Product Description
SALSA® MLPA® Probemix P426-A2 Cystinuria

To be used with the MLPA General Protocol.

Version A2
For complete product history see page 8.

Catalogue numbers:
- **P426-025R:** SALSA MLPA Probemix P426 Cystinuria, 25 reactions.
- **P426-050R:** SALSA MLPA Probemix P426 Cystinuria, 50 reactions.
- **P426-100R:** SALSA MLPA Probemix P426 Cystinuria, 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 P426 Cystinuria is a **research use only (RUO)** assay for the detection of deletions or duplications in the *SLC3A1*, *PREPL* and *SLC7A9* genes, which are associated with cystinuria and hypotonia-cystinuria syndrome.

Cystinuria (OMIM #220100) is a disorder characterised by impaired reabsorption of cystine and dibasic amino acids (lysine, ornithine and arginine) in the brush border membrane of the proximal renal tubule and in the epithelial cells of the gastrointestinal tract. This eventually leads to accumulation of (cystine) crystals or stones in the kidneys and bladder, resulting in obstructive uropathy, pyelonephritis and sometimes renal failure. Thus far, two genes have been identified to cause cystinuria, *SLC3A1* and *SLC7A9*, which encode parts of a transporter protein complex.

A large number of mutations in these genes have been identified in cystinuria, including deletions and duplications. Larger deletions affecting *SLC3A1* might result in the so-called hypotonia-cystinuria syndrome (OMIM #606407). This autosomal recessive congenital disorder is associated with deletions of at least the *SLC3A1* and nearby *PREPL* genes on chromosome 2p21. The main clinical features include a generalised hypotonia at birth, failure to thrive, intellectual disability and cystinuria.

SLC3A1 (~46 kb of genomic DNA; 10 exons) and *PREPL* (~41 kb of genomic DNA; 15 exons) are consecutively located on chromosome 2p21, about 44 Mb from the p-telomere. The *SLC7A9* gene (13 exons) spans ~39 kb of genomic DNA and is located on chromosome 19q13.11, about 38 Mb from the p-telomere.

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 *SLC3A1* exon numbering used in this P426-A2 Cystinuria product description is the exon numbering from the NG_008233.1 sequence. The *PREPL* exon numbering used in this P426-A2 Cystinuria product description is the exon numbering from the NG_016429.1 sequence. The *SLC7A9* exon numbering used in this P426-A2 Cystinuria product description is the exon numbering from the NG_008258.1 sequence. 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 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 P426-A2 Cystinuria contains 48 MLPA probes with amplification products between 124 and 503 nucleotides (nt). This includes ten probes for the *SLC3A1* gene (one for each exon), 13 probes for the *SLC7A9* gene (one for each exon) and 12 probes for the *PREPL* gene (one probe for each exon with the exception of exon 3, 8 and 14). Furthermore, a single probe upstream and a single probe downstream are included for both chromosomal regions to determine the extent of a potential copy number change. 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 cystinuria. It is recommended to use samples of the same sex to facilitate interpretation. 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. Sample ID numbers NA10401 and NA13451 from the Coriell Institute have been tested with this P426-A2 probemix at MRC Holland and can be used as positive control samples to detect a heterozygous duplication and a heterozygous deletion of *SLCA3A1* and *PREPL* and their flanking probes (see Table 2a), respectively. 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 *SLC3A1*, *PREPL* and *SLC7A9* genes are small (point) mutations, most of which will not be detected by using SALSA MLPA Probemix P426 Cystinuria.
- 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.

***SLC3A1*, *PREPL* and *SLC7A9* mutation databases**

https://databases.lovd.nl/shared/genes/SLC3A1, https://databases.lovd.nl/shared/genes/PREPL and https://databases.lovd.nl/shared/genes/SLC7A9. 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 *SLC7A9* exons 8 and 10 but not exon 9) to MRC Holland: info@mrcholland.com.

Table 1. SALSA MLPA Probemix P426-A2 Cystinuria

Length (nt)	SALSA MLPA probe	Chromosomal position (hg18)[a]			
		Reference	*SLC3A1*	*PREPL*	*SLC7A9*
64-105	Control fragments – see table in probemix content section for more information				
124	Reference probe 15370-L13762	7q			
136	Reference probe 16416-L18869	18q			
142	**SLC3A1 probe** 17857-L22116		**Exon 7**		
148	**SLC3A1 probe** 17858-L22117		**Exon 10**		
155	**PREPL probe** 17859-L22118			**Exon 10**	
162	**SLC3A1 probe** 18561-L24710		**Exon 8**		
171	**PREPL probe** 17860-L22119			**Exon 5**	
178	**SLC7A9 probe** 17861-L22120				**Exon 3**
184	**SLC7A9 probe** 17862-L22121				**Exon 12**
190	**SLC7A9 probe** 17863-L22122				**Exon 8**
196 Ж	**PREPL probe** 17864-SP0564-L22123			**Exon 4**	
203	**SLC7A9 probe** 17865-L23449				**Exon 9**
208	Reference probe 08353-L14414	17q			
214	**SLC3A1 probe** 17866-L22125		**Exon 4**		
220	**SLC7A9 probe** 17867-L22126				**Exon 4**
226 ¬	CEP89 probe 17868-L23461				Telomeric
233	**PREPL probe** 17869-L22128			**Exon 15**	
238	**PREPL probe** 17870-L22129			**Exon 7**	
244	**SLC7A9 probe** 17856-L24714				**Exon 11**
250	**PREPL probe** 17871-L22467			**Exon 6**	
257	**SLC7A9 probe** 17872-L24713				**Exon 13**
265	Reference probe 11438-L12168	1q			
274 ¬	PPM1B probe 17873-L22132		Telomeric		
283	**SLC7A9 probe** 17874-L22133				**Exon 10**
292 ¬	CAMKMT probe 17875-L22134			Centromeric	
301	**SLC7A9 probe** 17876-L22135				**Exon 2**
310	**PREPL probe** 17877-L22136			**Exon 13**	
319	Reference probe 17454-L21210	12p			
328	**PREPL probe** 17879-L22138			**Exon 12**	
337	**SLC7A9 probe** 17880-L22139				**Exon 6**
346	**PREPL probe** 17881-L22140			**Exon 11**	
355	Reference probe 15523-L17378	16q			
365 ¥ ¬	TDRD12 probe 22419-L31604				Centromeric
373	**PREPL probe** 17883-L22142			**Exon 2**	
381	**PREPL probe** 18563-L23896			**Exon 9**	
391	**PREPL probe** 17885-L22144			**Exon 1**	
400 Ж	**SLC3A1 probe** 17886-SP0565-L22145		**Exon 1**		
409	Reference probe 16934-L19877	4q			
418	**SLC3A1 probe** 17887-L22146		**Exon 5**		
427 Ж	**SLC7A9 probe** 17888-SP0566-L23462				**Exon 5**
436	**SLC3A1 probe** 17889-L22148		**Exon 3**		
447 Ж	**SLC7A9 probe** 17890-SP0567-L22149				**Exon 7**
454	**SLC3A1 probe** 17891-L23463		**Exon 6**		
463	**SLC7A9 probe** 17892-L22151				**Exon 1**
472	Reference probe 15127-L16898	13q			
481	**SLC3A1 probe** 17893-L22152		**Exon 9**		
493	**SLC3A1 probe** 18564-L23897		**Exon 2**		
503	Reference probe 06676-L23439	11p			

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

¥ Changed in version A2. Minor alteration, no change in sequence detected.

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.

¬ Flanking probe. Included to help determine the extent of a deletion/duplication. Copy number alterations of only the flanking or reference probes are unlikely to be related to the condition tested.

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. P426-A2 probes arranged according to chromosomal location

Table 2a. *SLC3A1* and *PREPL* genes

Length (nt)	SALSA MLPA probe	*SLC3A1*/ *PREPL* exon[a]	Ligation site	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
274 ¬	17873-L22132	*PPM1B* gene		AGCAGAAAATCA-TTAGCATTTCCC	43.0 kb
		SLC3A1	**NM_000341.4**		
		start codon	*57-59 (Exon 1)*		
400 Ж	17886-SP0565-L22145	Exon 1	13-14; 38-39	CTCTTCCACCTC-25 nt spanning oligo-GACATAAGTCGG	5.4 kb
493	18564-L23897	Exon 2	651-652	ATCTGGTTGCAG-CCATACATGATA	0.7 kb
436	17889-L22148	Exon 3	819-818 *reverse*	GATACTTACCCA-GTTGTTGGGTGG	4.4 kb
214	17866-L22125	Exon 4	120 nt before exon 4	TGCTGCTCTCTG-TAGAAGGAAAAC	14.1 kb
418	17887-L22146	Exon 5	1035-1034 *reverse*	TTGGATCTCATC-TCTCAGGTGCTT	1.1 kb
454	17891-L23463	Exon 6	47 nt after exon 6 *reverse*	ATACACTGCAGA-TCACACACTAAG	3.0 kb
142	17857-L22116	Exon 7	1223-1224	TATGCAGAGAGT-ATTGACAGGACC	8.5 kb
162	18561-L24710	Exon 8	1485-1486	CTGGAACTCCTA-TAACTTACTATG	1.2 kb
481	17893-L22152	Exon 9	3 nt before exon 9	GGTCTTTTGACA-TAGAATACCCTT	6.4 kb
148	17858-L22117	Exon 10	1697-1698	CAGCCCAGATCG-GCTTTGAAGTTA	1.1 kb
		stop codon	*2112-2114 (Exon 10)*		
		PREPL	**NM_001171603.1**		
		stop codon	*2556-2558 (Exon 15)*		
233	17869-L22128	Exon 15	2527-2528	CACCAGTGTTTT-CGAGGATCTTAA	1.3 kb
	No probe	Exon 14			
310	17877-L22136	Exon 13	100 nt after exon 13 *reverse*	CTAAATCCTGGG-CAGATGATTTGG	0.6 kb
328	17879-L22138	Exon 12	9 nt after exon 12	CAGGTAGTGAAA-GACAATTGTGTT	3.6 kb
346	17881-L22140	Exon 11	2044-2043 *reverse*	CAGCACTGAAAG-CAGTCAGGGTTG	2.2 kb
155	17859-L22118	Exon 10	1849-1850	GAATTTCAGGCC-TGAGAGGCGGGT	3.5 kb
381	18563-L23896	Exon 9	1688-1689	GACCCAATCACA-AAGACTAGTCGC	6.6 kb
	No probe	Exon 8			
238	17870-L22129	Exon 7	26 nt after exon 7	TCGTTGTTCCTA-TTTGGGCTGTTA	3.4 kb
250	17871-L22467	Exon 6	1049-1050	CAGAGGAACCTT-CGCTGTCATGAC	1.3 kb
171	17860-L22119	Exon 5	915-916	AAGATTCTGAAG-CATCTACCTGTG	0.8 kb
196 Ж	17864-SP0564-L22123	Exon 4	48 nt before exon 4; 2 nt before exon 4	TCAGACTATGAA-46 nt spanning oligo-AGGTTAAACATG	15.1 kb
	No probe	Exon 3			
373	17883-L22142	Exon 2	371-372	AGGGACTTTGAT-ATCATGCAGCAG	1.9 kb
391	17885-L22144	Exon 1	266-267	AAAGATGGCGAA-ATCTGCCTGTTG	11.3 kb
		start codon	*375-377 (Exon 2)*		

Length (nt)	SALSA MLPA probe	*SLC3A1*/ *PREPL* exon[a]	Ligation site	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
292 ¬	17875-L22134	*CAMKMT* gene		TCCAATATACAA-GCATCTTCTGTC	

Table 2b. *SLC7A9* gene

Length (nt)	SALSA MLPA probe	*SLC7A9* exon[a]	Ligation site NM_014270.5	Partial sequence[b] (24 nt adjacent to ligation site)	Distance to next probe
226 ¬	17868-L23461	*CEP89* gene		AGCAGACATCGC-AGCCGTCCAGCA	9.4 kb
		start codon	*194-196 (Exon 2)*		
463	17892-L22151	Exon 1	9 nt before exon 1	GGACTTCCTTTG-CTCCTGGGCACA	1.3 kb
301	17876-L22135	Exon 2	265-266	CCTAAGACCACC-AGTCTCCAAAAG	3.6 kb
178	17861-L22120	Exon 3	30 nt before exon 3 *reverse*	GAGGGCGTTAGT-GCCACGCCCGGA	0.5 kb
220	17867-L22126	Exon 4	475-476	ACCAAGTCAGGG-GGAGAGTATCCC	1.9 kb
427 Ж	17888-SP0566-L23462	Exon 5	45 nt after exon 5; 75 nt after exon 5	CACACCAAACGC-30 nt spanning oligo-CCACGAGCCCAT	0.2 kb
337	17880-L22139	Exon 6	833-832 *reverse*	AGACAGCTGGGC-GCCCTCGAAAGA	1.6 kb
447 Ж	17890-SP0567-L22149	Exon 7	35 nt after exon 7; 62 nt after exon 7	GACAGTAGCCGG-27 nt spanning oligo-AGGCTGGAGCTA	0.7 kb
190	17863-L22122	Exon 8	1046-1047	CCGAACTCCTGC-AGTCCCAGGCGG	1.4 kb
203	17865-L23449	Exon 9	1103-1104	CTGCTTCTTGGA-TCGTTCCACTTT	14.6 kb
283	17874-L22133	Exon 10	1219-1220	AAAGTGCTTTCT-TACATCAGCGTC	1.7 kb
244	17856-L24714	Exon 11	5 nt after exon 11	TATCAAGGTAAG-CTTGCAGCCCCA	8.9 kb
184	17862-L22121	Exon 12	1496-1497	GCAAGCCCACCT-GGGAGTACCTCT	2.6 kb
257	17872-L24713	Exon 13	1626-1627	GATGCTAATGGA-AGTGGTCCCACC	39.9 kb
		stop codon	*1655-1657 (Exon 13)*		
365 ¬	22419-L31604	*TDRD12* gene		CAACAATCCATT-CGATCGTTTCTA	

[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.

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.

¬ Flanking probe. Included to help determine the extent of a deletion/duplication. Copy number alterations of only the flanking or reference probes are unlikely to be related to the condition tested.

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

- P447 HPRT1: Contains probes for the *HPRT1* gene that encodes the protein HPRT. In the absence of HPRT, sodium urate crystals may abnormally accumulate in the joints and kidneys.

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 P426 Cystinuria

- Alghamdi M et al. (2020). Diversity of Phenotype and Genetic Etiology of 23 Cystinuria Saudi Patients: A Retrospective Study. *Front Pediatr*. 8:729.
- Krishnamurthy S et al. (2018). Cystinuria in a 13-month-old girl with absence of mutations in the SLC3A1 and SLC7A9 genes. *Indian J Nephrol*. 28:490.
- Olschok K et al. (2018). No evidence for point mutations in the novel renal cystine transporter AGT1/SLC7A13 contributing to the etiology of cystinuria. *BMC Nephrol*. 19:278.
- Shchagina O et al. (2020). A Family Case of Congenital Myasthenic Syndrome-22 Induced by Different Combinations of Molecular Causes in Siblings. *Genes (Basel)*. 11:821.
- Tostivint I et al. (2017). Spectrum of mutations in cystinuria patients presenting with prenatal hyperechoic colon. *Clin Genet*. 92:632-638.

P426 product history	
Version	*Modification*
A2	One probe has been adjusted in length.
A1	First release.

Implemented changes in the product description
Version A2-02 – 18 January 2022 (04P) - Product description rewritten and adapted to a new template. - Small changes of probe lengths in Table 1 and 2 in order to better reflect the true lengths of the amplification products. Version A2-01 — 26 August 2019 (02P) - Product description adapted to a new product version (version number changed, changes in Table 1 and Table 2). - Product description rewritten and adapted to a new template. - Ligation sites of the probes targeting the SLC3A1 and SLC7A9 gene updated according to new version of the NM_ reference sequence.

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