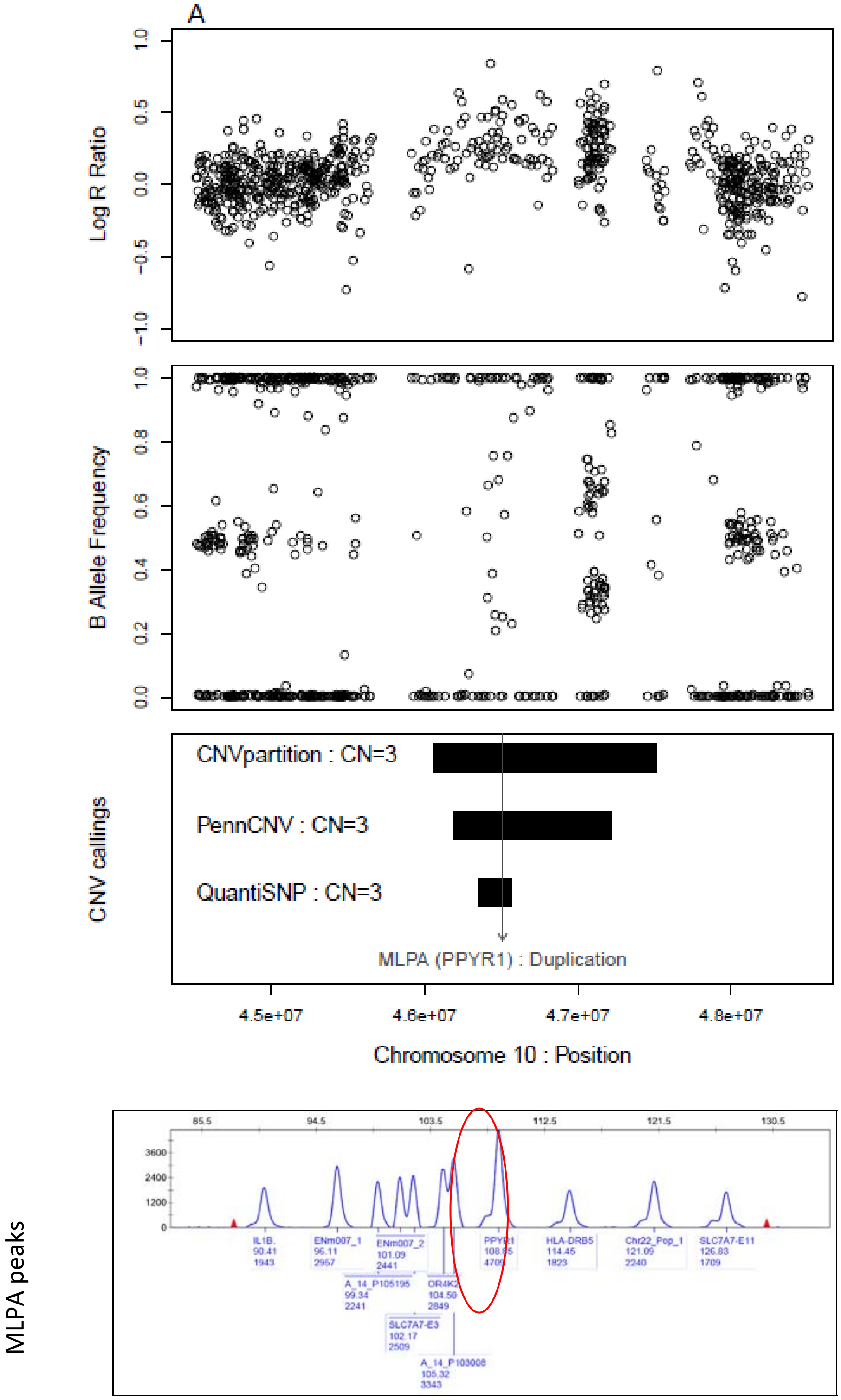
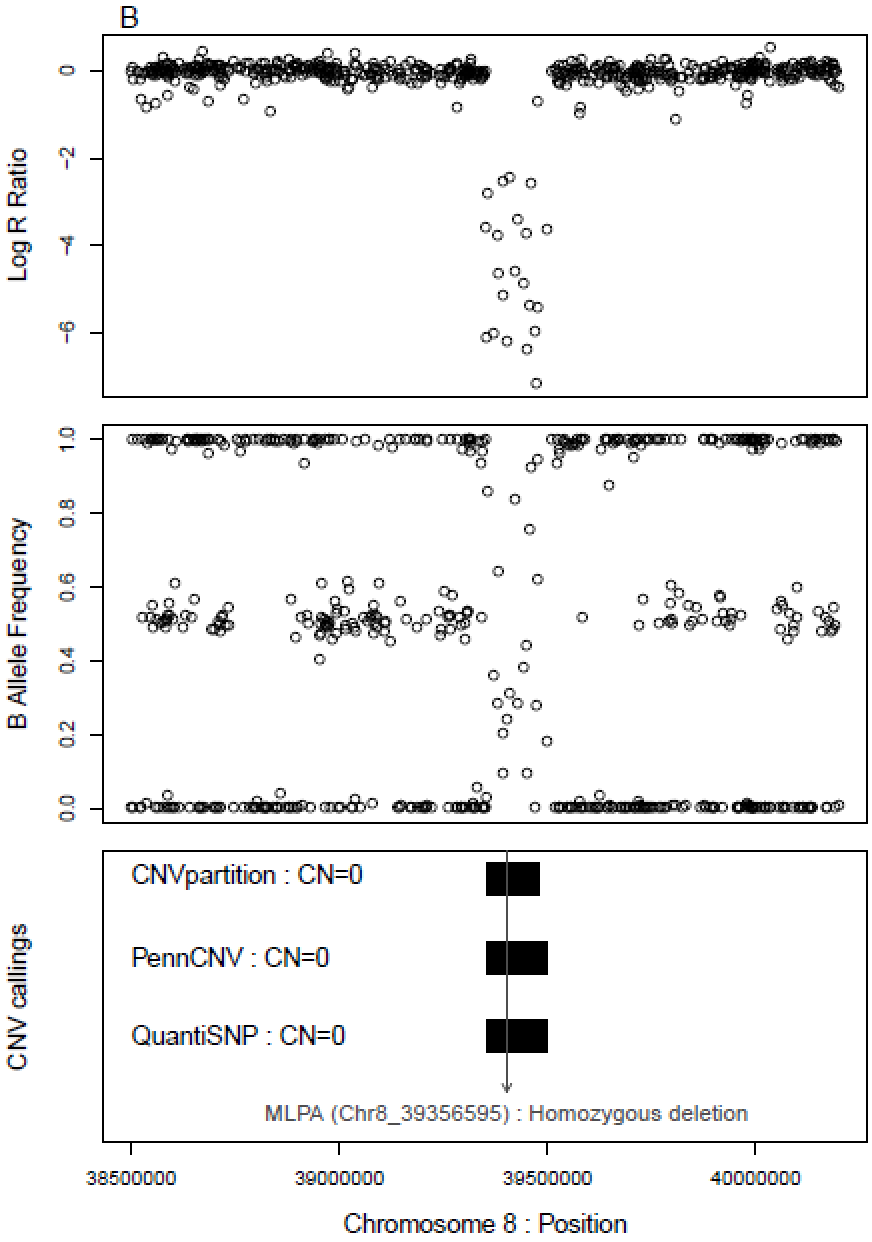
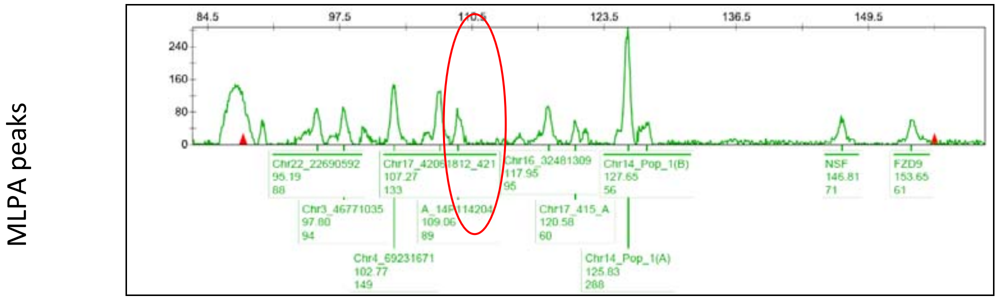
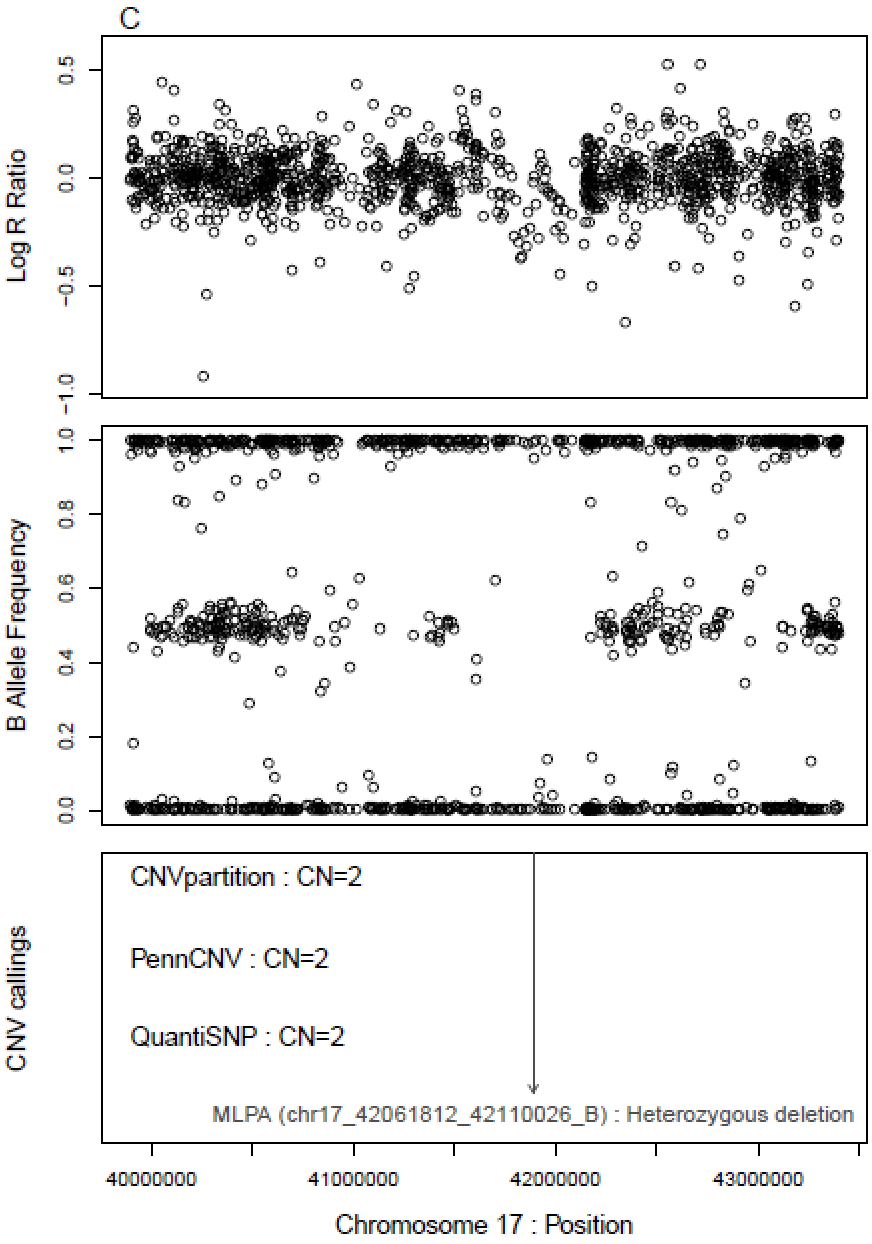
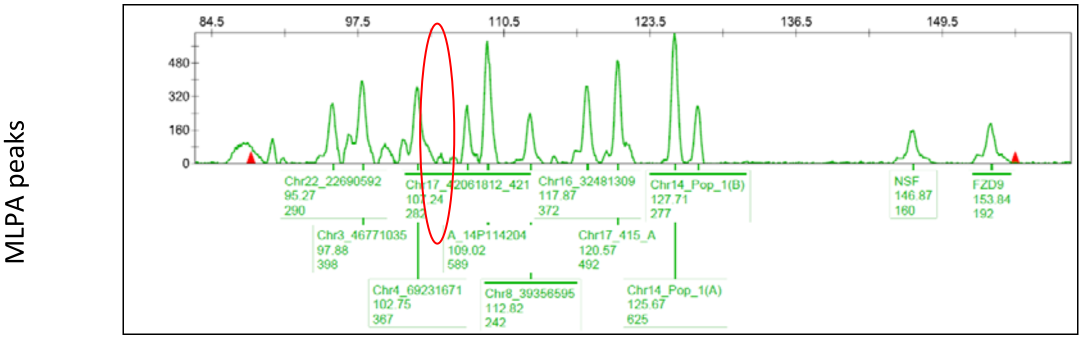
Supp. Figure S1. Log R Ratio (LRR), B Allele Frequency (BAF), algorithm and MLPA callings and MLPA peaks for A) a true positive duplication, B) a true positive homozygous deletion, C) a false negative heterozygous deletion and D) a false positive duplication. MLPA peaks are shown for the considering individual and for various probes used for validation.

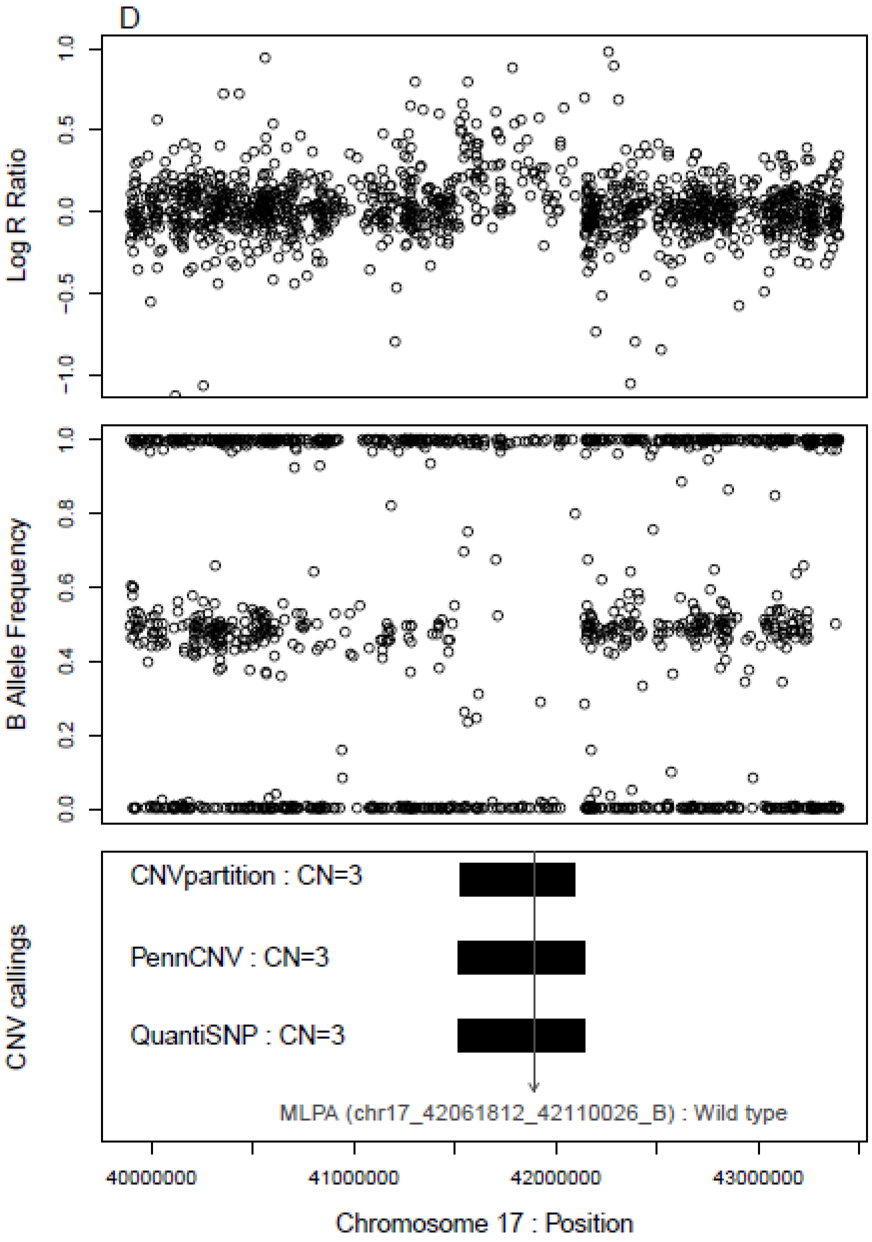


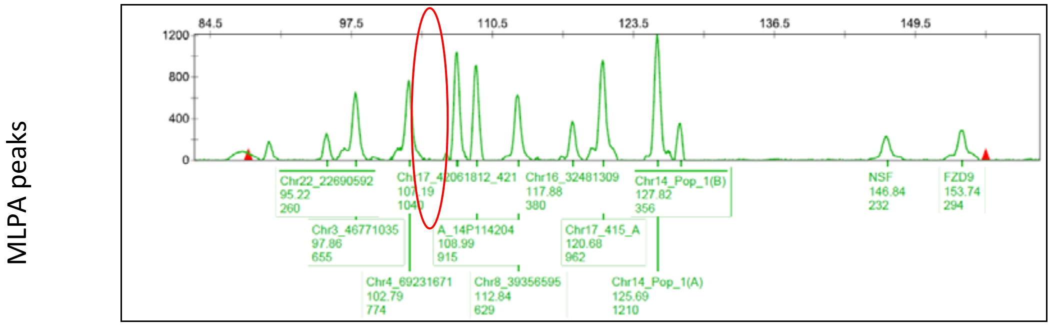

B
Log R Ratio
0
-2
-4
-6
B Allele Frequency
0.0
0.2
0.4
0.6
0.8
1.0
CNV callings
CNVpartition : CN=0
PennCNV : CN=0
QuantiSNP : CN=0
MLPA (Chr8_39356595) : Homozygous deletion
38500000
39000000
39500000
40000000
Chromosome 8 : Position

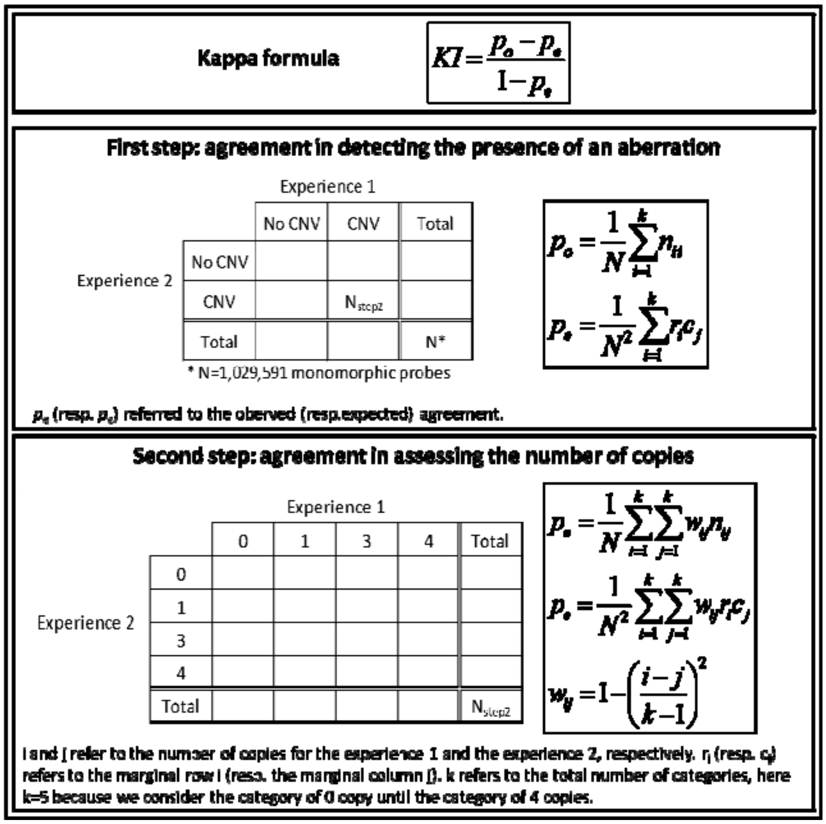

MLPA peaks
84.5
97.5
110.5
123.5
136.5
149.5
240
160
80
0
Chr22_22690592
95.19
88
Chr17_42061812_421
107.27
133
Chr16_32481309
117.95
95
Chr14_Pop_1(B)
127.65
56
NSF
146.81
71
FZD9
153.65
61
Chr3_46771035
97.80
94
A_14P114204
109.06
89
Chr17_415_A
120.58
60
Chr4_69231671
102.77
149
Chr14_Pop_1(A)
125.83
288


C
Log R Ratio
0.5
0.0
−0.5
−1.0
B Allele Frequency
1.0
0.8
0.6
0.4
0.2
0.0
CNV callings
CNVpartition : CN=2
PennCNV : CN=2
QuantiSNP : CN=2
MLPA (chr17_42061812_42110026_B) : Heterozygous deletion
40000000
41000000
42000000
43000000
Chromosome 17 : Position


MLPA peaks
84.5
97.5
110.5
123.5
136.5
149.5
480
320
160
0
Chr22_22690592
95.27
290
Chr17_42061812_421
107.24
282
Chr16_32481309
117.87
372
Chr14_Pop_1(B)
127.71
277
NSF
146.87
160
FZD9
153.84
192
Chr3_46771035
97.88
398
A_14P114204
109.02
589
Chr17_415_A
120.57
492
Chr4_69231671
102.75
367
Chr8_39356595
112.82
242
Chr14_Pop_1(A)
125.67
625


D
Log R Ratio
1.0
0.5
0.0
−0.5
−1.0
B Allele Frequency
1.0
0.8
0.6
0.4
0.2
0.0
CNV callings
CNVpartition : CN=3
PennCNV : CN=3
QuantiSNP : CN=3
MLPA (chr17_42061812_42110026_B) : Wild type
40000000
41000000
42000000
43000000
Chromosome 17 : Position


MLPA peaks
84.5
97.5
110.5
123.5
136.5
149.5
1200
800
400
0
Chr22_22690592
95.22
260
Chr17_42061812_421
107.19
1040
Chr16_32481309
117.88
380
Chr14_Pop_1(B)
127.82
356
NSF
146.84
232
FZD9
153.74
294
Chr3_46771035
97.86
655
A_14P114204
108.99
915
Chr17_415_A
120.68
962
Chr4_69231671
102.79
774
Chr8_39356595
112.84
629
Chr14_Pop_1(A)
125.69
1210



Kappa formula

$$KI = \frac{p_o - p_e}{1 - p_e}$$

First step: agreement in detecting the presence of an aberration

Experience 1

Experience 2	No CNV	CNV	Total
No CNV			
CNV		N_{step2}	
Total			N*

* N=1,029,591 monomorphic probes

$$p_o = \frac{1}{N}\sum_{i=1}^{k} n_{ii}$$

$$p_e = \frac{1}{N^2}\sum_{i=1}^{k} r_i c_j$$

p_o (resp. p_e) referred to the oberved (resp.expected) agreement.

Second step: agreement in assessing the number of copies

Experience 1

Experience 2	0	1	3	4	Total
0					
1					
3					
4					
Total					N_{step2}

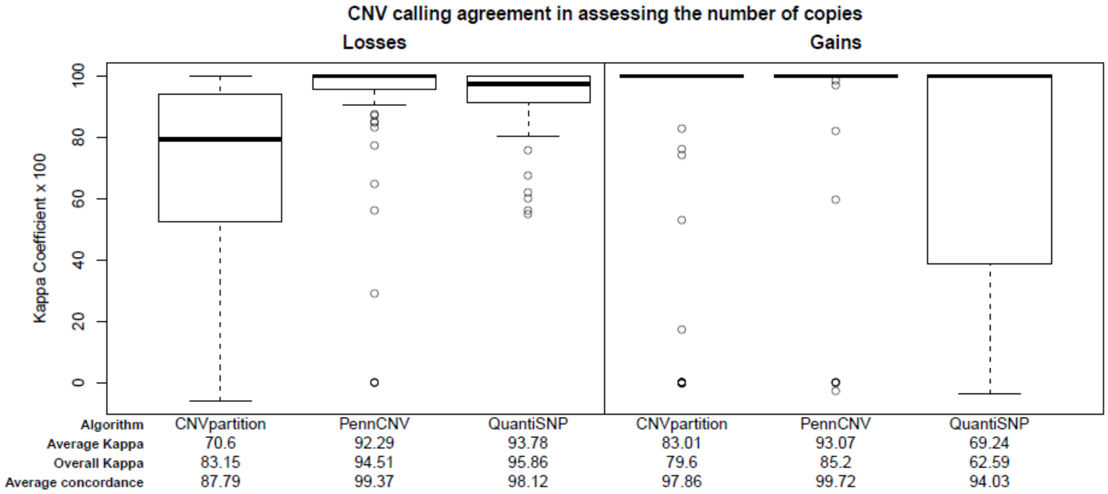
$$p_o = \frac{1}{N}\sum_{i=1}^{k}\sum_{j=1}^{k} w_{ij} n_{ij}$$

$$p_e = \frac{1}{N^2}\sum_{i=1}^{k}\sum_{j=1}^{k} w_{ij} r_i c_j$$

$$w_{ij} = 1 - \left(\frac{i-j}{k-1}\right)^2$$

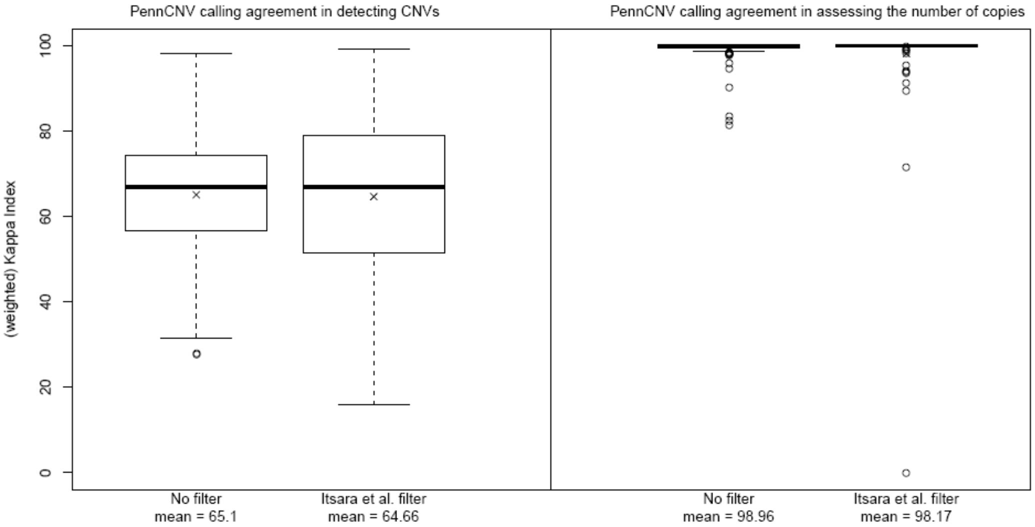
i and j refer to the number of copies for the experience 1 and the experience 2, respectively. r_i (resp. c_j) refers to the marginal row i (resp. the marginal column j). k refers to the total number of categories, here k=5 because we consider the category of 0 copy until the category of 4 copies.

Supp. Figure S2. Detail of the kappa calculation for the two-step agreement on calling CNVs.



Algorithm	CNVpartition	PennCNV	QuantiSNP	CNVpartition	PennCNV	QuantiSNP
Average Kappa	70.6	92.29	93.78	83.01	93.07	69.24
Overall Kappa	83.15	94.51	95.86	79.6	85.2	62.59
Average concordance	87.79	99.37	98.12	97.86	99.72	94.03

Supp. Figure S3. Agreement on assessing the number of copies once the type of CNV (loss or gain) was concordant for both replicates. For each type of CNV and each algorithm, we computed 1) the Kappa coefficient for each pair of duplicate and we provided the average Kappa across the 96 pairs, 2) a overall Kappa coefficient computed over all the 96 pairs of replicates and concordant probes, and 3) the classic concordance rate for each pair of duplicate and we provided the average concordance across the 96 pairs.



Supp. Figure S4. Impact of the filtering on PennCNV calling agreement. Box plots before and after filtering for the distribution of A) Kappa Index estimates for CNV detection on duplicated samples, and B) weighted Kappa Index estimates for copy-number assessment when a CNV was detected.

Supp. Table S1. Number of Individuals, assays, and pairs analyzed (before CNV criteria) and considered in the accuracy study (after CNV criteria) and according to DNA source

Overall			**Blood**			**Saliva**			**Blood / Saliva**		
Individuals	**Assays**	**Pairs**	**Individuals**	**Assays**	**Pairs**	**Individuals**	**Assays**	**Pairs**	**Individuals**	**Assays**	**Pairs**
Before CNV criteria											
141	299	178	71	142	71	66	146	97	4	11	10
127 dup			71 dup			55 dup			1 dup	5 Blood	1 B/B
11 trip						8 trip			3 trip	6 Saliva	2 S/S
3 quadrip						3 quadrip					7 B/S
After CNV criteria											
92	186	96	63	126	63	29	60	33	-	-	-
90 dup			63 dup			27 dup					
2 trip						2 trip					

Assays are count by summing all duplicate, triplicate and quadruplicate samples
Pairs refer to the by-two comparisons provided by duplicate (2), triplicate (3) and quadruplicate (6) samples.

Supp. Table S2. MLPA probes considered in the MLPA analysis

Probe	Chromosome	Band	Start	End
SKI	1	1p36.33	2,150,969	2,151,029
IL1B	2	2q13	113,306,801	113,306,852
A_14_P103008	2	2q37.3	242,228,984	242,229,042
PLCD1	3	3p22.3	38,026,650	38,026,709
Chr3_46771035	3	3p21.31	46,781,196	46,781,253
Chr4_69231671	4	4q13.2	69,109,638	69,109,698
PCDHA9	5	5q31.1	140,208,267	140,208,335
DOM3Z	6	6p21.32	32,047,183	32,047,228
HLA-DRB5	6	6p21.32	32,593,310	32,593,379
FZD9	7	7q11.23	72,294,840	72,294,901
Chr8_39356595	8	8p11.23	39,401,744	39,401,802
RXRa	9	9q34.2	136,453,357	136,453,414
NOTCH1	9	9q34.3	138,523,724	138,523,783
PPYR1	10	10q11.22	46,507,740	46,507,809
ADAM8	10	10q26.3	134,933,411	134,933,468
HRAS	11	11p15.5	523,758	523,813
A_14_P114204	11	11q13.1	66,952,984	66,953,039
OR4K2	14	14q11.2	19,414,387	19,414,452
Chr16_32481309	16	16p11.2	32,516,918	32,516,977
chr17_415_A	17	17q21.31	41,539,152	41,539,211
chr17_42061812_42110026_B	17	17q21.31	41,889,427	41,889,486
NSF	17	17q21.32	42,166,492	42,166,551
STK11	19	19p13.3	1,171,375	1,171,442
ENm007_1	19	19q13.42	59,427,206	59,427,263
ENm007_2	19	19q13.42	59,968,534	59,968,593
A_14_P105195	20	20q11.21	30,111,471	30,111,530
GSTT1	22	22q11.23	22,706,190	22,706,250
Chr22_22690592	22	22q11.23	22,709,442	22,709,496
Chr22_Pop_1	22	22q13.1	37,684,655	37,684,714

Supp. Table S3. Validity estimates for blood samples comparing the calling results with those obtained using MLPA as a reference

			CNVpartition				PennCNV				QuantiSNP			
			No filter		Itsara et al. filter		No filter		Itsara et al. filter		No filter		Itsara et al. filter	
Steps	**CNV type**		**Est.**	**95% CI**	**Est.**	**95% CI**	**Est.**	**95% CI**	**Est.**	**95% CI**	**Est.**	**95% CI**	**Est.**	**95% CI**
1	**CNV**	**SE**	0.19	[0.14 - 0.23]	0.05	[0.03 - 0.08]	0.23	[0.18 - 0.28]	0.07	[0.05 - 0.11]	0.28	[0.23 - 0.33]	0.08	[0.05 - 0.11]
		SP	0.99	[0.98 - 1.00]	1.00	[1.00 - 1.00]	0.98	[0.97 - 0.99]	1.00	[0.99 - 1.00]	0.97	[0.96 - 0.98]	1.00	[0.99 - 1.00]
		VPP	0.83	[0.73 - 0.91]	0.95	[0.75 - 1.00]	0.76	[0.66 - 0.85]	0.86	[0.68 - 0.96]	0.71	[0.62 - 0.79]	0.90	[0.73 - 0.98]
		VPN	0.83	[0.81 - 0.85]	0.80	[0.78 - 0.82]	0.84	[0.83 - 0.86]	0.81	[0.79 - 0.83]	0.86	[0.84 - 0.87]	0.81	[0.79 - 0.83]
2a	**Deletion***	**SE**	0.97	[0.86 - 1.00]	1.00	[0.73 - 1.00]	0.95	[0.84 - 0.99]	1.00	[0.79 - 1.00]	0.98	[0.91 - 1.00]	1.00	[0.81 - 1.00]
		SP	1.00	[0.79 - 1.00]	1.00	[0.09 - 1.00]	1.00	[0.83 - 1.00]	1.00	[0.09 - 1.00]	0.92	[0.73 - 0.99]	1.00	[0.01 - 1.00]
		VPP	1.00	[0.86 - 1.00]	1.00	[0.73 - 1.00]	1.00	[0.87 - 1.00]	1.00	[0.79 - 1.00]	0.97	[0.88 - 1.00]	1.00	[0.81 - 1.00]
		VPN	0.96	[0.79 - 1.00]	1.00	[0.09 - 1.00]	0.94	[0.79 - 0.99]	1.00	[0.09 - 1.00]	0.96	[0.78 - 1.00]	1.00	[0.01 - 1.00]
2b	**Homozygous deletion***	**SE**	1.00	[0.83 - 1.00]	1.00	[0.66 - 1.00]	0.86	[0.57 - 0.98]	1.00	[0.64 - 1.00]	0.68	[0.45 - 0.86]	1.00	[0.66 - 1.00]
		SP	0.94	[0.79 - 0.99]	1.00	[0.42 - 1.00]	1.00	[0.91 - 1.00]	1.00	[0.66 - 1.00]	0.92	[0.82 - 0.97]	1.00	[0.68 - 1.00]
		VPP	0.94	[0.79 - 0.99]	1.00	[0.66 - 1.00]	1.00	[0.64 - 1.00]	1.00	[0.64 - 1.00]	0.75	[0.51 - 0.91]	1.00	[0.66 - 1.00]
		VPN	1.00	[0.83 - 1.00]	1.00	[0.42 - 1.00]	0.97	[0.88 - 1.00]	1.00	[0.66 - 1.00]	0.89	[0.78 - 0.95]	1.00	[0.68 - 1.00]

			CNVpartition				**PennCNV**				**QuantiSNP**			
			No filter		**Itsara et al. filter**		**No filter**		**Itsara et al. filter**		**No filter**		**Itsara et al. filter**	
2c	**Heterozygous deletion***	**SE**	0.63	[0.24 - 0.91]	1.00	[0.28 - 1.00]	0.93	[0.76 - 0.99]	1.00	[0.62 - 1.00]	0.92	[0.78 - 0.98]	1.00	[0.66 - 1.00]
		SP	1.00	[0.9 - 1.00]	1.00	[0.7 - 1.00]	0.95	[0.84 - 0.99]	1.00	[0.68 - 1.00]	0.87	[0.74 - 0.95]	1.00	[0.68 - 1.00]
		VPP	1.00	[0.36 - 1.00]	1.00	[0.28 - 1.00]	0.93	[0.76 - 0.99]	1.00	[0.62 - 1.00]	0.85	[0.7 - 0.94]	1.00	[0.66 - 1.00]
		VPN	0.95	[0.85 - 0.99]	1.00	[0.7 - 1.00]	0.95	[0.84 - 0.99]	1.00	[0.68 - 1.00]	0.93	[0.81 - 0.99]	1.00	[0.68 - 1.00]
2d	**Duplication***	**SE**	1.00	[0.79 - 1.00]	1.00	[0.09 - 1.00]	1.00	[0.83 - 1.00]	1.00	[0.09 - 1.00]	0.92	[0.73 - 0.99]	1.00	[0.01 - 1.00]
		SP	0.97	[0.86 - 1.00]	1.00	[0.73 - 1.00]	0.95	[0.84 - 0.99]	1.00	[0.79 - 1.00]	0.98	[0.91 - 1.00]	1.00	[0.81 - 1.00]
		VPP	0.96	[0.79 - 1.00]	1.00	[0.09 - 1.00]	0.94	[0.79 - 0.99]	1.00	[0.09 - 1.00]	0.96	[0.78 - 1.00]	1.00	[0.01 - 1.00]
		VPN	1.00	[0.86 - 1.00]	1.00	[0.73 - 1.00]	1.00	[0.87 - 1.00]	1.00	[0.79 - 1.00]	0.97	[0.88 - 1.00]	1.00	[0.81 - 1.00]

*Estimates for each CNV type were calculated only for these true positive CNVs identified in step 1.

The estimates and their 95% confidence intervals (CI) for sensitivity (SE), specificity (SP), positive predictive value (VPP) and negative predictive value (VPN) are displayed according to the algorithms and the different types of aberrations with and without filtering using the Itsara et al. criteria.