07654	20p				
425	**CLN3 probe** 20793-L28806				**Exon 13**	
436 «	**TPP1 probe** 20816-L28829			**Exon 8**		
454 «	**TPP1 probe** 20819-L28832			**Exon 13**		
463 «	**CLN8 probe** 20805-L28818					**Exon 3**
474 «	**TPP1 probe** 20817-L28830			**Exon 11**		
483	**CLN3 probe** 20792-L28805				**Exon 11**	
492 ±	Reference probe 14882-L20266	14q				
502	Reference probe 18161-L25061	21q				

[a] See section Exon numbering on page 2 for more information.

« Probe located in or near a GC-rich region. A low signal can be caused by salt contamination in the DNA sample leading to incomplete DNA denaturation, especially of GC-rich regions.

+ This probe detects the 1.02-kb deletion in *CLN3*.

± SNP rs147586703 could influence the probe signal. In case of apparent deletions, it is recommended to sequence the region targeted by this probe.

SNVs located in the target sequence of a probe can influence probe hybridization and/or probe ligation. Single probe aberration(s) must be confirmed by another method.

Table 2. P470-A1 probes arranged according to chromosomal location

Table 2a. *PPT1*

Length (nt)	SALSA MLPA probe	*PPT1* exon[a]	Ligation site NM_000310.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*15-17 (Exon 1)*		
301	20814-L28827	Exon 1	118-119	GCCGCTGCCGTT-GGTGATCTGGCA	4.7 kb
251	20810-L28823	Exon 2	228-229	TATCTTTAGAGA-TTGGGAAGACCC	0.4 kb
166	20813-L28826	Exon 3	353-354	AATGCTATGGGA-TTCTCCCAGGGA	0.7 kb
232	20812-L28825	Exon 4	435-434, reverse	TTGATGTTGTCC-CCCAACCGAGAT	1.9 kb
373	20807-L28820	Exon 5	515-516	CGAAAAACACTG-AATGCTGGGGCG	9.0 kb
196	20806-L28819	Exon 6	635-636	GATATAAATCAG-GAGCGGGTAAGC	1.8 kb
245	20808-L28821	Exon 7	715-716	CCTCAATGATTC-CATTGTGGACCC	1.7 kb
257	20809-L28989	Exon 8	807-808	CCTCCCTGTACA-CACAGGTAACTG	2.8 kb
148	20811-L29153	Exon 9	983-984	TAACTCTTCCAA-ACCACATGGGAG	-
		stop codon	*933-935 (Exon 9)*		

Table 2b. *CLN8*

Length (nt)	SALSA MLPA probe	*CLN8* exon[a]	Ligation site NM_018941.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*221-223 (Exon 2)*		
226 «	20804-L28817	Exon 2	367-368	TCCTCTTCCCTG-AATGCCACTTAC	9.2 kb
463 «	20805-L28818	Exon 3	915-916	GCCTCATTTGAC-ACTGTTCCTTGT	-
		stop codon	*1079-1081 (Exon 3)*		

Table 2c. *TPP1*

Length (nt)	SALSA MLPA probe	*TPP1* exon[a]	Ligation site NM_000391.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*23-25 (Exon 1)*		
220 «	20821-L28834	Exon 1	6 nt before exon 1	TGTGATCCGTCA-CATGACAGCAGA	0.2 kb
409 «	20824-L28837	Exon 2	74-75	TCCTCTCTGGCA-AATGCAGTTACA	0.4 kb
264 «	20825-L28838	Exon 3	178-179	CTCACCTTTGCC-CTGAGACAGCAG	1.2 kb
154 «	20818-L28831	Exon 4	369-368, reverse	GAAAGTCCTGTG-TGATCACAGAAT	0.6 kb
	No probe	Exon 5			
184 «	20827-L28994	Exon 6	613-612, reverse	GTTACCCCCAGA-TGCAGGCCTACA	0.3 kb
364 «	20820-L28833	Exon 7	775-776	GGTGGCAACTTT-GCACATCAGGCA	0.4 kb
436 «	20816-L28829	Exon 8	1014-1015	TGATGAGGACTC-CCTCAGCAGCGC	0.4 kb
310 «	20823-L28836	Exon 9	1127-1128	GTTGGTCTGTCT-CTGGAAGACACC	0.6 kb
202 «	20815-L28828	Exon 10	1251-1252	TATCAGTGGTGG-TGGCTTCAGCAA	0.2 kb
474 «	20817-L28830	Exon 11	1372-1373	CGTGCCTACCCA-GATGTGGCTGCA	0.3 kb
391 «	20826-L28839	Exon 12	1484-1485	TCCTATCCTTGA-TCAATGAGCACA	0.3 kb
454 «	20819-L28832	Exon 13	1621-1622	GAGGTAGAGGGC-CAGGGTTTCTGC	-
		stop codon	*1712-1714 (Exon 13)*		

Table 2d. *CLN6*

Length (nt)	SALSA MLPA probe	*CLN6* exon[a]	Ligation site NM_017882.3l	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*145-147 (Exon 1)*		
319	20803-L28816	Exon 2	311-312	ACTGCAGAACTG-GGTTCTGGACTT	6.8 kb
337	20802-L28815	Exon 4	575-576	TGGCTACCAGCA-CCACCTGTCTGT	-
		stop codon	*1078-1080 (Exon 7)*		

Table 2e. *CLN3*

Length (nt)	SALSA MLPA probe	*CLN3* exon[a]	Ligation site NM_001042432.2	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*132-134 (Exon 2)*		
355	20790-L28803	Exon 1a	160 nt before exon 1	CGGCTCTGCTTG-CTGCTCCCACCC	0.8 kb
400	20795-L28808	Exon 2	14 nt after exon 2	GAGTGGCCTGAG-ACTTCAGCGAGT	2.2 kb
214	20798-L28811	Exon 3	328-327, reverse	CCGATGTCCTCT-TGTGGCTAAGGA	0.7 kb
136	S1119-L28982	Exon 4	355-356	CTCCCATTAGGT-GGACCCAGGCCC	0.9 kb
384	20794-L28807	Exon 5	459-460	TCCCCACACTCG-TCATCAAATTGT	0.2 kb
178	20801-L28993	Exon 6	576-577	CTCATTCTGTGG-GGACCAGCCTGT	0.8 kb
131 +	20789-L29152	Exon 7	69 nt before exon 7	AGGCCATGGCCA-GACACATTAGAG	0.1 kb
238 +	20799-L28812	Exon 7	623-624	TCATCAGGCCTT-GGGGAGGTCACC	0.1 kb
292 +	20800-L28813	Exon 8	8 nt before exon 8	TCCTGTGTTCTC-CTTCCCAGGGCC	2.5 kb
190	20797-L28995	Exon 9	890-891	CGGCAGCCCCTC-ATAAGAACCGAG	1.4 kb
274	20787-L28800	Exon 10	6 nt after exon 10, reverse	CCCAGCCATCAT-CCGAACCTTGAA	0.1 kb
483	20792-L28805	Exon 11	1025-1026	GAGTATTTCATT-AACCAGGGACTT	0.1 kb
144	20788-L28801	Exon 12	1040-1041	TTGTTGCAGTTT-GAACTCCTCTTT	0.2 kb
425	20793-L28806	Exon 13	1142-1141, reverse	CGACAGCAGCGG-AGAGAAGAGCGG	4.4 kb
344	20786-L28799	Exon 14	1275-1276	TTCTGTATGAGG-GGCTCCTGGGAG	0.3 kb
172	20919-L29090	Exon 15	1438-1439	CTTCCTCTGCCA-GCTCTCCTGATA	-
		stop codon	*1446-1448 (Exon 15)*		

[a] See section Exon numbering on page 2 for more information.

[b] Only partial probe sequences are shown. Complete probe sequences are available at www.mrcholland.com. Please notify us of any mistakes: info@mrcholland.com.

« Probe located in or near a GC-rich region. A low signal can be caused by salt contamination in the DNA sample leading to incomplete DNA denaturation, especially of GC-rich regions.

+ This probe detects the 1.02-kb deletion in *CLN3*.

SNVs located in the target sequence of a probe can influence probe hybridization and/or probe ligation. Single probe aberration(s) must be confirmed by another method.

References

- International Batten Disease Consortium et al. (1995). Isolation of a novel gene underlying Batten disease, CLN3. *Cell*, 82(6), 949-957.
- Järvelä I et al. (1996). Rapid diagnostic test for the major mutation underlying Batten disease. *J Med Genet*, 33(12), 1041-1042.
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- Schwartz M et al. (2007). Deletion of exon 16 of the dystrophin gene is not associated with disease. *Hum Mutat.* 28:205.
- Varga RE et al. (2012). MLPA-based evidence for sequence gain: pitfalls in confirmation and necessity for exclusion of false positives. *Anal Biochem.* 421:799-801.

Selected publications using SALSA MLPA Probemix P470 NCL

- Sheth J et al. (2018). Batten disease: biochemical and molecular characterization revealing novel PPT1 and TPP1 gene mutations in Indian patients. *BMC neurol*, 18(1), 203.

P470 product history	
Version	*Modification*
A1	First release.

Implemented changes in the product description
Version A1-02 – 15 November 2022 (04P) - Product description rewritten and adapted to a new template. - Ligation sites of the probes targeting the PPT1, TPP1, CLN3, CLN6, and CLN8 genes updated according to new version of the NM_ reference sequence. - Warning added to Table 1 for the 492 nt reference probe. Version A1-01 — 25 July 2019 (02P) - Product description rewritten and adapted to a new template. Version 02 – 14 March 2018 (55) - Information added on positive control DNA samples on page 2. - Minor textual changes Version 01 – 06 April 2016 (55) - Not applicable, new document.

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