Product Description

SALSA® MLPA® Probemix P411-B3 Porphyria mix 1

To be used with the MLPA General Protocol.

Version B3
As compared to version B2, three reference probes have been replaced. For complete product history see page 8.

Catalogue numbers:

- **P411-025R:** SALSA MLPA Probemix P411 Porphyria mix 1, 25 reactions.
- **P411-050R:** SALSA MLPA Probemix P411 Porphyria mix 1, 50 reactions.
- **P411-100R:** SALSA MLPA Probemix P411 Porphyria mix 1, 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 P411 Porphyria mix 1 is a **research use only (RUO)** assay for the detection of deletions or duplications in the *ALAD*, *HMBS* and *PPOX* genes, which are associated with acute hepatic porphyria. The *CPOX* gene, which is also associated with acute hepatic porphyria, is included in the P412 Porphyria mix 2.

Porphyrias are a group of disorders characterised by accumulation of porphyrins and porphyrin precursors owing to enzymatic deficiencies of the haem biosynthetic pathway. They can be divided into acute hepatic porphyrias and erythropoietic porphyrias based on their clinical manifestations. Acute hepatic porphyrias are characterised by abdominal pain, neuropsychiatric symptoms and neuropathy. Erythropoietic porphyrias do not cause neurologic symptoms, but are associated with photosensitive dermatologic eruptions and may be associated with additional hepatic injury and/or haemolysis (Simon & Herkes, 2011).

Acute hepatic porphyrias consist of ALA dehydratase deficiency porphyria (ADP), acute intermittent porphyria (AIP), hereditary coproporphyria (HCP) and variegate porphyria (VP). Erythropoietic porphyrias comprise congenital erythropoietic porphyria (CEP), porphyria cutanea tarda (PCT) and the related hepatoerythropoietic porphyria and erythropoietic protoporphyria (EPP); see Table 1.

Table 1. Genetic classification and clinical manifestations of the porphyrias

Porphyria	Enzyme	Inheritance	Classification	Clinical features
ADP	ALAD[$]	AR	Acute hepatic	Acute neurovisceral
AIP	HMBS[$]	AD	Acute hepatic	Acute neurovisceral
CEP	UROS	AR	Erythropoietic	Photosensitivity; Liver disease; Haemolytic anaemia
PCT	UROD	Sporadic 80%, AD 20%	Erythropoietic	Photosensitivity; Liver disease
HCP	CPOX	AD	Acute hepatic	Acute neurovisceral (100%); Photosensitivity (20%)
VP	PPOX[$]	AD	Acute hepatic	Acute neurovisceral (50%); Photosensitivity (80%)
EPP	FECH	AD	Erythropoietic	Photosensitivity; Liver disease

AD = autosomal dominant, AR = autosomal recessive, ADP = ALA dehydratase deficiency porphyria, AIP = acute intermittent porphyria, ALAD = ALA dehydratase, CEP = congenital erythropoietic porphyria, CPOX = coproporphyrinogen oxidase, EPP = erythropoietic

protoporphyria, FECH = ferrochetalase, HCP = hereditary coproporphyria, HMBS = hydroxymethylbillane synthase, PCT = porphyria cutanea tarda, PPOX = protoporphyrinogen oxidase, UROD = uroporphyrinogen dehydratase, UROS = uroporphyrinogen synthase, VP = variegate porphyria.

$ *ALAD*, *HMBS* and *PPOX* genes are included in SALSA MLPA probemix P411.

The *ALAD* gene (12 exons), spans ~15 kb of genomic DNA and is located on 9q32, 115 Mb from the p-telomere.
The *HMBS* gene (15 exons), spans ~8.7 kb of genomic DNA and is located on 11q23.3, 118 Mb from the p-telomere.
The *PPOX* gene, (13 exons) spans ~4.8 kb of genomic DNA and is located on 1q23.3, 159 Mb from the p-telomere.

More information is available at:
- https://omim.org/entry/125270?search=alad&highlight=alad
- https://omim.org/entry/609806?search=hmbs&highlight=hmbs
- https://omim.org/entry/600923?search=ppox&highlight=ppox-
- https://www.ncbi.nlm.nih.gov/books/NBK121283/
- https://www.ncbi.nlm.nih.gov/books/NBK1193/

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 *PPOX*, *ALAD* and *HMBS* exon numbering used in this P411-B3 Porphyria mix 1 product description is the exon numbering from the LRG_1078, NG_008716.1 and LRG_1076 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 or NG 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 P411-B3 Porphyria mix 1 contains 46 MLPA probes with amplification products between 131 and 495 nucleotides (nt). This includes one probe for each exon of the *ALAD* gene with the exception of exon 7 and 9, one probe for each exon of the *HMBS* gene with the exception of exon 2 (exon 2 is only present in transcript variant 2; NM_001024382), and one probe for each exon of the *PPOX* gene. 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-fragments (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 porphyria. 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 NA00803 and NA15099 from the Coriell Institute have been tested with this P411-B3 probemix at MRC Holland and can be used as positive control samples to detect copy number alterations in the *PPOX* gene and *HMBS* gene, respectively. The quality of cell lines can change; therefore samples should be validated before use.

Sample name	Source	Chromosomal position of copy number alteration*	Altered target genes in P411-B3	Expected copy number alteration
NA00803	Coriell Institute	1q22-q24	*PPOX*	Heterozygous deletion
NA15099	Coriell Institute	11q14.1-q25	*HMBS*	Heterozygous duplication

* Indicated chromosomal bands 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 P411-B3 Porphyria mix 1 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. 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 *ALAD*, *HMBS* and *PPOX* gene are small (point) mutations, none of which will be detected by using SALSA MLPA Probemix P411 Porphyria mix 1.
- 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.

***ALAD*, *HMBS* and *PPOX* genes mutation database**

https://databases.lovd.nl/shared/genes/. We strongly encourage users to deposit positive results in the Leiden Open Variation Database. 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 *PPOX* exons 5 and 7 but not exon 6) to MRC Holland: info@mrcholland.com.

Table 2. SALSA MLPA Probemix P411-B3 Porphyria mix 1

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]			
		Reference	*ALAD*	*HMBS*	PPOX
64-105	Control fragments – see table in probemix content section for more information				
131 *	Reference probe 22089-L15549	17q			
136 Δ	**PPOX** probe 15979-L18134				**Exon 7**
142	**ALAD** probe 14742-L18790		**Exon 12**		
148	**HMBS** probe 15980-L18135			**Exon 11**	
155	**PPOX** probe 14744-L18791				**Exon 8**
166	Reference probe 22133-L31161	16p			
172	**HMBS** probe 14747-L16444			**Exon 7**	
178	Reference probe 13765-L18422	13q			
184	**PPOX** probe 15981-L18136				**Exon 11**
190	**HMBS** probe 14749-L16446			**Exon 15**	
197	**ALAD** probe 17467-L21243		**Exon 8**		
202	**ALAD** probe 14751-L16448		**Exon 1**		
209	**HMBS** probe 14752-L16449			**Exon 12**	
217	Reference probe 14640-L29118	19q			
225	**HMBS** probe 14754-L16451			**Exon 9**	
232	**PPOX** probe 14755-L16452				**Exon 2**
238	**HMBS** probe 14756-L18788			**Exon 6**	
250	**ALAD** probe 20581-L16454		**Exon 2**		
256	**ALAD** probe 14758-L16455		**Exon 10**		
265	**HMBS** probe 14759-L16456			**Exon 10**	
274	Reference probe 07600-L07285	15q			
283	**ALAD** probe 14760-L16457		**Exon 3**		
292	**PPOX** probe 14761-L16458				**Exon 1**
301	**PPOX** probe 14762-L16459				**Exon 13**
310	**PPOX** probe 14763-L16460				**Exon 5**
319	**HMBS** probe 15982-L18137			**Exon 4**	
328	**ALAD** probe 14765-L17163		**Exon 4**		
335	**HMBS** probe 14766-L18044			**Exon 1**	
346 *	Reference probe 16277-L18569	20q			
355	Reference probe 20582-L21773	10q			
361	**HMBS** probe 14767-L29120			**Exon 14**	
366	**PPOX** probe 14768-L29121				**Exon 3**
372	**PPOX** probe 15588-L18789				**Exon 12**
382	**ALAD** probe 15589-L17443		**Exon 5**		
391 Δ	**ALAD** probe 15336-L16476		**Exon 11**		
403	Reference probe 16447-L18900	18q			
409	**PPOX** probe 14772-L16469				**Exon 10**
418	**PPOX** probe 14773-L16470				**Exon 4**
427	**HMBS** probe 14774-L16471			**Exon 8**	
436	**PPOX** probe 14775-L16472				**Exon 9**
445	**ALAD** probe 14776-L17165		**Exon 6**		
454	**HMBS** probe 14777-L16474			**Exon 3**	
463	**PPOX** probe 14778-L16475				**Exon 6**
474	**HMBS** probe 17468-L21244			**Exon 13**	
483	**HMBS** probe 14780-L16477			**Exon 5**	
495 *	Reference probe 22488-L24472	12q			

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

* New in version B3.

Δ More variable. This probe may be sensitive to certain experimental variations. Aberrant results should be treated with caution.

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 3. P411-B3 probes arranged according to chromosomal location

Table 3a. *PPOX* gene

Length (nt)	SALSA MLPA probe	*PPOX* exon[a]	Ligation site NM_001122764.3	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*256-258 (exon 2)*		
292	14761-L16458	Exon 1	57-58	GGATTTGAAGCA-CTTGTTGGCCTA	0.5 kb
232	14755-L16452	Exon 2	25 nt after exon 2	TTGTGCCAGAGG-GAGCTTCATTTA	0.2 kb
366	14768-L29121	Exon 3	353-354	GGTGGTCCTAGT-GGAGAGCAGTGA	0.3 kb
418	14773-L16470	Exon 4	514-515	GAAGTGCTGCCT-GTCCGGGGAGAC	0.7 kb
310	14763-L16460	Exon 5	697-698	AGACTGTGCACA-GTTTTGCCCAGC	0.3 kb
463	14778-L16475	Exon 6	40 nt before exon 6	TCAGTCAGTGTA-GATTATTTTTTC	0.6 kb
136 Δ	15979-L18134	Exon 7	894-895	CAGCCAGACTCA-GCACTCATTCGC	0.7 kb
155	14744-L18791	Exon 8	1110-1111	GTTATTAGTGCC-ATTCCAGCTTCA	0.3 kb
436	14775-L16472	Exon 9	1193-1194	CACTGCAGTGTC-TGTAGCTGTGGT	0.5 kb
409	14772-L16469	Exon 10	1266-1267	TTGGTGCCATCT-TCAGAAGATCCA	0.3 kb
184	15981-L18136	Exon 11	1480-1481	AGATGCCGAGCC-ACTGCTTGGTCC	0.1 kb
372	15588-L18789	Exon 12	37 nt before exon 12	TAGGACATCAAT-AATAAACTTTTC	0.2 kb
301	14762-L16459	Exon 13	1574-1575	CCTGACTGCTCA-CAGGTTGCCCCT	
		stop codon	*1687-1689 (exon 13)*		

Δ More variable. This probe may be sensitive to certain experimental variations. Aberrant results should be treated with caution.

Table 3b. *ALAD* gene

Length (nt)	SALSA MLPA probe	*ALAD* exon[a]	Ligation site NM_000031.6	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*149-151 (exon 2)*		
202	14751-L16448	Exon 1	46-47	GGTGACAGGAGC-AGCGGCCGGGAG	7.7 kb
250	20581-L16454	Exon 2	182-183	ACAGCGGCTACT-TCCACCCACTAC	1.4 kb
283	14760-L16457	Exon 3	290-291	TACAGCCTATCA-CCAGCCTCCCAG	0.6 kb
328	14765-L17163	Exon 4	372-373	GGGCCTACGCTG-TGTCTTGATCTT	0.7 kb
382	15589-L17443	Exon 5	455-456	CCCCAGCTATTG-AGGCAATCCATC	0.3 kb
445	14776-L17165	Exon 6	37 nt after exon 6	GCACCTCTGGGT-CAGGAGGTGGCA	0.7 kb
197	17467-L21243	Exon 8	723-724	CCCATAGGTATC-GGTGATGAGCTA	0.4 kb
256	14758-L16455	Exon 10	948-949	GGTAAAGGACAA-GGTGAGCACAGG	0.4 kb
391 Δ	15336-L16476	Exon 11	1021-1022	GGAGCCCAGGCC-GGGGCATTTGAT	0.9 kb
142	14742-L18790	Exon 12	1313-1314	TGCTAACTCTTG-TAACTCGCAGCT	
		stop codon	*1139-1141 (exon 12)*		

Δ More variable. This probe may be sensitive to certain experimental variations. Aberrant results should be treated with caution.

Table 3c. *HMBS* gene

Length (nt)	SALSA MLPA probe	*HMBS* exon[a]	Ligation site NM_000190.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*154-156 (exon 1)*		
335	14766-L18044	Exon 1	163-164	CCATGTCTGGTA-ACGGCAATGCGG	3.2 kb
454	14777-L16474	Exon 3	225-226	ATTCGCGTGGGT-ACCCGCAAGAGC	0.4 kb
319	15982-L18137	Exon 4	269-270	GGACAGTGTGGT-GGCAACATTGAA	0.5 kb
483	14780-L16477	Exon 5	354-355	CTTGATACTGCA-CTCTCTAAGGTA	0.1 kb
238	14756-L18788	Exon 6	400-401	AGGAGCTTGAAC-ATGCCCTGGAGA	0.4 kb
172	14747-L16444	Exon 7	420-421	CATCTCTATAGA-GTGGACCTGGTT	0.3 kb
427	14774-L16471	Exon 8	542-543	CCCAAAATTTGT-TGGGAAGACCCT	0.2 kb
225	14754-L16451	Exon 9	intron 8-576	CTCTCTGGGCAG-TGTGGTGGGAAC	1.2 kb
265	14759-L16456	Exon 10	11 nt before exon 10	TGGTCCTTAGCA-ACTCTCCACAGC	0.8 kb
148	15980-L18135	Exon 11	8 nt after exon 11	CCAGGTACACTT-GACCAGGGAAGC	0.3 kb
209	14752-L16449	Exon 12	865-866	TGGTGGGTGTGC-TGCACGATCCCG	0.3 kb
474	17468-L21244	Exon 13	953-954	GCCAGTAGCCGT-GCATACAGCTAT	0.2 kb
361	14767-L29120	Exon 14	1015-1016	GTCTAGACGGCT-CAGATAGCATAC	0.2 kb
190	14749-L16446	Exon 15	1105-1106	AGTTGGTAGGCA-TCACTGCTCGTA	
		stop codon	*1237-1239 (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.

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.

Related SALSA MLPA probemixes

- P412 Porphyria mix 2: Contains probes for the *FECH, UROS*, *UROD* genes linked to Erythropoietic porphyria and the *CPOX* gene (Acute hepatic porphyria).

References

- Schouten JP et al. (2002). Relative quantification of 40 nucleic acid sequences by multiplex ligation-dependent probe amplification. *Nucleic Acids Res.* 30:e57.
- Schwartz M et al. (2007). Deletion of exon 16 of the dystrophin gene is not associated with disease. *Hum Mutat.* 28:205.
- Simon NG, Herkes GK (2011). The neurologic manifestations of the acute porphyrias. *J Clin Neurosci.* Sep;18:1147-53
- 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 P411 Porphyria mix 1

- Barbaro M et al. (2013). Partial protoporphyrinogen oxidase (PPOX) gene deletions, due to different Alu-mediated mechanisms, identified by MLPA analysis in patients with variegate porphyria. *Orphanet J Rare Dis*. 1186/1750-1172-8-13.

P411 product history	
Version	*Modification*
B3	Three reference probes have been replaced.
B2	Three reference probes have been replaced.
B1	One target probe was removed and the length of several probes have been adjusted.
A1	First release.

Implemented changes in the product description
Version B3-01 – 13 December 2022 (04P) - Product description rewritten and adapted to a new template. - Product description adapted to a new product version (version number changed, changes in Table 2 and Table 3). - Warning added to Table 2 and 3 regarding the variability of probe 15979-L18134 under certain experimental conditions. Version B2-01 – 19 May 2020 (02P) - Product description rewritten and adapted to a new template. - Product description adapted to a new product version (version number changed, changes in Table 2 and Table 3). - Ligation sites of the probes targeting the PPOX, ALAD and HMBS genes are updated according to new version of the NM_ reference sequence.

More information: www.mrcholland.com; www.mrcholland.eu	
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