Product Description
SALSA® MLPA® Probemix P209-C2 Glycine Encephalopathy

To be used with the MLPA General Protocol.

Version C2
For complete product history see page 8.

Catalogue numbers:
- **P209-025R:** SALSA MLPA Probemix P209 Glycine Encephalopathy, 25 reactions.
- **P209-050R:** SALSA MLPA Probemix P209 Glycine Encephalopathy, 50 reactions.
- **P209-100R:** SALSA MLPA Probemix P209 Glycine Encephalopathy, 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 P209 Glycine Encephalopathy is a **research use only (RUO)** assay for the detection of deletions or duplications in the *GLDC*, *AMT*, and *GCSH* genes, which are associated with Glycine encephalopathy (GCE).

GCE, also known as nonketotic hyperglycinemia (NKH), is an inborn error of glycine metabolism in which large quantities of glycine accumulate in all body tissues, including the brain. This is due to deficient glycine cleavage enzymes. The majority of the GCE cases present themselves in the neonatal phase. This leads to progressive lethargy, hypotonia, and myoclonic jerks which in turn leads to apnea and often death.

Three genes are known to cause GCE. Glycine dehydrogenase (*GLDC*) encodes the P-protein component in the glycine cleavage system (GCS). This gene is responsible for 70-75% of the disease cases. Aminomethyltransferase (*AMT*) encodes the T-protein of the GCS complex and accounts for 20% of the GCE cases. Glycine cleavage system protein H (*GCSH*), which is the H-protein of the GCS complex accounts for <1% of the disease cases. Around 5% of individuals with GCE do not have a mutation in any of these three genes.

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1357/.

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 *GLDC*, *AMT*, and *GCSH* exon numbering used in this P209-C2 Glycine Encephalopathy product description is the exon numbering from the LRG_643, LRG_537, and LRG_541 sequences. 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 P209-C2 Glycine Encephalopathy contains 50 MLPA probes with amplification products between 124 and 463 nucleotides (nt). This includes 26 probes for the *GLDC* gene, one probe for each exon and two probes for exon 1, nine probes for the *AMT* gene, one probe for each exon, and five probes for the *GCSH* gene, one probe for each exon. 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.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).

MLPA technique validation
Internal validation of the MLPA technique using 16 DNA samples from healthy individuals is required, in particular when using MLPA for the first time, or when changing the sample handling procedure, DNA extraction method or instruments used. This validation experiment should result in a standard deviation ≤0.10 for all probes over the experiment.

Required specimens
Extracted DNA free from impurities known to affect MLPA reactions. For more information please refer to the section on DNA sample treatment found in the MLPA General Protocol.

Reference samples
A sufficient number (≥3) of reference samples should be included in each MLPA experiment for data normalisation. All samples tested, including reference DNA samples, should be derived from the same tissue type, handled using the same procedure, and prepared using the same DNA extraction method when possible. Reference samples should be derived from different unrelated individuals who are from families without a history of GCE. 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 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.mrcholland.com. Use of other non-proprietary software may lead to inconclusive or false results. For more details on MLPA quality control and data analysis, including normalisation, see the Coffalyser.Net Reference Manual.

Interpretation of results

The standard deviation of each individual probe over all the reference samples should be ≤0.10 and the final ratio (FR) of each individual reference probe in the patient samples should be between 0.80 and 1.20. When these criteria are fulfilled, the following cut-off values for the FR of the probes can be used to interpret MLPA results for autosomal chromosomes or pseudo-autosomal regions:

Copy number status	Final ratio (FR)
Normal	0.80 < FR < 1.20
Homozygous deletion	FR = 0
Heterozygous deletion	0.40 < FR < 0.65
Heterozygous duplication	1.30 < FR < 1.65
Heterozygous triplication/homozygous duplication	1.75 < FR < 2.15
Ambiguous copy number	All other values

Note: The term "dosage quotient", used in older product description versions, has been replaced by "final ratio" to become consistent with the terminology of the Coffalyser.Net software. (Calculations, cut-offs and interpretation remain unchanged.) Please note that the Coffalyser.Net software also shows arbitrary borders as part of the statistical analysis of results obtained in an experiment. As such, arbitrary borders are different from the final ratio cut-off values shown here above.

- Arranging probes according to chromosomal location facilitates interpretation of the results and may reveal more subtle changes such as those observed in mosaic cases. Analysis of parental samples may be necessary for correct interpretation of complex results.
- False positive results: Please note that abnormalities detected by a single probe (or multiple consecutive probes) still have a considerable chance of being a false positive result. Sequence changes (e.g. SNVs, point mutations) in the target sequence detected by a probe can be one cause. Incomplete DNA denaturation (e.g. due to salt contamination) can also lead to a decreased probe signal, in particular for probes located in or near a GC-rich region. The use of an additional purification step or an alternative DNA extraction method may resolve such cases. Additionally, contamination of DNA samples with cDNA or PCR amplicons of individual exons can lead to an increased probe signal (Varga et al. 2012). Analysis of an independently collected secondary DNA sample can exclude these kinds of contamination artefacts.
- Normal copy number variation in healthy individuals is described in the database of genomic variants: http://dgv.tcag.ca/dgv/app/home. Users should always consult the latest update of the database and scientific literature when interpreting their findings.
- Not all abnormalities detected by MLPA are pathogenic. In some genes, intragenic deletions are known that result in very mild or no disease (as described for *DMD* by Schwartz et al. 2007). For many genes, more than one transcript variant exists. Copy number changes of exons that are not present in all transcript variants may not have clinical significance. Duplications that include the first or last exon of a gene (e.g. exons 1-3) might not result in inactivation of that gene copy.
- Copy number changes detected by reference probes or flanking probes are unlikely to have any relation to the condition tested for.
- False results can be obtained if one or more peaks are off-scale. For example, a duplication of one or more exons can be obscured when peaks are off-scale, resulting in a false negative result. The risk on off-scale peaks is higher when probemixes are used that contain a relatively low number of probes. Coffalyser.Net

software warns for off-scale peaks while other software does not. If one or more peaks are off-scale, rerun the PCR products using either: a lower injection voltage or a shorter injection time, or a reduced amount of sample by diluting PCR products.

Limitations of the procedure

- In most populations, the major cause of genetic defects in the *GLDC*, *AMT*, and *GCSH* genes are small (point) mutations, most of which will not be detected by using SALSA MLPA Probemix P209 Glycine Encephalopathy.
- MLPA cannot detect any changes that lie outside the target sequence of the probes and will not detect copy number neutral inversions or translocations. Even when MLPA did not detect any aberrations, the possibility remains that biological changes in that gene or chromosomal region *do* exist but remain undetected.
- Sequence changes (e.g. SNVs, point mutations) in the target sequence detected by a probe can cause false positive results. Mutations/SNVs (even when >20 nt from the probe ligation site) can reduce the probe signal by preventing ligation of the probe oligonucleotides or by destabilising the binding of a probe oligonucleotide to the sample DNA.

Confirmation of results

Copy number changes detected by only a single probe always require confirmation by another method. An apparent deletion detected by a single probe can be due to e.g. a mutation/polymorphism that prevents ligation or destabilises the binding of probe oligonucleotides to the DNA sample. Sequence analysis can establish whether mutations or polymorphisms are present in the probe target sequence. The finding of a heterozygous mutation or polymorphism indicates that two different alleles of the sequence are present in the sample DNA and that a false positive MLPA result was obtained.

Copy number changes detected by more than one consecutive probe should be confirmed by another independent technique such as long range PCR, qPCR, array CGH or Southern blotting, whenever possible. Deletions/duplications of more than 50 kb in length can often be confirmed by FISH.

LOVD mutation database

https://databases.lovd.nl/shared/genes/. 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 SNVs and unusual results (e.g., a duplication of *GLDC* exons 5 and 7 but not exon 6) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P209-C2 Glycine Encephalopathy

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]			
		Reference	*GLDC*	*AMT*	*GCSH*
64-105	Control fragments – see table in probemix content section for more information				
124	Reference probe 19616-L26275	4p			
130	Reference probe 18709-L24593	5q			
142 «	**GLDC probe** 06850-L06444		**Exon 1**		
148	**AMT probe** 19812-L26936			**Exon 3**	
154	**GLDC probe** 19813-L26935		**Exon 10**		
160	**GLDC probe** 06865-L06459		**Exon 16**		
166	**GLDC probe** 19669-L27064		**Exon 19**		
172	**GLDC probe** 19814-L26649		**Exon 6**		
180	**GLDC probe** 19815-L26650		**Exon 25**		
188	**GLDC probe** 19816-L26651		**Exon 8**		
193	Reference probe 05986-L05411	20p			
199	**GCSH probe** 19817-L26933				**Exon 1**
205	**GLDC probe** 19818-L26653		**Exon 22**		
210 Ж	**GLDC probe** 19819-SP0874-L27070		**Exon 7**		
218	Reference probe 14288-L27063	15q			
225 «	**GLDC probe** 19820-L26655		**Exon 1**		
229	**GLDC probe** 19821-L26656		**Exon 11**		
235	**AMT probe** 19822-L26657			**Exon 4**	
240	**GCSH probe** 19823-L26934				**Exon 4**
247	**GLDC probe** 06870-L06464		**Exon 21**		
254	**GLDC probe** 19824-L30207		**Exon 9**		
261	**GLDC probe** 19825-L30208		**Exon 13**		
265	**AMT probe** 19826-L30398			**Exon 2**	
274	Reference probe 01039-L00617	8q			
281	**GLDC probe** 19827-L26662		**Exon 15**		
286	**AMT probe** 19828-L26932			**Exon 9**	
292	**GLDC probe** 19829-L26664		**Exon 17**		
299	**GCSH probe** 19830-L26665				**Exon 5**
307	**GLDC probe** 19831-L26666		**Exon 3**		
313	**AMT probe** 19832-L27062			**Exon 1**	
319	Reference probe 08800-L08860	2p			
328 «	**GLDC probe** 19833-L26668		**Exon 2**		
337	**GLDC probe** 19834-L26669		**Exon 5**		
346	**GCSH probe** 19835-L26931				**Exon 3**
352 Ж	**AMT probe** 19836-SP0875-L27164			**Exon 6**	
359	**GLDC probe** 19837-L26930		**Exon 20**		
364	Reference probe 14768-L16465	1q			
372	**GLDC probe** 19838-L27061		**Exon 24**		
379	**GLDC probe** 19839-L26674		**Exon 18**		
388	**GCSH probe** 19840-L27163				**Exon 2**
393	**AMT probe** 19841-L26676			**Exon 8**	
400	Reference probe 03004-L02443	19p			
409	**GLDC probe** 19842-L27377		**Exon 23**		
417	**AMT probe** 20062-L27361			**Exon 5**	
424	**GLDC probe** 19844-L26679		**Exon 14**		
427	**GLDC probe** 19845-L26928		**Exon 12**		
438	**AMT probe** 19846-L26681			**Exon 7**	
445	**GLDC probe** 19847-L26682		**Exon 4**		
454	Reference probe 12526-L23849	4q			
463	Reference probe 00979-L00568	10p			

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

« 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.
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.

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. P209-C2 probes arranged according to chromosomal location

Table 2a. *GLDC*

Length (nt)	SALSA MLPA probe	*GLDC* exon[a]	Ligation site NM_000170.3	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*231-233 (Exon 1)*		
225 «	19820-L26655	Exon 1	1449 nt before exon 1	GCTGTCTCATGA-CAGTTTTAGCAA	1.5 kb
142 « #	06850-L06444	Exon 1	112-113	GTCCGGCCGACT-GTCCAGCGAAAG	0.9 kb
328 «	19833-L26668	Exon 2	490-491	ATTTTAGAGCAT-TGATGAATTGAT	24.4 kb
307	19831-L26666	Exon 3	582-581, reverse	ATGCAGAGTTGC-AAGGATTTCATT	10.0 kb
445	19847-L26682	Exon 4	707-706, reverse	GGAGTATACTGG-GTGATCCTGCAA	3.8 kb
337	19834-L26669	Exon 5	942-943	AGACTCGAGCCA-AGTAATTAATTT	1.4 kb
172	19814-L26649	Exon 6	1088-1087, reverse	ATACCTACCCCA-CTCTGATGAGCT	0.5 kb
210 Ж #	19819-SP0874-L27070	Exon 7	1220-1219 and 1190-1189, reverse	AAAAATGCTGCA-30 nt spanning oligo-AATCTCTGGGAG	2.5 kb
188	19816-L26651	Exon 8	3 nt after exon 8, reverse	AGACGTGTGATT-TACCTGAGCTGT	7.0 kb
254	19824-L30207	Exon 9	1388-1387, reverse	TTCGCCAAGAGG-GCCTAAAAGATA	2.1 kb
154	19813-L26935	Exon 10	3 nt before exon 10	TCCTATCTTGTG-TAGGTCTCAAGC	0.8 kb
229	19821-L26656	Exon 11	1706-1705, reverse	CTTACTGCAGAT-GACTCACAACCA	2.9 kb
427	19845-L26928	Exon 12	1723-1724	GGAACTGGTTGC-TGAAAGCATGGG	0.6 kb
261	19825-L30208	Exon 13	1883-1882, reverse	AGTGGAATCATG-CTGTGAACAAGG	0.2 kb
424	19844-L26679	Exon 14	1905-1906	AGGGATCCTGCA-CCATGAAACTGA	1.3 kb
281	19827-L26662	Exon 15	2075-2076	TGTTTCCAGCCA-AACAGGTAAGGG	21.8 kb
160	06865-L06459	Exon 16	7 nt after exon 16	GAACGGTGAGTA-TGGCAGGAGGTG	6.8 kb
292	19829-L26664	Exon 17	4 nt after exon 17	AGGCCATGGTAC-TTGTCTTCTCCT	2.4 kb
379	19839-L26674	Exon 18	2428-2427, reverse	TTCCCACCTGAG-CATTCATATTTG	1.5 kb
166	19669-L27064	Exon 19	7 nt after exon 19	GGAGTGTAAGTT-CTGGGCTGCTGG	1.3 kb
359	19837-L26930	Exon 20	2681-2680, reverse	CTCACCTTGATA-TAAGCCCAGGAA	2.5 kb
247 #	06870-L06464	Exon 21	2705-2704, reverse	GCTTGTTTAAGA-CCCTTGCCTCCC	10.8 kb
205	19818-L26653	Exon 22	2882-2881, reverse	TAATCCTGGAGT-CTCTTGGCCACA	4.0 kb
409	19842-L27377	Exon 23	16 nt after exon 23	GTAGGCCCTGGA-ACATTGCTTGAA	1.3 kb
372	19838-L27061	Exon 24	3136-3137	CAGAGAGGTGGC-AGCATTCCCACT	2.0 kb
180 #	19815-L26650	Exon 25	3598-3597, reverse	AGCCTCTATGAC-ATCTGCAAACTT	
		stop codon	*3291-3293 (Exon 25)*		

Table 2b. *AMT*

Length (nt)	SALSA MLPA probe	*AMT* exon[a]	Ligation site NM_000481.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*24-26 (Exon 1)*		
313	19832-L27062	Exon 1	123 nt before exon 1	TGCTCTAAATCC-CAGCCTGCCCTT	0.5 kb
265	19826-L30398	Exon 2	262-263	CTCGCTCTTTGA-CGTGTCTCATAT	0.6 kb
148	19812-L26936	Exon 3	290-291	CAGACCAAGATA-CTTGGTAGTGAC	1.3 kb
235	19822-L26657	Exon 4	419-420	GACTTGATTGTA-ACCAATACTTCT	0.5 kb
417	20062-L27361	Exon 5	497-496, reverse	TCCCTGACCTTG-TCCTAAAAGACA	0.5 kb
352 Ж	19836-SP0875-L27164	Exon 6	667-668 and 697-698	GGTGTTTGGCGT-30 nt spanning oligo-CACAGGAGAGGA	0.2 kb
438	19846-L26681	Exon 7	751-750, reverse	TAGCTGTTGCCA-GGTGAACTGCCC	1.2 kb

393	19841-L26676	Exon 8	909-908, reverse	AGCAGCTCGGCG-GCGCTTCCCTGG	0.9 kb
286	19828-L26932	Exon 9	1723-1722, reverse	CTGTGAGTCAGC-AATCATTCCTGA	
		stop codon	*1233-1235 (Exon 9)*		

Table 2c. *GCSH*

Length (nt)	SALSA MLPA probe	*GCSH* exon[a]	Ligation site NM_004483.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*118-120 (Exon 1)*		
199	19817-L26933	Exon 1	256-255, reverse	ACCCGAGAGCAG-AGCGGGTCCAGT	5.6 kb
388	19840-L27163	Exon 2	24 nt after exon 2, reverse	GCACACTGGGAC-AAATATTTCAAT	2.9 kb
346	19835-L26931	Exon 3	355-354, reverse	AACAACATCTCC-CAACGCTTCCTA	3.2 kb
240	19823-L26934	Exon 4	534-535	AAATCTTGTTAT-GAAGATGGTAAG	1.5 kb
299	19830-L26665	Exon 5	553-554	GTTGGCTGATCA-AGATGACACTGA	
		stop codon	*637-639 (Exon 5)*		

[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.

« 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.
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.
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.

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.

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.
- 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 P209 Glycine Encephalopathy

- Azize NAA et al. (2014). Mutation analysis of glycine decarboxylase, aminomethyltransferase and glycine cleavage system protein-H genes in 13 unrelated families with glycine encephalopathy. *J Hum Genet*, 59(11), 593-597.
- Bayrak H et al. (2021). Genotypic and phenotypic features in Turkish patients with classic nonketotic hyperglycinemia. *Metab Brain Dis*, 1-10.
- Khraim W et al. (2017). Clinical heterogeneity of glycine encephalopathy in three Palestinian siblings: A novel mutation in the glycine decarboxylase (GLDC) gene. *Brain Dev*, 39(7), 601-605.
- Lin Y et al. (2018). A novel compound heterozygous variant identified in GLDC gene in a Chinese family with non-ketotic hyperglycinemia. *BMC Med Genet*, 19(1), 1-6.
- Sel ÇG et al. (2018). Nonketotic hyperglycinemia: Clinical range and outcome of a rare neurometabolic disease in a single-center. *Brain Dev*, 40(10), 865-875.

P209 product history	
Version	*Modification*
C2	Compared to previous version, one reference probe has been replaced and the length of several probes adjusted.
C1	Compared to previous version, probes for the *AMT* and *GCSH* gene have been added. Most of the GLDC probes have been redesigned, and reference probes have been replaced.
B1	Five reference probes have been replaced.
A1	First release.

Implemented changes in the product description

Version C2-01 – 23 September 2021 (04P)
- Product description rewritten and adapted to a new template.
- Ligation sites of the probes targeting the *GLDC*, *AMT*, and *GCSH* genes updated according to new version of the NM_ reference sequence.
- Warning added to Table 2 for probe specificity relying on a single nucleotide difference between target gene and related gene or pseudogene.

Version 09 – 06 December 2017 (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).
- Various minor textual and layout changes.

Version 08 (53)
- Product description adapted to a new product version (version number changed, lot number added, changes in Table 1 and Table 2, new picture included).
- The name of the product has been changed.
- Various textual changes.
- Various layout changes.

Version 07 (48)
- Electropherogram pictures using the new MLPA buffer (introduced in December 2012) added.

Version 06 (46)
- Remark on RefSeqGene standard added below Table 2.
- Small correction of chromosomal locations in Table 1 and 2.
- Small changes of probe lengths in Table 1 and 2 in order to better reflect the true lengths of the amplification products.
- Various minor textual changes throughout the document.

Version 05 (44)
- 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).
- Tables have been numbered.
- Data analysis section has been modified.
- Various minor textual changes on page 1.

Various minor layout changes.

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