Product Description SALSA® MLPA® Probemix P214-C1 COL2A1

To be used with the MLPA General Protocol.

Version C1. For complete product history see page 7.

Catalogue numbers:
- **P214-025R:** SALSA MLPA Probemix P214 COL2A1, 25 reactions.
- **P214-050R:** SALSA MLPA Probemix P214 COL2A1, 50 reactions.
- **P214-100R:** SALSA MLPA Probemix P214 COL2A1, 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 P214 COL2A1 is a **research use only (RUO)** assay for the detection of deletions or duplications in the *COL2A1* gene, which is associated with type II collagen disorders.

The *COL2A1* gene (54 exons) spans ~31.5 kb of genomic DNA and is located on 12q13.11, ~47 Mb from the p-telomere. It encodes the pro-alpha-1 (II) chain of type II collagen, the major collagen found in cartilage and the vitreous humour of the eye. Defects in the *COL2A1* gene lead to a number of different disorders, collectively called type II collagen disorders, which include amongst others achondrogenesis type 2, Stickler syndrome type 1, Kniest dysplasia, and spondyloepiphyseal dysplasia congenita. These disorders are characterised by abnormalities in the ocular, skeletal, orofacial, and audiological systems.

Mutations in *COL2A1* have also been identified in individuals with chondrosarcoma, the second most common primary bone malignancy after osteosarcoma. Tarpey et al. (2013) reported insertions, deletions and rearrangements in 37% of the chondrosarcoma cases.

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK540447/ (type II collagen disorders) and https://www.ncbi.nlm.nih.gov/books/NBK1302/ (Stickler syndrome).

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 *COL2A1* exon numbering used in this P214-C1 COL2A1 product description is the exon numbering from the RefSeq transcript NM_001844.5, which is identical to the NG_008072.1 sequence. The exon numbering and NM_ sequence used have been retrieved on 11/2019. 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 P214-C1 COL2A1 contains 58 MLPA probes with amplification products between 124 and 500 nucleotides (nt). This includes 46 probes for the *COL2A1* gene, covering 43 different exons. In addition, 12 reference probes are included that detect autosomal chromosomal locations. These reference probe target relatively copy number stable regions in various cancer types including chondrosarcoma. 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 type II collagen disorders. 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 *COL2A1* gene are small (point) mutations, most of which will not be detected by using SALSA MLPA Probemix P214 COL2A1.
- 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.

***COL2A1* mutation database:** https://databases.lovd.nl/shared/genes/COL2A1. 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 SNPs and unusual results (e.g., a duplication of *COL2A1* exons 2 and 4 but not exon 3) to MRC-Holland: info@mlpa.com.

Table 1. SALSA MLPA Probemix P214-C1 COL2A1

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a] Reference	COL2A1
64-105	Control fragments – see table in probemix content section for more information		
124	Reference probe 19616-L26241	4p13	
130	**COL2A1 probe** 20226-L27557		**Exon 40**
139	**COL2A1 probe** 07387-L27860		**Exon 1**
145	**COL2A1 probe** 07397-L27861		**Exon 24**
150	**COL2A1 probe** 20227-L28154		**Exon 33**
154	**COL2A1 probe** 07393-L29025		**Exon 16**
160	Reference probe 02417-L27862	6p21	
165	**COL2A1 probe** 20228-L28265		**Exon 26**
170	**COL2A1 probe** 07394-L28264		**Exon 17**
175	**COL2A1 probe** 15449-L28263		**Exon 10**
180	Reference probe 20361-L28262	3q24	
184	**COL2A1 probe** 20229-L27560		**Exon 18**
190	**COL2A1 probe** 20230-L27561		**Exon 6**
196	Reference probe 18769-L27864	3p22	
201	**COL2A1 probe** 15450-L27865		**Exon 23**
207	**COL2A1 probe** 20232-L27866		**Exon 12**
213	**COL2A1 probe** 07404-L27958		**Exon 46**
218	**COL2A1 probe** 15291-L27868		**Exon 1**
225	**COL2A1 probe** 07405-L28736		**Exon 49**
229	**COL2A1 probe** 15451-L27870		**Exon 14**
234	Reference probe 16398-L27959	17q22	
238	**COL2A1 probe** 07406-L27872		**Exon 51**
244	**COL2A1 probe** 20233-L27564		**Exon 4**
252	**COL2A1 probe** 15452-L25045		**Exon 25**
257	**COL2A1 probe** 15453-L25046		**Exon 29**
265 Ж	**COL2A1 probe** 20234-SP0942-L27565		**Exon 22**
273	**COL2A1 probe** 20235-L27566		**Exon 37**
278	Reference probe 18594-L28268	2q33	
283	**COL2A1 probe** 07390-L27874		**Exon 8**
289	**COL2A1 probe** 15289-L27875		**Exon 35**
298	**COL2A1 probe** 07398-L27877		**Exon 27**
305 Ж	**COL2A1 probe** 20463-SP0949-L28266		**Exon 50**
312	**COL2A1 probe** 15455-L27878		**Exon 53**
319	Reference probe 08987-L28685	9q21	
325	**COL2A1 probe** 07407-L28267		**Exon 54**
331	**COL2A1 probe** 20238-L27569		**Exon 7**
337 Ж	**COL2A1 probe** 20239-SP0944-L27954		**Exon 34**
346 Ж	**COL2A1 probe** 20241-SP0946-L27572		**Exon 48**
353	**COL2A1 probe** 07402-L27881		**Exon 39**
361 Ж	**COL2A1 probe** 20242-SP0947-L27882		**Exon 41**
368	**COL2A1 probe** 07863-L27883		**Exon 13**
374	**COL2A1 probe** 15456-L27884		**Exon 52**
382	Reference probe 17429-L27885	8p21	

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]	
		Reference	COL2A1
389	Reference probe 11001-L28914	4q22	
395 Ж	**COL2A1 probe** 20243-SP0948-L28915		**Exon 44**
403	**COL2A1 probe** 20244-L28689		**Exon 9**
409	**COL2A1 probe** 20245-L27576		**Exon 42**
418	**COL2A1 probe** 15459-L28687		**Exon 31**
427	**COL2A1 probe** 15460-L28026		**Exon 54**
434	Reference probe 08839-L27962	2p13	
441	**COL2A1 probe** 20246-L27963		**Exon 20**
445	**COL2A1 probe** 20247-L27964		**Exon 43**
454	**COL2A1 probe** 20248-L27579		**Exon 11**
463	**COL2A1 probe** 20249-L27580		**Exon 2**
476	Reference probe 20551-L28686	11q21	
484	**COL2A1 probe** 20252-L28688		**Exon 3**
494	**COL2A1 probe** 20253-L27584		**Exon 50**
500	Reference probe 14894-L27890	15q15	

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

Ж This probe consists of three parts and has two ligation sites. A low signal of this probe can be due to depurination of the sample DNA, e.g. due to insufficient buffering capacity or a prolonged denaturation time. When this occurs in reference samples, it can look like an increased signal in the test samples.

Table 2. *COL2A1* probes arranged according to chromosomal location

Length (nt)	SALSA MLPA probe	*COL2A1* exon[a]	Ligation site NM_001844.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*156-158 (Exon 1)*		
218	15291-L27868	Exon 1	387 nt before exon 1	CGTCCTTGGTCT-AGGGCTCTCGGC	0.7 kb
139	07387-L27860	Exon 1	40 nt after exon 1	GCCTGCTTTCCA-TGCGTCCCTCAG	4.3 kb
463	20249-L27580	Exon 2	444-445	TCGCCACTGCCA-GTGGTTGTAATT	1.5 kb
484	20252-L28688	Exon 3	455-456	GCAGGGCAACCA-GGACCAAAGGTA	0.2 kb
244	20233-L27564	Exon 4	494-495	GGAGACATCAAG-GATGTAAGTGCA	0.3 kb
190	20230-L27561	Exon 6	17 nt after exon 6; reverse	AGGGTCAAGCAG-CATTGCTTTTTA	0.3 kb
331	20238-L27569	Exon 7	19 nt after exon 7; reverse	GCCTGAAGGAAT-GGGAAGTAAGGA	1.0 kb
283	07390-L27874	Exon 8	722-723	GGATTTGATGAA-AAGGCTGGTGGC	0.7 kb
403	20244-L28689	Exon 9	802-801; reverse	TTACAGGAGCAC-CTGCAGGGCCTG	0.1 kb
175	15449-L28263	Exon 10	13 nt before exon 10	CTGGTATCCTCA-TTTTACTTTTTA	0.5 kb
454	20248-L27579	Exon 11	913-914	AAAGCCTGGTGA-TGATGTGAGTAT	0.8 kb
207	20232-L27866	Exon 12	30 nt before exon 12	GCGTCTCTGAGG-AAGCTGGGATAT	0.5 kb
368	07863-L27883	Exon 13	992-993	GGTTTCCCAGGA-ACCCCAGGCCTT	0.2 kb
229	15451-L27870	Exon 14	2 nt before exon 14	CTCTTGTTCCCT-AGGGTTATCCAG	1.0 kb
154	07393-L29025	Exon 16	1147-1148	CCTGCCTGGTGA-AAGAGGACGGAC	3.1 kb
170	07394-L28264	Exon 17	9 nt before exon 17	TCACTTCCTTCT-TGCTCACAGGGT	0.6 kb
184	20229-L27560	Exon 18	1270-1271	TGGTGCTCCTGG-AGCCAAGGTACG	1.9 kb
441	20246-L27963	Exon 20	1397-1398	GGAACAGATGGA-ATTCCTGGAGCC	0.5 kb
265 Ж	20234-SP0942-L27565	Exon 22	1550-1551 and 6 nt after exon 22	GGCTTCAAAGGT-30 nt spanning oligo-ATCTGCCCCCAA	0.5 kb
201	15450-L27865	Exon 23	9 nt after exon 23	AGAGTTAAGTGA-ATGTGGAGGCTC	0.4 kb
145	07397-L27861	Exon 24	1735-1736	GGCAGGTCCCAA-GGTGAGTGGGAG	0.1 kb
252	15452-L25045	Exon 25	3 nt before exon 25	TGTGTACCCTTG-TAGGGAGCCCCT	0.3 kb
165	20228-L28265	Exon 26	10 nt after exon 26; reverse	AGCCCTCAGAGG-ATAGACTTACAG	0.5 kb
298	07398-L27877	Exon 27	1919-1920	GGTCGTCCTGGA-CCTCCAGGTCCT	0.8 kb
257	15453-L25046	Exon 29	98 nt before exon 29	ACCGTGGAGGTC-TGGAAACTCTGG	0.8 kb
418	15459-L28687	Exon 31	11 nt before exon 31	ACGCTTGTCACT-TCGGCTTCTAGG	0.5 kb
150	20227-L28154	Exon 33	2273-2274	TTCCCAGGTGAA-CGTGGCTCTCCC	0.4 kb
337 Ж	20239-SP0944-L27954	Exon 34	2418-2419 and 2441-2442	TGCCTGGCGAGA-23 nt spanning oligo-CCCAAAGGCGAC	0.4 kb
289	15289-L27875	Exon 35	35 nt after exon 35	CTGCTGGGCATT-AGGATCCTAGCC	0.7 kb
273	20235-L27566	Exon 37	2568-2569	ACCCTCAGGGAG-AAGTTGGACCTC	0.7 kb
353	07402-L27881	Exon 39	27 nt before exon 39	CCTGCCCCTCAT-TCACCTGCTTCC	0.6 kb
130	20226-L27557	Exon 40	2796-2797	CTACTGGAGTGA-CTGGTCCTAAAG	0.5 kb
361 Ж	20242-SP0947-L27882	Exon 41	30 nt before exon 41 and 2834-2835	TGAGGGCTTGAG-30 nt spanning oligo-GGAGCCACTGGA	0.8 kb
409	20245-L27576	Exon 42	2888-2889	TTCTCCTTCTAG-GGCAACCCTGGA	0.4 kb
445	20247-L27964	Exon 43	3090-3091	GTCTGGCTGGTC-AGAGAGGCATCG	0.3 kb
395 Ж	20243-SP0948-L28915	Exon 44	3192-3193 and 3227-3228	CTCCTGGAGCAT-35 nt spanning oligo-CCTGGCCTGACG	0.6 kb
213	07404-L27958	Exon 46	34 nt before exon 46	TCTTCTGGAACA-TTCTTCTCTGAG	0.7 kb
346 Ж	20241-SP0946-L27572	Exon 48	3587-3588 and 26 nt after exon 48	CTGCCCGGCCCT-29 nt spanning oligo-TCCCGAGGCCTC	0.2 kb
225	07405-L28736	Exon 49	3597-3598	CACAGGGTCCTT-CTGGAGACCAAG	0.5 kb
305 Ж	20463-SP0949-L28266	Exon 50	57 nt and 27 nt before exon 50	CCAGCCCCAGCG-30 nt spanning oligo-TTTCCTCACGAC	0.1 kb
494	20253-L27584	Exon 50	2 nt after exon 50	CGGCCCTGCTGT-AAGTGTCCTGAC	0.6 kb
238	07406-L27872	Exon 51	4007-4008	CGCACCTGCAGA-GACCTGAAACTC	0.5 kb
374	15456-L27884	Exon 52	11 nt before exon 52	GGTGCTGCCTCT-TCCCCCTGCAGG	0.4 kb
312	15455-L27878	Exon 53	99 nt before exon 53	CCCCAGTACCCT-TGAGGTCCTTGA	1.1 kb
325	07407-L28267	Exon 54	4660-4661	TTGCAAACCCAA-AGGACCCAAGTA	0.5 kb
427	15460-L28026	Exon 54	67 nt after exon 54	AGGCATGCCCAA-ATAGCAGTCCTA	
		stop codon	*4617-4619 (Exon 54)*		

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.

Ж This probe consists of three parts and has two ligation sites. A low signal of this probe can be due to depurination of the sample DNA, e.g. due to insufficient buffering capacity or a prolonged denaturation time. When this occurs in reference samples, it can look like an increased signal in the test samples.

Related SALSA MLPA probemixes

P381/P382 COL11A1 Probes for *COL11A1*, involved in type 2 Stickler syndrome and Marshall syndrome.

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.
- Tarpey PS et al. (2013). Frequent mutation of the major cartilage collagen gene COL2A1 in chondrosarcoma. *Nat Genet*. 45:923-926.
- 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 P214 COL2A1

- Hoornaert KP et al. (2010). Stickler syndrome caused by COL2A1 mutations: genotype-phenotype correlation in a series of 100 patients. *Eur J Hum Genet*. 18:872-880.
- Nagendran S et al. (2012). Somatic mosaicism and the phenotypic expression of COL2A1 mutations. *Am J Med Genet A*. 158A:1204-1207.
- Richards AJ et al. (2010). Stickler syndrome and the vitreous phenotype: mutations in COL2A1 and COL11A1. *Hum Mutat*. 31:E1461–E1471.
- Wang X et al. (2016). Mutation survey and genotype-phenotype analysis of COL2A1 and COL11A1 genes in 16 Chinese patients with Stickler syndrome. *Mol Vis*. 22:697-704.

P214 Product history	
Version	*Modification*
C1	23 new target probes have been included and five target probes have been removed. Furthermore, all reference probes have been replaced.
B2	One reference probe has been removed and three reference probes have been replaced, in addition the control fragments have been adjusted (QDX2).
B1	Twelve COl2A1 probes, seven reference probes and two control fragments at 100 and 105 nt have been added. Six reference probes have been replaced.
A1	First release.

Implemented changes in the product description

Version C1-01 — 21 November 2019 (02P)
- Product description rewritten and adapted to a new template.
- Chromosomal position of the 500 nt reference probe 14894-L27890 corrected in Table 1.
- Ligation sites of the probes targeting the *COL2A1* gene updated according to 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.

Version 10 – 28 July 2016 (55)
- Product description adapted to a new product version (version number changed, lot number added, small changes in Table 1 and Table 2, new picture included).
- New references added on page 1.
- Various minor textual changes on page 1.

- Various minor layout changes. *Version 09 – 12 March 2015 (54)* - New sample picture included in product description. - Updated link for "Database of Genomic Variants".

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