Product Description
SALSA® MLPA® Probemix P059-B2 Dystonia

To be used with the MLPA General Protocol.

Version B2
For complete product history see page 8.

Catalogue numbers:
- **P059-025R:** SALSA MLPA Probemix P059 Dystonia, 25 reactions.
- **P059-050R:** SALSA MLPA Probemix P059 Dystonia, 50 reactions.
- **P059-100R:** SALSA MLPA Probemix P059 Dystonia, 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 P059 Dystonia is a **research use only (RUO)** assay for the detection of deletions or duplications in the *TOR1A, THAP1, ATP1A3, and PRKRA* genes, which are associated with Dystonia. This probemix can also be used to detect the presence of the c.907_909delGAG point mutation.

Dystonias comprise a heterogeneous group of neurological movement disorders, characterized by involuntary sustained muscle contractions affecting one or more sites of the body. Dystonia can have several causes, including genetic defects. Multiple genes in different forms of dystonia have been described so far. The *TOR1A* gene is associated with early-onset generalized dystonia (DYT1), whereas the *THAP1* gene is associated with adolescent-onset segmental/generalized dystonia (DYT6), and the *ATP1A3* (DYT12) and *PRKRA* (DYT16) genes are associated with rapid onset dystonia with parkinsonism and autosomal recessive dystonia with parkinsonism, respectively. This probemix can also detect the presence of the 3-bp deletion c.907_909delGAG involving the highly conserved GAGGAG sequence in exon 5 of the *TOR1A* gene.

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1155/.

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 *TOR1A, THAP1, ATP1A3, and PRKRA* exon numbering used in this P059-B2 Dystonia product description is the exon numbering from the LRG_1029, NG_011837.1, LRG_1186, and NG_009053.1 sequences, respectively. 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 or NG 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 P059-B2 Dystonia contains 44 MLPA probes with amplification products between 130 and 483 nucleotides (nt). This includes five probes for the *TOR1A* gene, three probes for the *THAP1* gene, 17 probes for the *ATP1A3* gene, and nine for the *PRKRA* gene Furthermore, this probemix also contains one probe specific for the c.907_909delGAG mutation in the *TOR1A* gene, which will only generate a signal when the mutation is present. In addition, nine 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 Dystonias. 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.

SALSA Binning DNA SD044

The SD044 Binning DNA provided with this probemix can be used for binning of all probes including the mutation-specific probe (166 nt probe 15798-SP0278-L17858 for the c.907_909delGAG mutation). SD044 Binning DNA is a mixture of genomic DNA from healthy individuals and plasmid DNA that contains the target sequence detected by the above mentioned probe. Inclusion of one reaction with 5 µl SD044 Binning DNA in initial MLPA experiments is essential as it can be used to aid in data binning of the peak pattern using Coffalyser.Net software. Furthermore, Binning DNA should be included in the experiment whenever changes have been applied to the set-up of the capillary electrophoresis device (e.g. when capillaries have been renewed). Binning DNA should never be used as a reference sample in the MLPA data analysis, neither should it be used in quantification of mutation signal(s). It is strongly advised that all samples tested are extracted with the same method and derived from the same source of tissue. For further details, please consult the SD044 Binning DNA product description, available online: www.mrcholland.com. **This product is for research use only (RUO).**

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 *TOR1A, THAP1, ATP1A3, and PRKRA* genes are small (point) mutations, except for the c.907_909delGAG mutation in *TOR1A*, none of which will be detected by using SALSA MLPA Probemix P059 Dystonia.
- 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.

MDSGene mutation database

https://www.movementdisorders.org/MDS/Resources/MDSGene.htm. We strongly encourage users to deposit positive results in the Movement Disorder Society Genetic mutation database (MDSGene). 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 *ATP1A3* exons 11 and 13 but not exon 12) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P059-B2 Dystonia

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]				
		Reference	*TOR1A*	*THAP1*	*ATP1A3*	*PRKRA*
64-105	Control fragments – see table in probemix content section for more information					
130	Reference probe 00797-L13645	5q				
136	**ATP1A3 probe** 15794-L17854				**Exon 21**	
142 «	**THAP1 probe** 15795-L17855			**Exon 1**		
148	**TOR1A probe** 15796-L17856		**Exon 4**			
154 «	**ATP1A3 probe** 17207-L20840				**Exon 1b**	
160 «	**ATP1A3 probe** 15797-L17857				**Exon 9**	
166 Ж §	**TOR1A probe** 15798-SP0278-L17858		**Exon 5**			
178 «	**ATP1A3 probe** 15799-L18987				**Exon 11**	
184	Reference probe 08788-L08812	10q				
191 «	**ATP1A3 probe** 15800-L17861				**Exon 10**	
196 «	**THAP1 probe** 15801-L21051			**Exon 2**		
202	**TOR1A probe** 15802-L17863		**Exon 5**			
208 Ø	**PRKRA probe** 15803-L17864					**Intron 7**
214	Reference probe 10698-L11280	6p				
220	**ATP1A3 probe** 15804-L17865				**Exon 18**	
227 Ж	**PRKRA probe** 15805-SP0279-L20810					**Exon 8**
232 «	**ATP1A3 probe** 15806-L20669				**Exon 5**	
238	**THAP1 probe** 15807-L17868			**Exon 3**		
250	Reference probe 15065-L16823	15q				
256	**ATP1A3 probe** 15809-L17870				**Exon 13**	
263	**PRKRA probe** 22093-L31061					**Exon 5**
274 «	**ATP1A3 probe** 15811-L17872				**Exon 12**	
283	**PRKRA probe** 15812-L19901					**Exon 7**
292	Reference probe 13325-L14751	18q				
301	**ATP1A3 probe** 15813-L17874				**Exon 19**	
310	**PRKRA probe** 15814-L17875					**Exon 2c**
319 «	**ATP1A3 probe** 15815-L30927				**Exon 6**	
328	**TOR1A probe** 15816-L17877		**Exon 3**			
337	**ATP1A3 probe** 15817-L17878				**Exon 20**	
346	Reference probe 08684-L08696	13q				
353 «	**ATP1A3 probe** 17267-L21094				**Exon 3b**	
364	**PRKRA probe** 15819-L17880					**Exon 6**
373	**ATP1A3 probe** 15820-L17881				**Exon 14**	
382	**PRKRA probe** 15821-L18424					**Exon 3**
391 «	**ATP1A3 probe** 15822-L17883				**Exon 7**	
400	Reference probe 09433-L09682	11q				
409	**TOR1A probe** 15823-L17884		**Exon 1**			
420	**ATP1A3 probe** 15824-L17885				**Exon 16**	
427	**PRKRA probe** 15825-L17886					**Exon 3**
436 «	**ATP1A3 probe** 15826-L17887				**Exon 4**	
445	Reference probe 05916-L14204	21q				
463	**PRKRA probe** 15828-L17889					**Exon 4**
474	**TOR1A probe** 15829-L17890		**Exon 2**			
483	Reference probe 13439-L14894	17p				

[a] See section Exon numbering on page 1 for more information.

§ Mutation-specific probe. This probe will only generate a signal when the c.907_909delGAG mutation is present. It has been tested on artificial DNA **but not on positive human samples!**

« 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.

Ø Intron probe. Only included to help determine the extent of a deletion/duplication. Copy number alterations of only this probe are of unknown clinical significance.

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. P059-B2 probes arranged according to chromosomal location

Table 2a. *PRKRA*

Length (nt)	SALSA MLPA probe	*PRKRA* exon[a]	Ligation site NM_003690.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*146-148 (Exon 1)*		
310	15814-L17875	Exon 2c	77 nt after exon 2c	AGTTCGGAAAAG-TTCTCTTTTTGC	2.6 kb
427	15825-L17886	Exon 3	392-393	GTGAAGGTACAA-GTAAGAAGCTGG	0.2 kb
382	15821-L18424	Exon 3	104 nt after exon 3	AACAGTTGTTAG-CATCCTACCTCT	3.0 kb
463	15828-L17889	Exon 4	28 nt after exon 4	TTTGCCTACTGA-TGAAATATATAA	1.1 kb
263	22093-L31061	Exon 5	657-658	ATTTATGGAAAC-TGGTACTTATTT	1.7 kb
364	15819-L17880	Exon 6	65 nt after exon 6	GGAAACTTTCCT-TGATTTCTTATT	5.2 kb
283	15812-L19901	Exon 7	47 nt before exon 7	GTACGGGTGTTG-GAACCCAGTCCT	2.5 kb
208 Ø	15803-L17864	Intron 7	1555 nt before exon 8	AACCTAGATATT-CTCCAAAGGAGA	2.5 kb
227 Ж	15805-SP0279-L20810	Exon 8	103 nt after exon 8 and 135 nt after exon 8	AAAAGCATTTGA-32 nt spanning oligo-CTCTTTCGGAGG	
		stop codon	*1085-1087 (Exon 8)*		

Table 2b. *THAP1*

Length (nt)	SALSA MLPA probe	*THAP1* exon[a]	Ligation site NM_018105.3	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*232-234 (Exon 1)*		
142 «	15795-L17855	Exon 1	275-276	GAACCGCTACGA-CAAGGACAAGCC	3.8 kb
196 «	15801-L21051	Exon 2	406-407	CAGAGCACTTTA-CTCCAGACTGCT	1.3 kb
238	15807-L17868	Exon 3	810-811	AAAGACGACGTA-TCAGAAAGAGGT	
		stop codon	*871-873 (Exon 3)*		

Table 2c. *TOR1A*

Length (nt)	SALSA MLPA probe	*TOR1A* exon[a]	Ligation site NM_000113.3	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*52-54 (Exon 1)*		
409	15823-L17884	Exon 1	178-179	ACCCGCGTCTCT-ACTGCCTCTTCG	1.3 kb
474	15829-L17890	Exon 2	424-425	AGGGTGGTCTGA-ACAGTGACTATG	3.8 kb
328	15816-L17877	Exon 3	547-548	GTGCGAGGTCCA-TCTTCATATTTG	0.3 kb
148	15796-L17856	Exon 4	750-751	GACATCAAGCTC-AAAGACATTGAA	4.5 kb
166 § Ж	15798-SP0278-L17858	Exon 5	955-954 and 920-919, reverse	AAATGTCATCTC-35 nt spanning oligo-AGCCTCGGGACT	0.7 kb
202	15802-L17863	Exon 5	1666-1667	GACAAGTAGGTA-AGAGGACGCCTT	
		stop codon	*1048-1050 (Exon 5)*		

Table 2d. *ATP1A3*

Length (nt)	SALSA MLPA probe	*ATP1A3* exon[a]	Ligation site NM_152296.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*155-157 (Exon 1)*		
154 «	17207-L20840	Exon 1b	155-156	GAGCCGCCAAGA-TGGGGGTAGGTG	5.5 kb
353 «	17267-L21094	Exon 3b	162-163	CACCTCGCAGGA-CAAGAAAGATGA	0.2 kb
436 «	15826-L17887	Exon 4	294-295	GAAATACAACAC-AGACTGTGTGCA	0.2 kb
232 «	15806-L20669	Exon 5	335-336	AAGCCCAGGAGA-TCCTGGCCCGGG	1.9 kb
319 «	15815-L30927	Exon 6	23 nt before exon 6, reverse	TGTGGGGATGTT-GATCAGGGGCCG	0.4 kb
391 «	15822-L17883	Exon 7	724-725	GACCGAGTGCCA-GCTGACCTGCGG	1.0 kb
160 «	15797-L17857	Exon 9	1120-1121	GTGGCCAATGTC-CCAGAGGGTCTG	2.8 kb
191 «	15800-L17861	Exon 10	26 nt before exon 10	TTGTCCCTGTAA-CTTGCCTGCCCT	0.3 kb
178 «	15799-L18987	Exon 11	1369-1370	GACAAGAGTTCG-CACACCTGGGTG	0.2 kb
274 «	15811-L17872	Exon 12	1515-1516	CGAGCTGTCCTC-TGGCTCCGTGAA	2.8 kb
256	15809-L17870	Exon 13	1627-1628	CCCAACGACAAC-CGATACCTGCTG	0.5 kb
373	15820-L17881	Exon 14	1849-1850	GACTGTGATGAC-GTGAACTTCACC	1.7 kb
420	15824-L17885	Exon 16	2134-2135	GGCACCGACCTC-AAGGACTTCACC	6.0 kb
220	15804-L17865	Exon 18	2440-2441	TTCGACAACCTA-AAGAAGTCCATT	0.2 kb
301	15813-L17874	Exon 19	2602-2603	GCGTACGAGGCT-GCCGAAAGCGAC	0.7 kb
337	15817-L17878	Exon 20	2713-2714	ATCCAGGCTCTC-GGTGGCTTCTTC	0.7 kb
136	15794-L17854	Exon 21	2847-2848	CCTGCAGACATA-CGAGCAGAGGAA	
		stop codon	*3194-3196 (Exon 23)*		

[a] See section Exon numbering on page 1 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.

§ Mutation-specific probe. This probe will only generate a signal when the c.907_909delGAG mutation is present. It has been tested on artificial DNA **but not on positive human samples!**

« 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.

Ø Intron probe. Only included to help determine the extent of a deletion/duplication. Copy number alterations of only this probe are of unknown clinical significance.

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.

Related SALSA MLPA probemixes

P099 GCH1-TH-SGCE-PRRT2 Contains probes for the *GCH1, TH, SGCE* and *PRRT2* genes involved in Dystonia.

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 P059 Dystonia

- García-Payá E et al. (2021). An 88.8-kb Novel Deletion of 19q13. 2 Encompassing the ATP1A3Gene Detected by Array CGH in a Patient with Delayed Psychomotor Development, Generalized Hypotonia and Macrocephaly. *Mol Syndromol*, 12(4), 234-239.
- Vila-Pueyo M et al. (2014). Clinical and genetic analysis in alternating hemiplegia of childhood: Ten new patients from Southern Europe. *J Neurol Sci*. 344:37-42.

P059 product history	
Version	*Modification*
B2	Two reference probes have been replaced and the length of several probes adjusted.
B1	One target probe for *ATP1A3* has been removed and one reference probe has been replaced.
A1	First release.

Implemented changes in the product description
Version B2-02 – 13 December 2021 (04P) - Product description rewritten and adapted to a new template. - Ligation sites of the probes targeting the TOR1A, THAP1, and PRKRA genes 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. - Related Probemix P099 added Version B2-01 – 12 July 2018 (01P) - Product description restructured and adapted to a new template. - Product description adapted to a new product version (version number changed, lot number added, changes in Table 1 and Table 2, new picture included). - Exon number and ligation sites of the probes targeting the ATP1A3 gene updated. Version 04 (55) – 05 October 2017 - Product description adapted to a new lot (lot number added, small changes in Table 1 and Table 2, new pictures included). - ATP1A3 exon numbering adjusted. - Warnings added in Table 1 and Table 2: 160 nt probe 15797-L17857, 178 nt probe 15799-L18987, 191 nt probe 15800-L17861, 274 nt probe 15811-L17872, 481 nt probe 15830-L17891. - Various small textual changes.

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