Product Description
SALSA® MLPA® Probemix P466-A1 CDC73

To be used with the MLPA General Protocol.

Version A1
First version. For a complete product history see page 8.

Catalogue numbers:
- **P466-025R:** SALSA MLPA Probemix P466 CDC73, 25 reactions.
- **P466-050R:** SALSA MLPA Probemix P466 CDC73, 50 reactions.
- **P466-100R:** SALSA MLPA Probemix P466 CDC73, 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 P466 CDC73 is a **research use only (RUO)** assay for the detection of deletions or duplications in the *CDC73* gene, which is associated with hyperparathyroidism-jaw tumour syndrome (HPT-JT), familial isolated hyperparathyroidism (FIHP) and parathyroid carcinoma.

Germ line inactivating point mutations and deletions of the *CDC73* gene (also known as *HRTP2*) underlie HPT-JT (OMIM: 145001), and *CDC73* aberrations are also detected in familial primary hyperparathyroidism (OMIM: 145000). HPT-TJ is an autosomal dominant syndrome, characterized by the predisposition to develop parathyroid adenoma or carcinoma, and by the prevalence to develop malignant neoplastic lesions also in jaw bones, kidneys or uterus. Defects in the tumour suppressor gene *CDC73* on chromosome 1q, are identified in approximately 60% of HPT-JT cases (Carpten et al. 2002), and are represented by both intragenic and gross germline deletions of *CDC73* (Cascon et al. 2011; Bricaire et al. 2013; Korpi-Hyövälti et al. 2014; Muscarella et al. 2018; Le Collen et al. 2021). Moreover, bi-allelic inactivation or mutations of *CDC73* leading to dysfunction of the parafibromin protein have been reported in the majority of sporadic parathyroid carcinomas and also in subsets of parathyroid adenomas (Shattuck et al. 2003; Howell et al. 2003).

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK3789/

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 *CDC73* exon numbering used in this P466-A1 CDC73 product description is the exon numbering from the LRG_507 sequence. 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 P466-A1 CDC73 contains 38 MLPA probes with amplification products between 124 and 409 nucleotides (nt). This includes 18 probes for the *CDC73* gene. Furthermore, this probemix also contains one probe for the *B3GALT2* gene that is located in intron 10 of the *CDC73* gene, and five probes for flanking regions of the *CDC73* gene to aid in the determination of the extent of the possible copy number aberration. In addition, 14 reference probes are included that target relatively copy number stable regions in various cancer types including tumours of the parathyroid gland. Complete probe sequences and the identity of the genes detected by the reference probes are available in Table 3 and 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). More information on the use of MLPA in tumour applications can be found in Hömig-Hölzel and Savola (2012).

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, which includes DNA derived from formalin-fixed paraffin-embedded (FFPE) tissues, 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. More information on the use of FFPE tissue samples for MLPA can be found in Atanesyan et al. (2017).

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 tumours of the parathyroid gland. 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. The samples listed in the table below have been tested with P466-A1 probemix and can be used as positive control DNA samples in your MLPA experiments. 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 and flanking genes in P466-A1	Expected copy number alteration
NA00214	Coriell Institute	1p22.1-q31.3	*TROVE2, GLRX2,* ***CDC73****, B3GALT2, LINC01031, KCNT2*	Heterozygous deletion
U-266 (ACC-9) ◊	DSMZ	1q31.2	*TROVE2, GLRX2,* ***CDC73 exons 1-2***	Heterozygous deletion

* 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 P466-A1 CDC73 probemix.

◊ In this cell line DNA sample some of the reference probes are affected by CNAs.

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. The 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 additionally when tested on germline samples 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.

Please note that these above mentioned final ratios are only valid for germline testing. Final ratios are affected both by percentage of tumour cells and by possible subclonality.

- Arranging probes according to chromosomal location facilitates interpretation of the results and may reveal more subtle changes such as those observed in mosaic or subclonal cases. Analysis of parental samples may be necessary for correct interpretation of complex results for germline testing.
- 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.

P466 specific note

- In samples from tumour tissues, reference probes are more prone to have deviating copy number results as compared to blood derived germline samples. When regions targeted by reference probes are affected by copy number alterations, it can help to turn the slope correction off in Coffalyser.Net analysis to get the correct copy number interpretation on the target region.

Limitations of the procedure

- In most populations, the major cause of genetic defects in the *CDC73* gene are small (point) mutations, most of which will not be detected by using SALSA MLPA Probemix P466 CDC73.
- 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.
- MLPA analysis on tumour samples provides information on the *average* situation in the cells from which the DNA sample was purified. Gains or losses of genomic regions or genes may not be detected if the percentage of tumour cells is low. In addition, subclonality of the aberration affects the final ratio of the corresponding probe. Furthermore, there is always a possibility that one or more reference probes *do* show a copy number alteration in a patient sample, especially in solid tumours with more chaotic karyotypes.

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.

***CDC73* mutation database**
https://databases.lovd.nl/shared/genes/CDC73. We strongly encourage users to deposit positive results in the LOVD 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 *CDC73* exons 6 and 8 but not exon 7) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P466-A1 CDC73

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]		
		Reference	*CDC73*	Flanking probes
64-105	Control fragments – see table in probemix content section for more information			
124	Reference probe S0863-L28580	10q22		
130	Reference probe 19551-L26105	2p13		
136 ¬	GLRX2 probe 20515-L28105			1q31.2
142	**CDC73 probe** 20516-L28106		Exon 13	
148	**CDC73 probe** 20517-L28107		Exon 5	
154	**CDC73 probe** 20518-L28108		Exon 10	
162	Reference probe 10694-L26548	6p12		
167	**CDC73 probe** 20519-L28375		Exon 12	
172	**CDC73 probe** 20520-L28110		Exon 8	
178	Reference probe 07032-L28099	14q11		
185	**CDC73 probe** 20521-L28111		Exon 14	
190	Reference probe 12780-L28100	2q13		
196	**CDC73 probe** 20522-L28461		Exon 1	
205 ¬	LINC01031 probe 20523-L28113			1q31.2
214	**CDC73 probe** 20524-L28114		Exon 9	
220	Reference probe 17444-L21200	16p13		
229	**CDC73 probe** 20525-L28115		Exon 3	
236	Reference probe 19652-L26684	4p13		
244	**CDC73 probe** 20526-L28116		Exon 17	
252 ¬	KCNT2 probe 20527-L28117			1q31.3
258	Reference probe 16472-L26940	17q23		
267	**CDC73 probe** 20528-L28118		Exon 15	
274 ¬	ABCA4 probe 17140-L20332			1p22.1
283	Reference probe 13796-L26436	3q25		
292	**CDC73 probe** 20529-L28119		Exon 2	
301	**CDC73 probe** 20530-L28120		Exon 16	

310	Reference probe 08739-L28101	9q21		
319 Ø	B3GALT2 probe 20531-L28121			1q31.2
328	Reference probe 18779-L28102	3p22		
337	**CDC73 probe** 20533-L28123		Exon 4	
346	**CDC73 probe** 20534-L28124		Exon 7	
352	Reference probe 06708-L24718	10p11		
363	**CDC73 probe** 20535-L28125		Exon 11	
372 ¬	TROVE2 probe 20536-L28126			1q31.2
382	**CDC73 probe** 20537-L28127		Exon 6	
391	Reference probe 05914-L28104	18p11		
400	**CDC73 probe** 20538-L28128		Exon 17	
409	Reference probe 10638-L28103	8q12		

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

¬ 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.

Ø Intron probe. This probe detects the *B3GALT2* gene that is located in reverse orientation in intron 10 of the *CDC73* gene. This probe is only included to help determine the extent of a deletion/duplication of the *CDC73* gene. Copy number alterations of a single intron probe are unlikely to be related to the condition tested.

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. *CDC73* probes arranged according to chromosomal location

Length (nt)	SALSA MLPA probe	Gene / Exon[a]	Chromosomal band (hg18) / Ligation site	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
Flanking probes upstream of *CDC73*					
274 ¬	17140-L20332	*ABCA4*	1p22.1	ACAGCGACCCAT-TCATCCTCTTCC	97,0 Mb
372 ¬	20536-L28126	*TROVE2*	1q31.2	CCTTTGCTGGAG-GTGTCCATCCTG	15,0 kb
136 ¬	20515-L28105	*GLRX2*	1q31.2	CTTGAATATGGA-AACCAGTTCCAA	24,7 kb
***CDC73*, at 1q31.2.** Indicated ligation sites below are in NM_024529.5, unless otherwise specified.					
		start codon	*171-173 (Exon 1)*		
196	20522-L28461	Exon 1	249-250	ACGAAGTGATCT-TCGGGGAGTTCT	2,9 kb
292	20529-L28119	Exon 2	371-370 reverse	TGAGAAAGGTGC-ACGTTATTAAGT	5,0 kb
229	20525-L28115	Exon 3	435-436	TGGTTAGAAGAC-CTGATCGAAAAG	5,2 kb
337	20533-L28123	Exon 4	512-513	AGCGCTCCCTTA-GAAATAGGTCTT	0,1 kb
148	20517-L28107	Exon 5	570-571	AAGTTTTAGCAG-AAGCAAAGAAAC	2,6 kb
382	20537-L28127	Exon 6	645-646	CCCGTTTGGAGG-GTCACAAAGAAG	3,8 kb
346	20534-L28124	Exon 7	790-791	TGACATAACTGC-CCTTAAACAGAG	6,0 kb
172	20520-L28110	Exon 8	991-990 reverse	TTACCACAGGTG-CTGCATTTGGGG	2,4 kb
214	20524-L28114	Exon 9	1064-1063 reverse	TCTTTTCCTTTG-AATCTTTCCTGA	2,1 kb
154	20518-L28108	Exon 10	1129-1128 reverse	TTACAGATTTCA-GTGTCATACCAT	28,2 kb
319 Ø	20531-L28121	*B3GALT2*, Exon 2	NM_003783.3; 1615-1614 reverse	GGGTAGAGGTCT-GGTGGCATGTAC	23,2 kb
363	20535-L28125	Exon 11	1172-1171 reverse	TGGGCTGCAGGA-GTCTGAGTCTTC	8,3 kb
167	20519-L28375	Exon 12	1223-1224	AGACCTCCCCCA-AATCAGAAGAAA	0,3 kb
142	20516-L28106	Exon 13	1261-1262	CATTATCATAAT-TCCTGCAGCTAC	20,7 kb
185	20521-L28111	Exon 14	1433-1432 reverse	TAAGGTACTGTA-ACACTAATTGCA	3,2 kb
267	20528-L28118	Exon 15	1541-1542	TTCAAAGGTTGG-CCATGGCTTTTG	13,5 kb
301	20530-L28120	Exon 16	1651-1652	GAAATGGGATGT-AACAGTATTAGA	0,9 kb

400	20538-L28128	Exon 17	1762-1763	GCACTTGAGATT-CTGAATTATTTG	0,8 kb

244	20526-L28116	Exon 17	2550-2549 reverse	GTTATACTGCAA-TAGGGCTGATAC	114,3 kb
		stop codon	*1774-1766 (Exon 17)*		
Flanking probes downstream of *CDC73*					
205 ¬	20523-L28113	*LINC01031*	1q31.2	GGACATGAATTC-AGTAAGCTCCTT	3,1 Mb
252 ¬	20527-L28117	*KCNT2*	1q31.3	TTGGCAAGCCAA-CAGTTCAGAAAG	-

[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.

¬ 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.

Ø Intron probe. This probe detects the *B3GALT2* gene that is located in reverse orientation in intron 10 of the *CDC73* gene. This probe is only included to help determine the extent of a deletion/duplication of the *CDC73* gene. Copy number alterations of a single intron probe are unlikely to be related to the condition tested.

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. Reference probes arranged according to chromosomal location.

Length (nt)	SALSA MLPA probe	Gene	Chromosomal band (hg18)	Partial sequence (24 nt adjacent to ligation site)	Location (hg18) in kb
130	19551-L26105	*DYSF*	2p13	CCATTGCCAAGA-AGGTCAGTGTCC	02-071,750
190	12780-L28100	*EDAR*	2q13	TGGACATTGCAA-TGATCAGGGCAG	02-108,894
328	18779-L28102	*ACVR2B*	3p22	TTGCCCACAGGT-ACCTGGGTCAGC	03-038,496
283	13796-L26436	*KCNAB1*	3q25	CTTTTCCAGAGA-GAGAAAGTGGAG	03-157,716
236	19652-L26684	*ATP8A1*	4p13	CAGATTCTTCTT-CGAGGAGCTCAG	04-042,278
162	10694-L26548	*PKHD1*	6p12	CAGTTTCTGTAT-TTCCTAAAACAG	06-051,717
409	10638-L28103	*CHD7*	8q12	GACTCAATGGTA-ATGGTGTGGGTT	08-061,913
310	08739-L28101	*PCSK5*	9q21	TCTCACAGGTCT-GTGTGCTTTGCT	09-078,143
352	06708-L24718	*ZNF25*	10p11	CAGGTGATTCCT-GGGGCTGCCAGC	10-038,301
124	S0863-L28580	*KAT6B*	10q22	GATCCCATTCCA-ATATGTAGCTTC	10-076,390
178	07032-L28099	*RPGRIP1*	14q11	GCTGAATGGACA-AGATCCTGATCA	14-020,883
220	17444-L21200	*GRIN2A*	16p13	CGTGGATTCCAT-ACGCCAGGATTC	16-009,766
258	16472-L26940	*MED13*	17q23	TTCTGGTCAGCA-TGTCCTCAAGCA	17-057,383
391	05914-L28104	*RNMT*	18p11	TACAATGAACTT-CAGGAAGTTGGT	18-013,724

Complete probe sequences are available at www.mrcholland.com.

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Selected publications using SALSA MLPA Probemix P466 CDC73

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P466 product history	
Version	*Modification*
A1	First release.

Implemented changes in the product description
Version A1-02 – 13 October 2021 (04P) - Product description restructured and adapted to a new template and to a new lot. - Various minor textual or layout changes. - Ligation sites of the probes targeting the CDC73 gene updated according to a new version of the NM_ reference sequence. - Small changes of probe lengths in Table 1 and 2 in order to better reflect the true lengths of the amplification products. - For uniformity, the chromosomal locations and bands in this document are now all based on hg18 (NCBI36). - New references added to page 8-9.
Version A1-01 – 04 July 2018 (01P) - Product description restructured and adapted to a new template. - Various minor textual or layout changes.
Version 01 – 28 April 2015 (T07) - Not applicable, new document.

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