Product Description
SALSA® MLPA® Probemix P107-B3 Neurometabolic disorders

To be used with the MLPA General Protocol.

Version B3
As compared to version B2, three reference probes have been replaced, and three probes have been adjusted in length but not in the sequence detected. For complete product history see page 8.

Catalogue numbers:
- **P107-025R:** SALSA MLPA Probemix P107 Neurometabolic disorders, 25 reactions.
- **P107-050R:** SALSA MLPA Probemix P107 Neurometabolic disorders, 50 reactions.
- **P107-100R:** SALSA MLPA Probemix P107 Neurometabolic disorders, 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 P107 Neurometabolic disorders is a **research use only (RUO)** assay for the detection of deletions or duplications in the D*2HGDH*, *L2HGDH*, *MLYCD* and *MLC1* genes, which are associated with neurometabolic disorders.

The *D2HGDH* gene encodes D-2-hydroxyglutarate dehydrogenase, a mitochondrial enzyme belonging to the FAD-binding oxidoreductase/transferase type 4 family. This enzyme converts D-2-hydroxyglutarate to 2-ketoglutarate. Mutations in the *D2HGDH* gene are present in D-2-hydroxyglutaric aciduria, a rare recessive neurometabolic disorder causing developmental delay, epilepsy, hypotonia, and dysmorphic features.
The *L2HGDH* gene encodes L-2-hydroxyglutarate dehydrogenase, an FAD-dependent enzyme that oxidizes L-2-hydroxyglutarate to alpha-ketoglutarate in a variety of mammalian tissues. Mutations in this gene cause L-2-hydroxyglutaric aciduria, a rare autosomal recessive neurometabolic disorder resulting in moderate to severe intellectual disability.
Malonyl-CoA decarboxylase deficiency is a rare autosomal recessive (liver, brain, heart, and skeletal muscle) metabolic disorder characterized by malonic aciduria, developmental delay, seizures, hypoglycemia, acidosis, short stature and cardiomyopathy. The disorder is caused by mutations in the malonyl-CoA decarboxylase gene (*MLYCD*).
Megalencephalic leukoencephalopathy with subcortical cysts (MLC) is an inherited neurological disorder with macrocephaly before the age of one and slowly progressive deterioration of motor functions. Mutations in the *MLC1* gene, encoding a putative membrane protein, have been identified as a cause for MLC.

The *D2HGDH* gene (10 exons), spans ~34 kb of genomic DNA and is located on 2q37.3, ~242 Mb from the p-telomere (close to the q-telomere). The *L2HGDH* gene (10 exons), spans ~70 kb of genomic DNA and is located on 14q22.1, ~50 Mb from the p-telomere. The *MLYCD* gene (5 exons), spans ~28 kb of genomic DNA and is located on 16q23.3, ~82 Mb from the p-telomere. The *MLC1* gene (12 exons), spans ~26 kb of genomic DNA and is located on 22q13.33, ~49 Mb from the p-telomere.

More information is available at https://www.ncbi.nlm.nih.gov/books/NBK1535/.

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 D*2HGDH*, *L2HGDH*, *MLYCD* and *MLC1* exon numbering used in this P107-B3 Neurometabolic disorders product description is the exon numbering from the MANE project (release version 1.0) based on MANE Select transcripts NM_152783.5 (*D2HGDH*), NM_024884.3 (*L2HGDH*), NM_012213.3 (*MLYCD*) and NM_015166.4 (*MLC1*) as indicated in Table 2. 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 MANE sequence. 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 P107-B3 Neurometabolic disorders contains 44 MLPA probes with amplification products between 130 and 481 nucleotides (nt). This includes five probes for the *D2HGDH* gene, ten probes for the *L2HGDH* gene, five probes for the *MLYCD* gene and 12 probes for the *MLC1* gene. In addition, 12 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 neurometabolic disorders. 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 or in or near the *MLC1* gene. 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 D*2HGDH*, *L2HGDH*, *MLYCD* and *MLC1* genes are small (point) mutations, none of which will be detected by using SALSA MLPA Probemix P107 Neurometabolic disorders.
- 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.

D*2HGDH*, *L2HGDH*, *MLYCD* and *MLC1* mutation databases

https://databases.lovd.nl/shared/genes/D2HGDH
https://databases.lovd.nl/shared/genes/L2HGDH
https://databases.lovd.nl/shared/genes/MLYCD
https://databases.lovd.nl/shared/genes/MLC1

We strongly encourage users to deposit positive results in the Leiden Open Variation Database. Recommendations for the nomenclature to describe deletions/duplications of one or more exons can be found on http://varnomen.hgvs.org/.

Please report copy number changes detected by the reference probes, false positive results due to SNVs and unusual results (e.g., a duplication of *MLC1* exons 5 and 7 but not exon 6) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P107-B3 Neurometabolic disorders

Length (nt)	SALSA MLPA probe		Chromosomal position (hg18)[a]			
		Reference	*D2HGDH*	*L2HGDH*	*MLYCD*	*MLC1*
64-105	Control fragments – see table in probemix content section for more information					
130	Reference probe 00797-L13645	5q				
136 «	**MLC1 probe** 06331-L07451					**Exon 2**
142	**L2HGDH probe** 05594-L05045			**Exon 1**		
148	**D2HGDH probe** 05604-L05055		**Exon 2**			
154 *	Reference probe 10195-L10655	16q				
161	**L2HGDH probe** 05596-L05047			**Exon 3**		
166	**D2HGDH probe** 05606-L05057		**Exon 7**			
172	**MLYCD probe** 07339-L05904				**Exon 5**	
178	**L2HGDH probe** 05603-L05054			**Exon 10**		
184	Reference probe 10067-L10491	8q				
190 «	**MLC1 probe** 06341-L05916					**Exon 12**
196	**MLYCD probe** 06327-L05902				**Exon 3**	
202	**D2HGDH probe** 05605-L05056		**Exon 6**			
208 *	Reference probe 13384-L25019	6q				
214	**MLYCD probe** 06326-L05901				**Exon 2**	
222	**L2HGDH probe** 05602-L32140			**Exon 9**		
227	Reference probe 14739-L16436	4q				
234 ¥	**D2HGDH probe** 05607-L32141		**Exon 9**			
242 ¥	**MLYCD probe** 06328-L33052				**Exon 4**	
247 *	Reference probe 11138-L16379	13q				
252 «	**MLC1 probe** 06332-L05907					**Exon 3**
274	Reference probe 03917-L21563	15q				
283 «	**MLC1 probe** 06340-L20723					**Exon 11**
296 «	**MLC1 probe** 06333-L20725					**Exon 4**
303	Reference probe 09564-L10018	20p				
319 Δ	**MLYCD probe** 07936-L23527				**Exon 1**	
329 «	**MLC1 probe** 06334-L05909					**Exon 5**
337	Reference probe 13869-L17590	7p				
346 «	**MLC1 probe** 06339-L05914					**Exon 10**
355	**L2HGDH probe** 05595-L05046			**Exon 2**		
364	**L2HGDH probe** 05597-L05048			**Exon 4**		
373 «	**MLC1 probe** 06335-L05910					**Exon 6**
384 ¥	**D2HGDH probe** 07365-L33051		**Exon 10**			
391	**L2HGDH probe** 05601-L05052			**Exon 8**		
400 «	**MLC1 probe** 06336-L05911					**Exon 7**
409	**L2HGDH probe** 05598-L05049			**Exon 5**		
417	**L2HGDH probe** 07336-L05050			**Exon 6**		
427	Reference probe 15731-L17711	21q				
438 «	**MLC1 probe** 06338-L32181					**Exon 9**
445	**L2HGDH probe** 07337-L05051			**Exon 7**		
454	Reference probe 14844-L16552	18q				
463 «	**MLC1 probe** 06337-L20726					**Exon 8**
471 «	**MLC1 probe** 06330-L20727					**Exon 1**
481	Reference probe 13595-L15052	1q				

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

* New in version B3.
¥ Changed in version B3. Minor alteration, no change in sequence detected.
Δ More variable. This probe may be sensitive to certain experimental variations. Aberrant results should be treated with caution.
« 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.

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. P107-B3 probes arranged according to chromosomal location

Table 2a. *D2HGDH* gene

Length (nt)	SALSA MLPA probe	*D2HGDH* exon[a]	Ligation site NM_152783.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*159-161 (Exon 2)*		
148	05604-L05055	Exon 2	343-344	GTTCTCCACGGT-GTCTAAGCAGGA	9.4 kb
202	05605-L05056	Exon 6	934-935	CATCGGGTCGGA-GGGCACTTTGGG	5.4 kb
166	05606-L05057	Exon 7	1086-1087	TCCTGTCTGCAT-TCGAGTTCATGG	5.7 kb
234	05607-L32141	Exon 9	1411-1412	CGTGACTGACCT-GCGCGCCCGCCT	12.0 kb
384	07365-L33051	Exon 10	1681-1682	GCTGGACCCCAA-GGGCATCCTCAA	
		stop codon	*1722-1724 (Exon 10)*		

Table 2b. *L2HGDH* gene

Length (nt)	SALSA MLPA probe	*L2HGDH* exon[a]	Ligation site NM_024884.3	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*80-82 (Exon 1)*		
142	05594-L05045	Exon 1	48-49	GTGGCTTCTTCT-GAGCGCTGAGGG	9.2 kb
355	05595-L05046	Exon 2	272-273	TTGCCTCTGCCA-GAGCACTCATCC	0.8 kb
161	05596-L05047	Exon 3	361-362	GGACATAACAGT-GGTGTCATACAT	7.9 kb
364	05597-L05048	Exon 4	540-541	GGCCCTATATGA-GAAAGGCCTCCA	10.2 kb
409	05598-L05049	Exon 5	684-685	GGCTTTGTCATT-TGCCCAGGATTT	5.5 kb
417	07336-L05050	Exon 6	817-818	AAGAATACAAAG-GTAAAGATTCTT	9.2 kb
445	07337-L05051	Exon 7	868-869	GGACTTTACTCA-GACCGTATTTCA	1.4 kb
391	05601-L05052	Exon 8	1015-1016	CCTTTCCTAGGA-GTTCACTTCACA	2.5 kb
222	05602-L32140	Exon 9	1224-1225	TGGTGCAACAGT-GAAGTATCTTCA	18.2 kb
178	05603-L05054	Exon 10	1368-1369	GGATATTGGAAA-TCGCATTCTTCA	
		stop codon	*1469-1471 (Exon 10)*		

Table 2c. *MLYCD* gene

Length (nt)	SALSA MLPA probe	*MLYCD* exon[a]	Ligation site NM_012213.3	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*31-33 (Exon 1)*		
319 Δ	07936-L23527	Exon 1	533-532 reverse	CCTCCACCAGCT-TGAGGGCCTGCG	7.4 kb
214	06326-L05901	Exon 2	629-630	CCTAGAACGGGT-TACCTGGCATTC	1.2 kb
196	06327-L05902	Exon 3	804-803 reverse	GAGATGTCACCA-GTCAGTGCCACG	4.0 kb
242	06328-L33052	Exon 4	893-892 reverse	TGATGGAATAAA-AGATCGCAGCAG	3.2 kb
172	07339-L05904	Exon 5	1455-1456	AAGATCATCAAA-GCCTCTGAGCAG	
		stop codon	*1510-1512 (Exon 5)*		

Table 2d. *MLC1* gene

Length (nt)	SALSA MLPA probe	*MLC1* exon[a]	Ligation site NM_015166.4	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
		start codon	*132-134 (Exon 2)*		
471 «	06330-L20727	Exon 1	17 nt before exon 1	TCAGCTCAAGTT-TGCTGAGCTTTT	0.6 kb
136 «	06331-L07451	Exon 2	228-229	CCCCAGACGCGA-AGCCGAGCGACC	1.7 kb
252 «	06332-L05907	Exon 3	335-336	ACCTCGGGGTTT-TCGCTGTACCTG	2.8 kb
296 «	06333-L20725	Exon 4	423-424	CAATTGTGAGCT-TCACCGTCTCCA	0.4 kb
329 «	06334-L05909	Exon 5	486-487	TTGTTTCCACGT-TTGCTGTGACCA	2.5 kb
373 «	06335-L05910	Exon 6	589-590	GCTCCTGCTGGA-GCTGCTCATGGC	0.6 kb
400 «	06336-L05911	Exon 7	682-683	CAGCGCCAACAT-TCTGGACGAAGT	2.6 kb
463 «	06337-L20726	Exon 8	791-792	CTGAACGTGGAT-GACTCAGTTTCA	3.7 kb
438 «	06338-L32181	Exon 9	8 nt after exon 9	TCTGGTGGGTGA-ACCCCTCAGCCC	2.1 kb
346 «	06339-L05914	Exon 10	992-993	ATGAGAATCGTG-GAGATGTTTAAG	4.4 kb
283 «	06340-L20723	Exon 11	1120-1121	CGTGCGCTTCAA-GGTCAGTGCAAG	2.5 kb
190 «	06341-L05916	Exon 12	1233-1234	AGGAGAAAGCCT-GGAGAGCCGTCG	
		stop codon	*1263-1265 (Exon 12)*		

[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.

Δ More variable. This probe may be sensitive to certain experimental variations. Aberrant results should be treated with caution.
« 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.

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

- P025 Canavan: Contains probes for the *ASPA* gene.
- P079 OTC: Contains probes for the *OTC* gene.

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 P107 Neurometabolic disorders

- Cao B et al. (2016). Ten novel mutations in Chinese patients with megalencephalic leukoencephalopathy with subcortical cysts and a long-term follow-up research. *PLoS One*. 11:e0157258.
- Choi SA et al. (2017). A unique mutational spectrum of MLC1 in Korean patients with megalencephalic leukoencephalopathy with subcortical cysts: P. Ala275Asp founder mutation and maternal uniparental disomy of chromosome 22. *Ann Lab Med*. 37:516.
- Lin AP et al. (2015). D2HGDH regulates alpha-ketoglutarate levels and dioxygenase function by modulating IDH2. *Nat Commun*. 6:7768.
- Kranendijk M et al. (2010). Evidence for genetic heterogeneity in D-2-hydroxyglutaric aciduria. *Hum Mutat*. 31:279-283.
- Scheper GC et al. (2010). Analysis of CLCN2 as candidate gene for megalencephalic leukoencepholopathy with subcortical cysts. *Genet Test Mol Biomarkers*. 14:255-257.

- Steenweg ME et al. (2010). An overview of L-2-hydroxyglutarate dehydrogenase gene (L2HGDH) variants: a genotype-phenotype study. *Hum Mutat*. 31:380-390.

P107 product history	
Version	*Modification*
B3	Three reference probes have been replaced, and three probes have been adjusted in length but not in the sequence detected.
B2	Three reference probes have been removed, one reference probe has been replaced and two probe lengths have been adjusted.
B1	The probes for the *ASPA* gene have been removed, as well as one probe for exon 1 of *MLYCD*. Several reference probes have been included.
A1	First release.

Implemented changes in the product description
Version B3-02 – 10 December 2024 (04P) - The term 'mental retardation' is considered outdated and was updated to 'intellectual disability' where appropriate. Version B3-01 – 22 February 2024 (04P) - 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). - Various minor textual or layout changes. - Ligation sites of the probes targeting the *MLYCD* and *MLC1* genes updated according to new versions of the NM_ reference sequences. Version B2-01 – 17 April 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). - Ligation sites of the probes targeting the *D2HGDH* and *L2HGDH* gene updated according to new version of the NM_ reference sequence.

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