

SALSA MLPA KIT P036-E1 HUMAN TELOMERE-3

Lot 0808: As compared to the previous version (P036-D2) the probes for 1p and 4q have been replaced.

MENTAL RETARDATION is caused by aberrant copy numbers of subtelomeric regions in 3-8 % of all cases. This P036-E1 human telomere-3 probemix contains one probe for each subtelomeric region and is designed to detect deletions/duplications of each subtelomeric region. No probes are present for the acrocentric arms of 13p, 14p, 15p, 21p and 22p. For these chromosomes, a second probe is present on the q arm close to the centromere. Further information on detection of abnormal copy numbers in subtelomeric regions involved in mental retardation is found on pages 4-7.

At the p-telomeric ends of the X and Y chromosomes exists a region of approximately 2500 Kb of DNA, which is identical in both sex chromosomes: the pseudoautosomal region 1, or PAR1. Similarly, the PAR2 region is an 800 Kb DNA region on the q-telomeric ends, which is also identical for chromosome X and Y. The genes in the PAR regions have identical copy numbers in most males and females and thus behave like autosomally inherited genes. The P036-E1 probemix contains one probe for each of the two X/Y PAR regions, as well as two small synthetic MLPA probes for non-telomeric Y-chromosome specific sequences.

A website with useful information on MLPA and FISH probe locations is <http://mlpa.omnilounge.co.uk/>

This SALSA MLPA kit is designed to detect deletions/duplications of one or more genes at the telomere ends. Heterozygote deletions of probe recognition sequences will be apparent by a 35-50% reduced relative peak area of the amplification product of that probe. However, mutations and/or polymorphisms very close to the probe ligation site may also result in a reduced relative peak area. Therefore, apparent deletions detected by a single probe always require confirmation by other methods. If results found by MLPA analysis and other methods results are discordant, please send us the data.

SALSA® MLPA® kits are sold by MRC-Holland for research purposes and to demonstrate the possibilities of the MLPA technique. This kit is not CE/FDA certified for use in diagnostic procedures. SALSA MLPA kits are supplied with all necessary buffers and enzymes. Purchase of the SALSA MLPA test kits includes a limited license to use these products for research purposes.

The use of this SALSA MLPA kit requires a thermocycler with heated lid and sequence type electrophoresis equipment. Different fluorescent PCR primers are available. The MLPA technique has been first described in Nucleic Acid Research 30, e57 (2002).

Related SALSA MLPA kits

- P070 Human telomere-5: Contains a probe for every human subtelomere. Can be used as confirmation kit of P036 Human telomere-3.
- P069 Human telomere-4: Same as P070 Human telomere-5, but does not contain probes for the acrocentric chromosome arms 13p, 14p, 15p, 21p and 22p.
- More kits for specific subtelomere analysis are available; see page 4-6.
- P245 Microdeletion: Probes are included for 21 different microdeletion syndromes and can be used for primary screening of microdeletion syndromes.
- P064 MR-1/P096 MR-2: Contain probes for several microdeletion syndromes
- P106 MRX: X-linked mental retardation
- More probes for specific syndromes, e.g. RETT, DiGeorge, Prader Willi, Lissencephaly, Canavan and Williams syndrome, are available. Please see our website for further information.

More information

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References of SALSA MLPA kit P036 Telomere-3

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Data analysis

The P036-E1 Telomere-3 probemixes contain 46 different probes with amplification products between 130 and 482 nt. In addition, it contains 10 control fragments generating amplification products smaller than 120 nt: four DNA Quantity fragments (Q-fragments) at 64-70-76-82 nt, three DNA denaturation control fragments (D-fragments) at 88-92-96 nt, one X-chromosome specific fragment at 100 nt and two chromosome Y-specific fragments at 105 & 118 nt. More information on how to interpret observations on these control fragments can be found in the MLPA protocol.

Data generated by this probemix can be intra-normalized by dividing the peak area of each amplification product by the combined peak area of all peaks in that sample (global normalization). Secondly, normalisation can be achieved by dividing the intra-normalized probe ratio in a sample by the average intra-normalized probe ratio of all reference samples.

When only small numbers of samples are tested, visual comparison of peak profiles should be sufficient to identify deletions. Comparison of results should preferably be performed within one experiment. Only samples purified by the same method should be compared.

Confirmation of most deletions can be done by FISH, or with the use of SALSA MLPA kit P069/P070 Human telomere. For further characterization of abnormalities detected, we recommend the use of SALSA MLPA kits for specific subtelomere analysis (page 5-6).

Note that Coffalyser, the MLPA analysis tool developed at MRC-Holland, can be downloaded free of charge from our website www.mlpa.com.

SALSA MLPA P036-E1 Human Telomere-3 probemix

Length (nt)	Chromosomal position	Gene detected	SALSA MLPA probe	MapView build 36 position
64-70-76-82	Q-fragments: DNA quantity; only visible with less than 100 ng sample DNA			
88-92-96	D-fragments: Low signal of 88 or 96 nt fragment indicates incomplete denaturation			
100	X-fragment: Specific for the X chromosome			
105	Y-fragment: Specific for the Y chromosome			
118	Y-fragment: Specific for the Y chromosome			
130 *	1p	TNFRSF4	2269-L01761	01-001.14
137	2p	ACP1	2274-L08758	02-000.25
144	3p	CHL1	1721-L01329	03-000.34
151	4p	FLJ20265	2005-L02047	04-000.50
158	5p	PDCD6	1723-L01327	05-000.37
165	6p	IRF4	1724-L02048	06-000.34
172	7p	CENTA1	2275-L02049	07-000.93
179	8p	FBXO25	2397-L01845	08-000.40
186	9p	DMRT1	1727-L02050	09-000.84
194	10p	KIAA0934	2277-L01768	10-000.48
202	11p	RIC-8	3315-L02733	11-000.20
208	12p	SLC6A12	2276-L01767	12-000.17
218	"13p"	PSPC1	2399-L01847	13-019.24 (Acrocentric)
226	"14p"	HEI10	1732-L01318	14-019.86 (Acrocentric)
234	"15p"	MKRN3	7291-L08858	15-021.36 (Acrocentric)
242	16p	POLR3K	1734-L01316	16-000.04
250	17p	RPH3AL	1735-L01315	17-000.17
258	18p	USP14	1736-L02051	18-000.19
266	19p	CDC34	1737-L01313	19-000.49
274	20p	SOX12	2396-L01844	20-000.26
282	"21p"	RBM11	1739-L01311	21-014.51 (Acrocentric)
290	"22p"	BID	1740-L01310	22-016.61 (Acrocentric)
298	X/Yp	SHOX	1148-L01331	X/Y-000.52 (PAR region)
306	1q	KIAA1720	2392-L02149	01-247.08 (0.2 Mb from telomere)
314	2q	CAPN10	1742-L01308	02-241.18 (1.6 Mb from telomere)
322	3q	BDH	2013-L02052	03-198.76 (0.7 Mb from telomere)
330 *	4q	TRIML2	12050-L11446	04-189.26 (2.0 Mb from telomere)
338	5q	GNB2L1	3319-L02737	05-180.60 (0.2 Mb from telomere)
346	6q	PSMB1	1746-L01304	06-170.69 (0.5 Mb from telomere)
354	7q	VIPR2	1747-L01303	07-158.60 (0.3 Mb from telomere)
362	8q	KIAA0150	1748-L01302	08-144.69 (1.6 Mb from telomere)
370	9q	EHMT1	8205-L08170	09-139.83 (0.2 Mb from telomere)
378	10q	PAO	9142-L09953	10-135.05 (0.2 Mb from telomere)
386	11q	KIAA0056	1751-L01299	11-133.60 (1.2 Mb from telomere)
394	12q	ZNF10	2687-L02154	12-132.24 (0.2 Mb from telomere)
402	13q	F7	1753-L01297	13-112.82 (1.3 Mb from telomere)
410	14q	MTA1	2778-L02201	14-105.00 (1.3 Mb from telomere)
418	15q	ALDH1A3	1755-L01295	15-099.26 (1.0 Mb from telomere)
426	16q	GAS11 / GAS8	3201-L02669	16-088.63 (0.2 Mb from telomere)
434	17q	TBCD	1757-L01293	17-078.45 (0.5 Mb from telomere)
442	18q	FLJ21172	1758-L01292	18-075.90 (0.2 Mb from telomere)
450	19q	BC-2	9143-L10626	19-063.75 (0.9 Mb from telomere)
458	20q	OPRL1	2688-L02884	20-062.19 (0.2 Mb from telomere)
466	21q	HMT1	2586-L02059	21-046.89 (0.1 Mb from telomere)
474	22q	RABL2B	1762-L08761	22-049.55 (0.1 Mb from telomere)
482	X/Yq	SYBL1	1763-L02150	X/Y-154.78 (PAR region; 0.1 Mb from tel.)

* New in version E1 (from lot 0808 onwards)

Note: Please notify us of any mistakes. The exact sequences detected by the probes are available on request: info@mlpa.com.

Finding the genetic cause of mental retardation with MLPA

The number of genes whose defect can result in mental retardation is very large. In some cases, particular phenotypic features suggest the involvement of a specific gene or chromosomal region. Numerous SALSA MLPA kits are available to find the cause of mental retardation with distinct (syndromic) features, such as RETT syndrome, Sotos syndrome and Prader Willi.

Unfortunately, for patients suffering from non-syndromic mental retardation, the genetic cause is found only in a minority of cases. Usually, primary screening of such patients is done by karyotyping or G-banding. When no abnormality is detected by these methods, we suggest screening the patients with the following two SALSA MLPA kits (see figure 1):

- SALSA MLPA kit *P245 Microdeletion syndromes* contain probes for 21 different microdeletion syndromes causing mental retardation. For more information, please see the P245 product description.
- SALSA MLPA kit *P036 Human telomere* contains one probe for each subtelomeric region and is designed to detect deletions/duplications of each subtelomeric region. Several studies have indicated that 3-8 % (see references p.2) of all cases of mental retardation is caused by aberrant copy numbers of subtelomeric regions.

SALSA MLPA kit P245 Microdeletion syndromes

In case an abnormality is found with the SALSA MLPA kit *P245 Microdeletion syndromes*, we recommend further investigation of the deletion or duplication with one of the microdeletion follow-up kits (see the P245 Microdeletion syndromes product description for an overview).

SALSA MLPA kit P036 Human telomere

The detection of abnormal copy numbers in subtelomeric regions is very complicated. Compared to other regions of the genome, these regions are rich in sequences with variable copy numbers. Copy number changes of sequences within these regions can also occur in unaffected individuals and the effect of a deletion or duplication will depend on the genes present in the affected region. Please note that abnormalities detected by our subtelomeric probemixes will therefore not always be the cause of the mental retardation.

When used correctly, MLPA will exclude the presence of abnormal copy numbers of subtelomeric regions in the majority of samples. In case an abnormality is detected by P036, there are three ways to confirm a result:

1. Using a SALSA MLPA telomere follow-up kit. Follow-up kits contain more probes per telomere (see table below) and can be used to examine a specific region more closely.
2. Using SALSA MLPA kit *P069* or *P070 Human telomere* for independent confirmation of the results. Since these probemixes also contain one probe for each subtelomere, they offer a broad subtelomeric screening similar to the P036.
3. Confirmation by another method such as FISH.

Which conformation method to choose depends on your resources. The advantage of option 2 (broad screening with P069 or P070) is that a single probemix suffices to confirm all P036 findings. However, option 1 (a specific follow-up kit) will generally offer the best screening. When you find an abnormality with the P036, most often a single probe will be affected. The detailed follow-up kits will allow you not only to confirm the actual presence of a deletion/duplication, but also to determine its length. To facilitate the detailed screening of all chromosomes, a telomere starter kit will be released mid 2008, containing 25 reactions of each of the 12 telomere follow-up kits. Also, it is always possible to order 25 reactions probemix only of a follow-up kit (see the overview on the next page).

For all abnormalities detected, we strongly recommend testing the patient's parents to determine whether a copy number aberration found in the patient is truly de novo. De novo deletions or duplications have a high probability of being the cause of the mental retardation. Please be aware that a considerable number of abnormalities detected by a single probe may not have a phenotypic effect, but can be due to a rare polymorphism or a copy number change which is also present in one of the parents. For some chromosome

arms, even a large subtelomeric deletion of more than 1 Mb can be inherited without a phenotypic effect. Some examples are given on the next page.

No method will be capable of detecting all chromosomal aberrations. MLPA will not detect inversions or balanced translocations. Frequent microdeletion syndromes can be detected with the P245 probemix, but many rare interstitial deletions will not be detected.

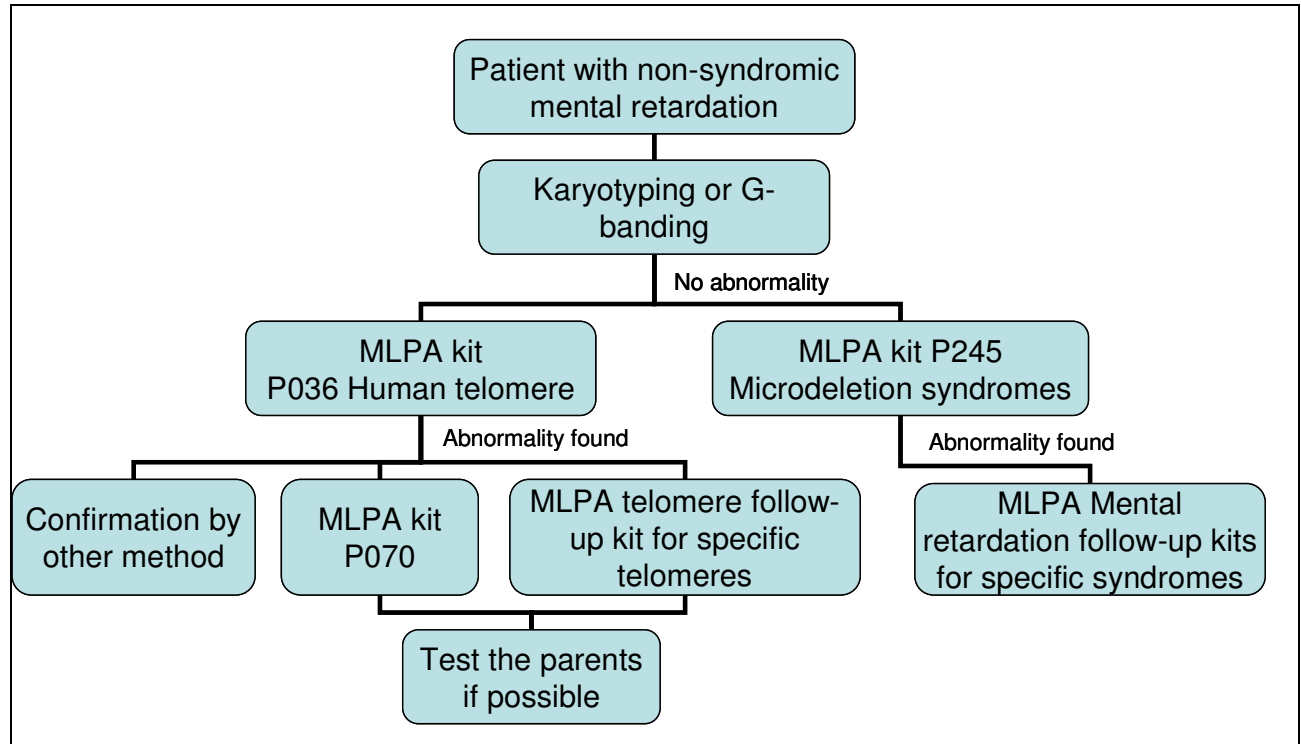


Figure 1: Flow scheme suggesting how to test a patient with non-syndromic mental retardation.

Probes in P036 and P070 MLPA probemixes

Most probes in the P036 and P070 probemixes target well-characterized genes that are located very close to the telomere. The exceptions are the probes for the p-arm of chromosomes 13, 14, 15, 21 and 22, as large parts of these arms are covered by >10 Mb of repeat sequences. For these chromosomes, the probe recognition sequence is therefore situated in one of the first genes following this region (on the q arm, close to centromere).

The development of a perfect MLPA assay for the detection of subtelomeric deletions and duplications is complicated. Genes that are located very close to the telomeres have a higher chance of being polymorphic in copy number (i.e. duplicated/deleted in a small percentage of unaffected individuals, sometimes only in certain populations), whereas situating probes at a larger distance from the telomere may lead to false negatives. Based on customer’s feedback, we will try to further improve this P036-E probemix.

More specific subtelomeric analysis

For a closer examination of samples in which aberrant copy numbers have been found, the following MLPA subtelomere follow-up kits are available:

Subtelomeric region	SALSA MLPA kit
1p (36 probes)	P147 1p36
2p (13 probes)	P208 Telo-6
3p (11 probes)	P208 Telo-6
4p (16 probes)	P096 MR2
5p (6 probes)	P096 MR2
6p (12 probes)	P208 Telo-6
7p	P365 Telo-14*

Subtelomeric region	SALSA MLPA kit
1q (14 probes)	P264 Telo-9
2q (12 probes)	P264 Telo-9
3q (11 probes)	P264 Telo-9
4q (8 probes)	P264 Telo-9
5q (13 probes)	P277 Telo-10
6q (10 probes)	P277 Telo-10
7q (10 probes)	P277 Telo-10

Subtelomeric region	SALSA MLPA kit
8p (12 probes)	P208 Telo-6
9p (12 probes)	P230 Telo-7
10p (11 probes)	P230 Telo-7
11p (7 probes)	P230 Telo-7
12p (11 probes)	P230 Telo-7
"13p" (18 probes)	P163 GJB
"14p"	-
"15p" (25 probes)	ME028 PWS/AS
16p (24 probes)	P140 HBA; P365 Telo-14*
17p (15 probes)	P249 Telo-8
18p (8 probes)	P249 Telo-8
19p (9 probes)	P249 Telo-8
20p (13 probes)	P249 Telo-8
"21p"	P365 Telo-14*
"22p" (30 probes)	P250 DiGeorge
Xp	P018 SHOX

Subtelomeric region	SALSA MLPA kit
8q (10 probes)	P277 Telo-10
9q (13 probes)	P286 Telo-11
10q (8 probes)	P286 Telo-11
11q (14 probes)	P286 Telo-11
12q (9 probes)	P286 Telo-11
13q (12 probes)	P291 Telo-12
14q (10 probes)	P291 Telo-12
15q (10 probes)	P291 Telo-12
16q (10 probes)	P291 Telo-12
17q	P320 Telo-13*
18q	P320 Telo-13*
19q	P320 Telo-13*
20q	P320 Telo-13*
21q	P365 Telo-14*
22q (37 probes)	P188 22q13
Xq	P015 MECP3; P049 SLC6A8; P178 F8; P257 TERT

* Expected to be available in the third quarter of 2008

Notes on specific telomeres:

- The P036-E **control fragments** for the **Y**-chromosome (105 and 118 nt) are synthetic probes (the longer probes are "phage M13-derived"). These small fragments seem to have a higher variability in peak area than the other probes and are not close to the Y telomeres.
- The 298 and 482 probes detect sequences located on both **X** and **Y** chromosome close to the telomeres and will thus indicate the combined copy number of X and Y.
- The P036-E probemix contains a new probe for **1p**, this time for the TNFRSF4 gene. This probe has been tested by several labs. The P036D probe for SCNN1D on 1p gave variable results in several labs. The P036-B CAB45 probe for 1p was found to be deleted or duplicated in some healthy families.
- The P036-E **probe for 2p** has been found to be deleted in several healthy persons in Nijmegen (Erik Sistermans, personal communication.) and Maastricht. We do not know whether this is due to a polymorphism in the Dutch population. In case deletions in healthy persons also occur elsewhere, this probe will be replaced in the future. Please inform us on aberrant results.
- The P036-E and P069/P070 **probes for 3p** (CHL1 gene) were found to be duplicated in healthy parents by Joo Wook Ahn (Guy's London) and Eric Sistermans, Nijmegen. In another family, a deletion of the P069-P070 probes for 3p was detected in a healthy parent (Joo Wook Ahn, London). According to Dijkhuizen et al (2006; *Am.J.Hum.Genet.* 140A, 2482-87), defects in the more centromeric CNTN4 and CRBN genes might be more important for the 3p syndrome than CHL1 loss. We recommend the use of the P208 probemix for further analysis of 3p deletions / duplications.
- The P036-E and P069 and P070 probes for **11p**, **20p**, and **5q**, detect sequences that have been found to be duplicated in sporadic cases in a normal individual (11p: M. Palomares Bralo, Madrid; 20p: V. Biancalana; Strasbourg; 5q: K. Mann, London + L. Rooms & S. Seneca, Antwerpen; all personal communication). As deletions of these regions might well have consequences, we will not replace these probes.
- The P036-E **probe for 3q** (BDH gene, 322 nt) was found to be duplicated in a healthy parent by Edwin Reyniers (Antwerpen). This was confirmed by FISH. The P069/P070 probe for 3q, which is located 200 Kb closer to the telomere, did not show this duplication. Apparently, copy number polymorphisms of the BDH gene region do occur in healthy individuals.
- A **3q29** microdeletion syndrome has been described recently: Willatt, L. et al *A. J. Hum. Genet.* 77: 154-160, 2005. Although this syndrome is due to an interstitial deletion, the commonly deleted region is located very close to the 3q telomere. The probe in this P036-E probemix detects a sequence which is within the commonly deleted region. The 3q probe in P069/P070 will not detect this microdeletion, as the sequence detected by this P070 probe is located between this interstitial deletion region and the telomere.
- The P036-E probemix contains a new probe for **4q**. This probe has been tested by several labs. The previous probes for 4q didn't perform well. The 4q telomeric region is complicated and very few genes are present. The FRG1 gene is the only well characterized gene in the terminal 2-3 Mb of 4q but the FRG1 specific probes in P036-B, P036-C and P036-D were not reliable due to the presence of population specific

- SNPs in the FRG1 gene. We have received reports about high frequency false positive results in several populations with these 4q probes. The 4q probe in P036-E is located at larger distance from the telomere but we do not expect this to cause many false-negative results as deletions of the telomeric 2-3Mb region of 4q do not seem to cause phenotypic effects (Shao, L. et al (2008) *Am.J.Hum.Genet.*)
- The P036-E **probe for 5q** was found to be influenced in one patient by a polymorphism in the first nucleotide after the ligation site by Kathlen Franke (Dresden). Please report similar findings. Probes that are reported more often to be influenced by polymorphisms will be replaced.
 - The P036-B **probe for 9q** was found to give variable results by two laboratories. It has been replaced by an EHMT1 probe (closer to the telomere) in the P036-D/-E probemix.
 - The **"13p", "14p", "15p", "21p" and "22p" probes** detect sequences that are in the q-arm, close to the centromere. The p-arms of these chromosomes do not contain well characterized genes.
 - The P036-E **probe for "15p"** (MKRN3 gene, 234 nt) detects a sequence which is close to the centromere on the 15q arm. This region is deleted in **some** Prader-Willi/Angelman syndrome patients. The PWS/AS critical region (SNRPN gene) is located at a distance of 1.3 Mb towards the q-telomere. We recommend to using the ME028 probemix in order to further characterize copy number changes of the MKRN3 region.
 - The sequence detected by the P036-E **probes for 22q** has only one mismatch with a related sequence on chromosome 2. Sufficient for us to generate a chr. 22q specific MLPA signal. However, when this region is to be sequenced, primer design is complicated. Only 4 mismatches are present in the 350 nt region that contains this probe sequence. SALSA MLPA kit P188 22q13 contains many probes close to the 22q13 telomere and can be used to confirm or further characterize 22q13 deletions.

Please notify us of any mistakes: info@mlpa.com. All sequences are available on request: info@mlpa.com.

Differences between P036-D and P036-E

The **1p** and **4q** probes have been replaced. Several alternative 1p and 4q probes have been tested at MRC-Holland and at various customers. Probes for TNFRSF4 (1p) and TRIML2 (4q) have been selected.

Differences between P036-B and P036-E

1. The CAB45 probe for **1p36** is replaced in P036-E by a probe for the TNFRSF4 gene.
2. The FRG1 probe for **4q** has been replaced in P036-E by a probe for the TRIML2 gene.
3. The P036-B probe for **9q** has been replaced in P036-E by a probe for the EHMT1 gene.
4. The CYFIP1 probe for **"15p"** is located in a polymorphic region and has been replaced by a MKRN3 probe in P036-E.
5. The 378 nt probe for 10q and the 450 nt probe for 19q have been recloned and have higher signals in P036-E, as compared to P036-B. Length of these probes has been slightly altered but the sequence detected have remained identical.
6. Two extra control fragments specific for the X- and Y-chromosome have been included at 100 and 105 nt.

SALSA MLPA kit P036-E1 sample pictures

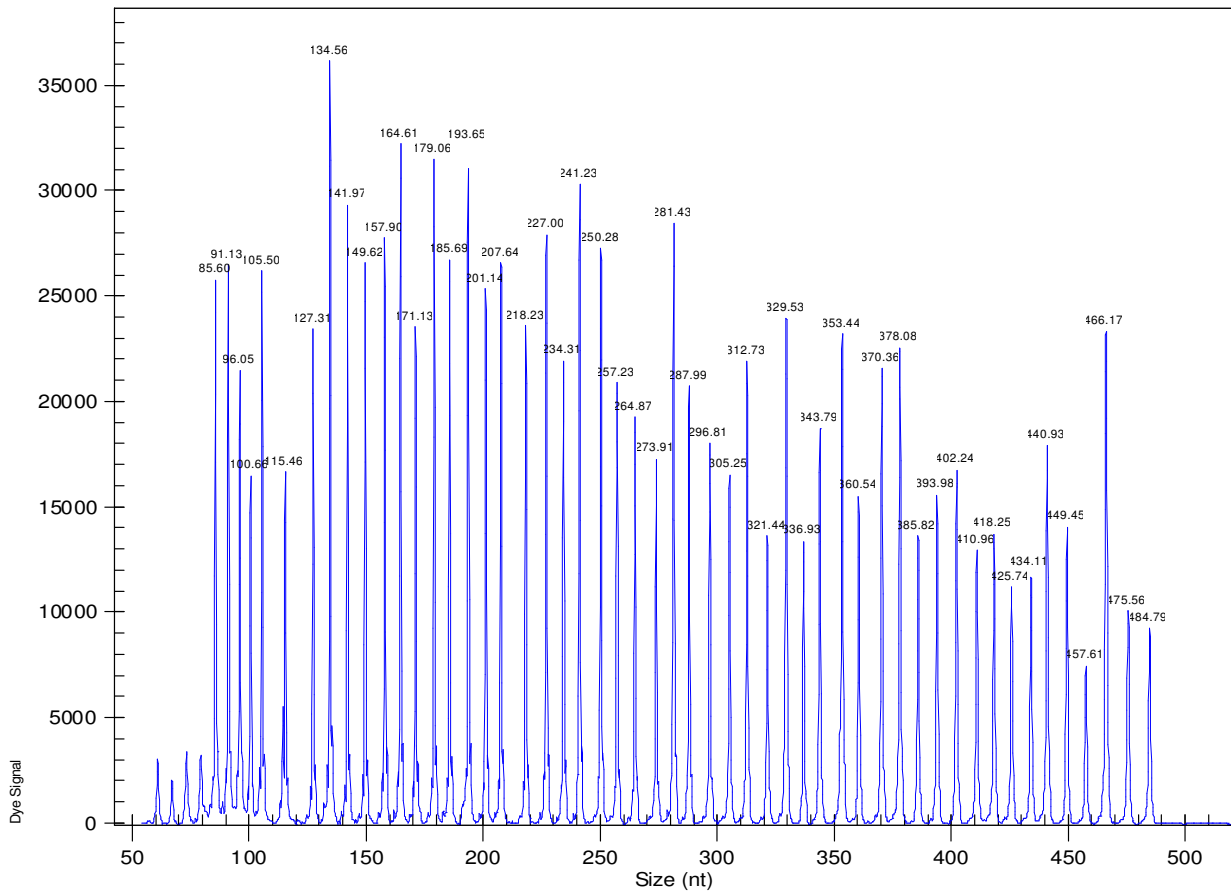


Figure 2. Capillary electrophoresis pattern from a sample of approximately 50 ng human male control DNA analyzed with SALSA MLPA kit P036-E1 Human Telomere-3 (lot 0808).