Product Description SALSA® MLPA® Probemix P122-D2 NF1-area

To be used with the MLPA General Protocol.

Version D2. As compared to version D1, two reference probes have been added and two reference probes have been replaced. For complete product history see page 8.

Catalogue numbers:
- **P122-025R:** SALSA MLPA Probemix P122 NF1-area, 25 reactions.
- **P122-050R:** SALSA MLPA Probemix P122 NF1-area, 50 reactions.
- **P122-100R:** SALSA MLPA Probemix P122 NF1-area, 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.

General information: The SALSA MLPA Probemix P122 NF1-area is a **research use only (RUO)** assay for the detection of deletions or duplications in the region surrounding the neurofibromin 1 (*NF1*) gene on chromosome 17q11.2, which is associated with neurofibromatosis.

Neurofibromatosis is an autosomal dominant disorder characterised by café-au-lait spots and fibromatous tumours of the skin. Neurofibromatosis type I (NF1) is caused by defects in the *NF1* gene on chromosome 17q11.2. NF1 is a cytoplasmic protein predominantly expressed in neurons, Schwann cells and leukocytes. Neurofibromatosis type II is caused by defects in the *NF2* gene on chromosome 22q12.2.
Partial deletions of the *NF1* gene as well as deletions and duplications of the complete *NF1* gene have been described. A deletion of a 1500 kb chromosomal region on 17q11.2 that includes the *NF1* gene accounts for 5-10% of NF1 cases. This interstitial 17q11.2 microdeletion arises from unequal crossover between two highly homologous 60 kb duplicons. The phenotype related to the 17q11.2 microdeletion is usually much more severe than most other NF1 cases and may include severe developmental delay.

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1109/.

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 exon numbering used in this P122-D2 NF1-area product description can be found in the table below. The exon numbering for the genes *ASPA* and *CPD* has changed. From product description version D2-01 onwards, we have adopted the NCBI exon numbering that is present in the NM_ sequence for these genes. The exon numbering used in previous versions of this product description can be found in between brackets in Table 2. The exon numbering and NM_ sequence used have been retrieved on 05/2020. As changes to the NCBI database can occur after release of this product description, exon numbering may not be up-to-date.

Gene	LRG or RefSeqGene	RefSeq Transcript
ADAP2	NG_051975.1	NM_018404.3
ASPA	NG_008399.2	NM_000049.4
ATAD5	-	NM_024857.5
BLMH	NG_011440.1	NM_000386.4
CPD	-	NM_001304.5
CRLF3	NG_032911.2	NM_015986.4
LRRC37B	-	NM_052888.3
MYO1D	-	NM_015194.3
NF1	LRG_214	NM_000267.3
PMP22	LRG_263	NM_000304.2
PSMD11	-	NM_002815.4
RNF135	NG_011701.1	NM_032322.4
SUZ12	NG_009237.1	NM_015355.4
SUZ12P1	-	NR_024187.2
TRAF4	-	NM_004295.4
UTP6	-	NM_018428.3
ZNF207	-	NM_003457.3

Probemix content: The SALSA MLPA Probemix P122-D2 NF1-area contains 35 MLPA probes with amplification products between 129 and 416 nucleotides (nt). This includes 25 probes for the *NF1* area on chromosome 17q11.2. 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 NF1. 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. The quality of cell lines can change; therefore samples should be validated before use.

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.

Limitations of the procedure:

- In most populations, the major cause of genetic defects in the *NF1* gene are small (point) mutations, most of which will not be detected by using SALSA MLPA Probemix P122 NF1-area.
- 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.

Mutation database: https://www.lovd.nl/. We strongly encourage users to deposit positive results in the Leiden Open Variation Database (LOVD). 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 to MRC-Holland: info@mlpa.com.

Table 1. SALSA MLPA Probemix P122-D2 NF1-area

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]		
		Reference	*NF1*	*NF1* area genes
64-105	Control fragments – see table in probemix content section for more information			
129	Reference probe 19616-L26684	4p13		
133 «	**TRAF4 probe** 09176-L19109			2347 kb upstream of *NF1*
137 *	Reference probe 05714-L05152	2q11		
142	**NF1 probe** 02491-L01922		**Exon 1**	
147	**NF1 probe** 02512-L01943		**Exon 30**	
154	**NF1 probe** 05220-L03309		**Exon 57**	
160	Reference probe 17436-L21192	16p13		
165	**PSMD11 probe** 09632-L09917			1086 kb downstream of *NF1*
175	**CRLF3 probe** 03780-L03289			297 kb upstream of *NF1*
184	**SUZ12 probe** 03786-L03295			628 kb downstream of *NF1*
190	**SUZ12P1 probe** 11798-L12590			363 kb upstream of *NF1*
197	**CPD probe** 09629-L09914			632 kb upstream of *NF1*
208	**SUZ12P1 probe** 11801-L12592			336 kb upstream of *NF1*
213 *	Reference probe 07404-L27958	12q13		
220 «	**RNF135 probe** 03783-L03292			110 kb upstream of *NF1*
226	**CPD probe** 09628-L21977			651 kb upstream of *NF1*
238	Reference probe 20555-L14777	1p31		
247	**ATAD5 probe** 03781-L03290			260 kb upstream of *NF1*
256	**UTP6 probe** 03785-L03294			515 kb downstream of *NF1*
265	**ASPA probe** 01325-L07456			23101 kb upstream of *NF1*
274 *	Reference probe 17349-L21793	3p25		
283	**PMP22 probe** 01463-L00928			11343 kb upstream of *NF1*
292	**ADAP2 probe** 03782-L03291			168 kb upstream of *NF1*
301	**LRRC37B probe** 03787-L03296			661 kb downstream of *NF1*
310 *	Reference probe 06719-L06305	15q24		
319	**NF1 probe** 02525-L01956		**Exon 49**	
328	**MYO1D probe** 09630-L09915			1420 kb downstream of *NF1*
337	**NF1 probe** 02507-L01938		**Exon 17**	
346	Reference probe 01232-L00780	10p14		
362	**ZNF207 probe** 09637-L09949			1006 kb downstream of *NF1*
373	**BLMH probe** 09627-L09912			822 kb upstream of *NF1*
382	**TRAF4 probe** 08620-L08632			2347 kb upstream of *NF1*
391	**MYO1D probe** 09631-L09916			1407 kb downstream of *NF1*
409	Reference probe 18498-L23723	19q13		
416	Reference probe 20960-L29094	6p12		

* New in version D2.

« 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.

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

Table 2. *NF1* area probes arranged according to chromosomal location

Length (nt)	SALSA MLPA probe	Gene/Exon[a]	RefSeq Transcript	Ligation site	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
Chromosome 17p12-17p13.3						
265	01325-L07456	*ASPA* exon 5 (6)	NM_000049.4	837-838	GGTCTATAAAAT-TATAGAGAAAGT	11758.7 kb
283	01463-L00928	*PMP22* exon 3	NM_000304.2	328-329	GATCTCTGGCAG-AACTGTAGCACC	8995.2 kb
Chromosome 17q11.2						
133 «	09176-L19109	*TRAF4* exon 2	NM_004295.4	19 nt after exon 2	ACACTGCCAGGA-AGAAGCCCAAGC	0.8 kb
382	08620-L08632	*TRAF4* exon 4	NM_004295.4	431-432	CAGCTTCAATGT-CATTCCCTGCCC	1524.5 kb
373	09627-L09912	*BLMH* exon 9	NM_000386.4	1108-1109	TGGCTGTGATGT-TGGAAAACACTT	171.3 kb
226	09628-L21977	*CPD* exon 11 (12)	NM_001304.5	2529-2530	CCAGTGACTACT-TACAAAACTGGA	18.5 kb
197	09629-L09914	*CPD* exon 20 (21)	NM_001304.5	3914-3915	GGTGATAGTCTT-TGACACAGATAA	269.0 kb
190	11798-L12590	*SUZ12P1* exon 1	NR_024187.2	321 nt before exon 1	GATCTAGACTCT-CTAAACCGCTCG	26.8 kb
208	11801-L12592	*SUZ12P1* exon 3	NR_024187.2	33 nt before exon 3	CCATGGAAATGA-CTTTCTTACTTG	39.2 kb
175	03780-L03289	*CRLF3* exon 3	NM_015986.4	403-404	GCTTGGTGGTGT-GGGAGAAGAGAA	37.7 kb
247	03781-L03290	*ATAD5* exon 2	NM_024857.5	1338-1339	GCAGGTACGCTT-TAAGACAGTTAC	91.8 kb
292	03782-L03291	*ADAP2* exon 3	NM_018404.3	335-336	TGAAGGCCAAGT-TCGAAGCCAGAG	57.8 kb
220 «	03783-L03292	*RNF135* exon 2	NM_032322.4	472-473	GGAACATCTTGT-AGACATTGTCAG	109.9 kb
142	02491-L01922	*NF1* exon 1	NM_000267.3	335 nt before exon 1	GCAGAGATCCGC-GCGCTGGGAGAA	130.6 kb
337	02507-L01938	*NF1* exon 17	NM_000267.3	2329-2330	GGATCATGAAGA-ATTACTACGTAC	23.8 kb
147	02512-L01943	*NF1* exon 30	NM_000267.3	4390-4391	TGAGGAAAACCA-GCGGAACCTCCT	100.1 kb
319	02525-L01956	*NF1* exon 49	NM_000267.3	7535-7536	TCACCTGCTATT-GTTGCAAGAACA	11.4 kb
154	05220-L03309	*NF1* exon 57	NM_000267.3	8563-8564	TGGAATTGATGA-AGAAACCAGTGA	514.8 kb
256	03785-L03294	*UTP6* exon 14	NM_018428.3	1280-1279, reverse	TCCCAGAGTCTC-TAAACAATTCAG	113.1 kb
184	03786-L03295	*SUZ12* exon 10	NM_015355.4	1346-1347	CAATGATAAATC-TACGGCTCCTAT	33.2 kb
301	03787-L03296	*LRRC37B* exon 1	NM_052888.3	454-455	TTCCGCTTCTCA-ACCGGGATCAGA	345.2 kb
362	09637-L09949	*ZNF207* exon 9	NM_003457.3	1009-1010	GCTCTGTTTCCT-AGCACAGCACAA	80.2 kb
165	09632-L09917	*PSMD11* exon 2	NM_002815.4	133-134	GGAAAACGATGA-AGAGGCAGTGCA	320.7 kb
391	09631-L09916	*MYO1D* exon 7	NM_015194.3	1015-1016	CTGATGCCATGA-AAGTCATTGGCT	12.9 kb
328	09630-L09915	*MYO1D* exon 2	NM_015194.3	486-487	CCGCCTCACCTT-TTTGCTATTGCG	

« 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.

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

P044 NF2	Contains probes for *NF2* involved in neurofibromatosis type II.
P081/P082 NF1	Contain probes for *NF1* involved in neurofibromatosis type I.

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P122 Product history	
Version	*Modification*
D2	Two reference probes have been added and two reference probes have been replaced.
D1	Four flanking probes and one reference probe have been removed, four reference probes have been replaced and several probe lengths have been adjusted
C2	One *SUZ12P1* probe has been removed and three reference probes have been replaced. Control fragments (QDX2) have been added.
C1	Three probes for *SUZ12P1* have been added.
B1	One target probe has been adjusted and 13 target probes have been added. One reference probe has been replaced, one reference probe has been added and five reference probes have been removed.
A1	First release.

Implemented changes in the product description

Version D2-01 – 03 June *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 1 and Table 2).
- Exon numbering of the gene *ASPA* and *CPD* has been changed.
- Ligation sites of the probes targeting the genes *ADAP2*, *ASPA*, *ATAD5*, *BLMH*, *CPD*, *CRLF3*, *LRRC37B*, *MYO1D*, *PMP22*, *PSMD11*, *RNF135*, *SUZ12*, *TRAF4* and *UTP6*, respectively, have been updated according to new versions of the NM_ reference sequences.
- The gene name *SUZ12P* has been updated to *SUZ12P1*.

Version 08 – 18 November 2016 (55)
- Product description adapted to a new product version (version number changed, lot number added, changes in Table 1 and Table 2, new picture included).

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