

Product Description SALSA® MLPA® Probemix P242-C1 Pancreatitis

To be used with the MLPA General Protocol.

Version C1. As compared to version B3, eight *CTRC* probes and two *SPINK1* probes have been added. One *SPINK1* probe has been removed. One probe has been adjusted in length. Seven reference probes have been replaced. For complete product history see page 7.

Catalogue numbers:

- **P242-025R:** SALSA MLPA Probemix P242 Pancreatitis, 25 reactions.
- **P242-050R:** SALSA MLPA Probemix P242 Pancreatitis, 50 reactions.
- **P242-100R:** SALSA MLPA Probemix P242 Pancreatitis, 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.mlpa.com).

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

Precautions and warnings: For professional use only. Always consult the most recent product description AND the MLPA General Protocol before use: www.mlpa.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.

In several presumed wild-type samples tested with the P242 probemix, a ratio of ~0.8 was obtained for all *PRSS1* probes. We have not yet been able to establish the cause. Reference selection is crucial and extraction methods should be identical between references and samples. However, even when these criteria are fulfilled, probe ratios of ~0.8 may still occur. Please notify us if you regularly observe something similar: info@mlpa.com.

General information: The SALSA MLPA Probemix P242 Pancreatitis is a **research use only (RUO)** assay for the detection of deletions or duplications in the *PRSS1*, *SPINK1* and *CTRC* genes, which are associated with Hereditary Pancreatitis.

Hereditary Pancreatitis (HP; OMIM # 167800) is characterised by recurrent episodes of inflammation of the pancreas that progresses to chronic pancreatitis. HP has an autosomal dominant pattern of inheritance, and is defined by two or more individuals with pancreatitis in two or more generations of a family, or pancreatitis associated with a known germline pathogenic variant.

PRSS1 encodes trypsin-1 (cationic trypsinogen), a major pancreatic digestive serine peptidase enzyme, which is produced and secreted by the pancreas. *PRSS1* pathogenic variants typically result in a trypsin protein that is either prematurely activated, while it is still in the pancreas, or resistant to degradation. Duplication of *PRSS1*, leading to an increase of the protein, also causes HP. Furthermore, gene conversion between *PRSS1* and *PRSS2* has been reported (Nemeth and Sahin-Toth 2014, Rygiel et al. 2015). In 90% of the cases, hereditary pancreatitis is caused by two point mutations in the *PRSS1* gene, R122H (~65%) and N29I (25%) (Nemeth and Sahin-Toth 2014). Gene conversion between *PRSS1* and *PRSS2* exon 2 and the subsequent intron can occur, resulting in the N29I mutation together with N54S, a non-pathogenic mutation (Teich et al. 2005). In less than 6% of the cases, HP is caused by *PRSS1* (large) deletions/duplications.

SPINK1 encodes the serine protease inhibitor Kazel-type 1. Pathogenic variants in *SPINK1* can lead to autosomal recessive pancreatitis, and have been identified in approximately 20% of families with hereditary pancreatitis, without a *PRSS1* germline pathogenic variant. The risk for developing acute pancreatitis is highly increased when the N34S mutation in *SPINK1* is present (Koziel et al. 2015).

CTRC encodes chymotrypsin C (*CTRC*), a low-abundance pancreatic digestive enzyme that is synthesized with *PRSS1*. *CTRC* is important for the degradation of the prematurely activated trypsin within the pancreas. Pathogenic variants of *CTRC* have been associated with chronic pancreatitis (Masson et al. 2008).

While identification of a heterozygous *PRSS1* pathogenic variant confirms a diagnosis of hereditary pancreatitis, the presence of isolated pathogenic variants in the *SPINK1* or *CTRC* genes is insufficient to cause pancreatitis (Masson et al. 2013).

More information is available at:

<https://www.ncbi.nlm.nih.gov/books/NBK190101/>; <https://www.ncbi.nlm.nih.gov/books/NBK84399/>.

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 *PRSS1* exon numbering used in this P242-C1 Pancreatitis product description is the exon numbering from the RefSeq transcript NM_002769.5. The *SPINK1* exon numbering has changed. From description version B3-01 onwards, we have adopted the NCBI exon numbering that is present in the NM_003122.4 sequence for this gene. The exon numbering used in previous versions of this product description can be found between brackets in Table 2b. For the *CTRC* gene the exon numbering used is the exon numbering from the RefSeq transcript NM_007272.3. The exon numbering and NM_ sequences used have been retrieved on 10/2019. As changes to the NCBI database can occur after release of this product description, exon numbering may not be up-to-date.

Probemix content: The SALSA MLPA Probemix P242-C1 Pancreatitis contains 32 MLPA probes with amplification products between 136 and 436 nucleotides (nt). This includes six probes for the *PRSS1* gene, including 2 probes for exon 1. Furthermore, it contains one upstream and two downstream probes on 7q34. Five probes are included for the *SPINK1* gene, detecting exons 2, 3, 4, 5 and a region upstream of exon 1. Eight probes are included detecting all exons of *CTRC* gene. In addition, ten 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.mlpa.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.mlpa.com.

Length (nt)	Name
64-70-76-82	Q-fragments (only visible with <100 ng sample DNA)
88-96	D-fragments (low signal of 88 nt and 96 nt fragment 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.mlpa.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 unrelated individuals who are from families without a history of pancreatitis. More information regarding the selection and use of reference samples can be found in the MLPA General Protocol.

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/home.html>) have a diverse collection of biological resources which may be used as a positive control DNA sample in your MLPA experiments. Sample ID number NA11949 from the Coriell Institute has been tested with this P242-C1 probemix at MRC-Holland and can be used as a positive control sample (see table below). The quality of cell lines can change; therefore samples should be validated before use.

Sample name	Genotype	Probes affected	Expected DQ
NA11949	Heterozygous deletion of <i>PRSS1</i>	All PRSS1 probes	~ 0.5

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.mlpa.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 dosage quotient (DQ) 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 DQ of the probes can be used to interpret MLPA results for autosomal chromosomes or pseudo-autosomal regions:

Copy number status	Dosage quotient
Normal	$0.80 < DQ < 1.20$
Homozygous deletion	$DQ = 0$
Heterozygous deletion	$0.40 < DQ < 0.65$
Heterozygous duplication	$1.30 < DQ < 1.65$
Heterozygous triplication/Homozygous duplication	$1.75 < DQ < 2.15$
Ambiguous copy number	All other values

- 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. Incomplete DNA denaturation (e.g. due to salt contamination) can 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.
- When running MLPA products, the capillary electrophoresis protocol may need optimization. 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: lower injection voltage / injection time settings, or a reduced amount of sample by diluting PCR products.

P242 specific note - *PRSS1* results:

- In several presumed wild-type samples tested with the P242 probemix, a ratio of ~0.8 was obtained for all *PRSS1* probes. We have not yet been able to establish the cause. Reference selection is crucial and extraction methods should be identical between references and samples. However, even when these criteria are fulfilled, probe ratios of ~0.8 may still occur. Please notify us if you regularly observe something similar: info@mlpa.com.

Limitations of the procedure:

- In most populations, the major cause of genetic defects in the *PRSS1*, *SPINK1* and *CTRC* genes are small (point) mutations, most of which will not be detected by using SALSA MLPA Probemix P242 Pancreatitis.
- 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. SNPs, point mutations, small indels) in the target sequence detected by a probe can cause false positive results. Mutations/SNPs (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.

***PRSS1*, *SPINK1* and *CTRC* mutation database:** <https://databases.lovd.nl/shared/genes/PRSS1>, <https://databases.lovd.nl/shared/genes/SPINK1>, and <https://databases.lovd.nl/shared/genes/CTRC>. We strongly encourage users to deposit positive results in the LOVD Database (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 SNPs and unusual results (e.g., a duplication of *PRSS1* exons 2 and 4 but not exon 3) to MRC-Holland: info@mlpa.com.

Table 1. SALSA MLPA Probemix P242-C1 Pancreatitis

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18) ^a			
		Reference	PRSS1	SPINK1	CTRC
64-105	Control fragments – see table in probemix content section for more information				
136	Reference probe 00662-L00158	6p21			
142	PRSS1 probe 09213-L09483	Exon 4			
148 *	CTRC probe 22402-L32009	Exon 1			
160 ↯	BRAF probe 04259-L03624	Upstream			
166	Reference probe 18955-L26262	2q36			
171 *	CTRC probe 22403-L31592	Exon 8			
178 †	PRSS1 probe 20261-L31886	Exon 5			
184	SPINK1 probe 08413-L08297	Exon 4			
196 *	CTRC probe 22404-L31746	Exon 6			
202	Reference probe 05706-L20677	3q21			
208 ↯	CASP2 probe 00552-L28279	Downstream			
218 *	CTRC probe 22405-L31594	Exon 4			
223	SPINK1 probe 08412-L28280	Exon 2			
229	Reference probe 10149-L27417	18q11			
235 *	CTRC probe 22406-L31595	Exon 2			
241	PRSS1 probe 08408-L09361	Exon 3			
247	Reference probe 21928-L30731	15q21			
254 *	CTRC probe 22408-L31597	Exon 3			
258 *	CTRC probe 22407-L31747	Exon 7			
265	PRSS1 probe 09210-L10056	Exon 1			
280	Reference probe 13350-L26120	9q21			
295	SPINK1 probe 09215-L28282	Exon 3			
304	PRSS1 probe 09211-L28284	Exon 1			
310	Reference probe 15855-L17948	11p15			
319 ↯	CASP2 probe 02051-L01583	Downstream			
335	PRSS1 probe 09212-L09482	Exon 2			
346	Reference probe 03874-L03322	20q13			
374 *	CTRC probe 22409-L31598	Exon 5			
391 *	SPINK1 probe 22581-L31780	Exon 5			
409	Reference probe 10063-L10487	8q22			
427 *	SPINK1 probe 22582-L31781	Upstream			
436	Reference probe 19646-L26317	17p13			

a) See above section on exon numbering for more information.

* New in version C1.

† Changed in version C1. Minor alteration, no change in sequence detected.

↯ Flanking probe. Included to help determine the extent of a deletion/duplication. Copy number alterations of only the flanking or reference probes are unlikely to be related to the condition tested.

Table 2. P242-C1 probes arranged according to chromosomal location

Table 2a. *PRSS1*

Length (nt)	SALSA MLPA probe	PRSS1 exon ^a	Ligation site NM_002769.5	Partial sequence ^b (24 nt adjacent to ligation site)	Distance to next probe
160 ↯ #	04259-L03624	<i>BRAF</i> gene		TTGGGCACTGA-TATTTCTGGCT	1982.6 kb
		<i>start codon</i>	<i>14-16 (Exon 1)</i>		
265	09210-L10056	Exon 1	32 nt before exon 1	CTGGATCCTCGT-GAGGTATAAAGA	0.1 kb
304 #	09211-L28284	Exon 1	53-54	TGGCAGCTGCTC-GTGAATCATG	1.2 kb
335 #+	09212-L09482	Exon 2	174-175	CTCCCTCATCAA-CGAACAGTGGGT	1.2 kb
241	08408-L09361	Exon 3	343-344	GACATCATGTTA-ATCAAGCTCTCC	0.7 kb
142 #	09213-L09483	Exon 4	598-599	GGCAAGGATTCA-TGTCAGGTGATT	0.4 kb
178 #	20261-L31886	Exon 5	722-723	ACAACATGTGA-AATGGATTAAGA	559.4 kb
		<i>stop codon</i>	<i>755-757 (Exon 5)</i>		
319 ↯	02051-L01583	<i>CASP2</i> gene		TTTCTTACAGTT-GAGCTGTGACTA	11.2 kb
208 ↯	00552-L28279	<i>CASP2</i> gene		TGGGTTGACCA-ACAAGATGGAAA	

↯ Flanking probe. Included to help determine the extent of a deletion/duplication. Copy number alterations of only the flanking or reference probes are unlikely to be related to the condition tested.

This probe's specificity relies on a single nucleotide difference compared to a related gene or pseudogene. As a result, an apparent duplication of only this probe can be the result of a non-significant single nucleotide sequence change in the related gene or pseudogene.

+ This probe's specificity relies on a single nucleotide difference compared to a related gene or pseudogene. As a result: **1)** an apparent duplication of only this probe can be the result of a non-significant single nucleotide sequence change in the related gene or pseudogene; **2)** an apparent deletion can be the result of gene conversion between *PRSS1* and *PRSS2* in exon 2 (Teich et al. 2005).

Note: In several presumed wild-type samples tested with the P242 probemix, a ratio of ~0.8 was obtained for all *PRSS1* probes. We have not yet been able to establish the cause. Reference selection is crucial and extraction methods should be identical between references and samples. However, even when these criteria are fulfilled, probe ratios of ~0.8 may still occur. Please notify us if you regularly observe something similar: info@mlpa.com.

Table 2b. *SPINK1*

Length (nt)	SALSA MLPA probe	SPINK1 exon ^a	Ligation site NM_003122.4	Partial sequence ^b (24 nt adjacent to ligation site)	Distance to next probe
427	22582-L31781	upstream	upstream exon 1	GCTACCATGTGG-TCAGCACACTAC	9.9 kb
		<i>start codon</i>	<i>290-292 (Exon 2)</i>		
	No Probe	Exon 1			
223	08412-L28280	Exon 2 (1)	258-259	GCGGTGCAGTTT-TCAACTGACCTC	2.0 kb
295	09215-L28282	Exon 3 (2)	347-348	TATTTCTAGGTA-ACACTGGAGCTG	1.5 kb
184	08413-L08297	Exon 4 (3)	416-417	GCACCAAGATAT-ATGACCCTGTCT	3.4 kb
391	22581-L31780	Exon 5 (4)	496-497	AAACGCCAGACT-TCTATCCTCATT	
		<i>stop codon</i>	<i>527-529 (Exon 5)</i>		

Table 2c. *CTRC*

Length (nt)	SALSA MLPA probe	CTRC exon ^a	Ligation site NM_007272.3	Partial sequence ^b (24 nt adjacent to ligation site)	Distance to next probe
		<i>start codon</i>	<i>23-25 (Exon 1)</i>		
148	22402-L32009	Exon 1	39-40	GGGCATCACTGT-CCTCGCTGCGCT	1.9 kb
235	22406-L31595	Exon 2	4 nt after exon 2	CCTGGCAGGTAA-GCCTGTGTAGGG	0.1 kb
254	22408-L31597	Exon 3	215-216	GGACTTTGATTG-CTAGCAACTTCG	1.9 kb
218	22405-L31594	Exon 4	292-293	GGAAAGAACAAC-CTGGAGGTGGAA	1.1 kb
374	22409-L31598	Exon 5	9 nt after exon 5	GGAGTGAGTATC-GTCCCTGGCAAA	1.2 kb
196	22404-L31746	Exon 6	661 - intron 6	TCAGCCTGCAAT-GTGAAGTGGCTAG	0.9 kb
258	22407-L31747	Exon 7	749-750	CCCGGGGGGGCT-GCAACACCCGCA	0.9 kb
171	22403-L31592	Exon 8	830-831	TGCAGCTGTGAT-TTGTTGCTGGGA	
		<i>stop codon</i>	<i>827-829 (Exon 8)</i>		

a) See above section on exon numbering for more information.

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

Related SALSA MLPA probemixes

- P091 CFTR Contains probes for the CFTR gene, related to chronic pancreatitis.

References

- Koziel D et al. (2015). Genetic mutations in SPINK1, CFTR, CTRC genes in acute pancreatitis. *BMC Gastroenterol.* 15:70.
- Masson E et al. (2008). Association of rare chymotrypsinogen C (CTRC) gene variations in patients with idiopathic chronic pancreatitis. *Hum Genet.* 123:83-91.
- Masson E et al. (2013). Characterization of two deletions of the CTRC locus. *Mol Genet Metab.* 109:296-300.
- Nemeth BC et al. (2014). Human cationic trypsinogen (PRSS1) variants and chronic pancreatitis. *Am J Physiol Gastrointest Liver Physiol.* 306:G466-73.
- Rygiel AM et al. (2015). Gene conversion between cationic trypsinogen (PRSS1) and the pseudogene trypsinogen 6 (PRSS3P2) in patients with chronic pancreatitis. *Hum Mutat.* 36:350-56.
- 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.
- Teich N et al. (2005). Gene conversion between functional trypsinogen genes PRSS1 and PRSS2 associated with chronic pancreatitis in a six-year-old girl. *Hum Mutat.* 25:343-347.
- 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 P242 Pancreatitis

- Cho SM et al. (2016). PRSS1, SPINK1, CFTR, and CTRC Pathogenic Variants in Korean Patients With Idiopathic Pancreatitis. *Ann Lab Med.* 36:555-60.
- Hegyi E et al. (2014). Chronic pancreatitis associated with the p.G208A variant of PRSS1 gene in a European patient. *JOP.* 15:49-52.
- Kujko AA et al. (2017). A novel p.Ser282Pro CPA1 variant is associated with autosomal dominant hereditary pancreatitis. *Gut.* 66:1728-30.
- Rygiel AM et al. (2015). Gene conversion between cationic trypsinogen (PRSS1) and the pseudogene trypsinogen 6 (PRSS3P2) in patients with chronic pancreatitis. *Hum Mutat.* 36:350-6.

P242 Product history	
Version	Modification
C1	Eight CTRC probes and two SPINK1 probes have been added. One SPINK1 probe has been removed. One probe has been adjusted in length. Seven reference probes have been replaced.
B3	One flanking probe has been removed and four reference probes have been replaced.
B2	Three reference probes have been replaced and the control fragments have been adjusted (QDX2).
B1	The PRSS2 probe at 165 nt has been removed because of its high standard deviation.
A1	First release.

Implemented changes in the product description
Version C1-01 — 10 December 2019 (02P) - Product description adapted to a new product version (version number changed, changes in Table 1 and Table 2).

- Positive control DNA samples section was updated.
- Ligation sites of the probes targeting the *PRSS1* gene updated according to new version of the NM_ reference sequence.
- Small changes of probe length in Table 1 and 2 in order to better reflect the true lengths of the amplification products.

Version B3-01 – 23 November 2018 (01P)

- Product description restructured and adapted to a new template.
- *SPINK1* NM sequence was updated in Table 2b.
- Exon numbering of the *SPINK1* gene was updated in Table 1 and Table 2.
- Warning added to Table 2a for probe specificity relying on a single nucleotide difference between target gene and related gene or pseudogene.
- Warning added to page 1 on PRSS1 probe ratios of ~0.8.
- Several references added to P242 selected publications section.

Version 09 – 15 April 2015 (54)

- Product descriptions adapted to a new product version (version number changed, lot number changed, changes in Table 1 and 2, new picture included).
- New reference added on page 1.

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

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