QC report（表6）

Sample: BRCA1女性84人、Normal女性49人、Sporadic ov.ca.女性42人
Software: Affymetrix Genotyping Console 4.0
Reference: HapMap 22 samples (Japanese female, 不死化リンパ球由来DNA)

	IN	OUT
BRCA1	17	67
Normal	5	*44*
Sporadic	0	42

"Bounds: out" ・・・ MAPD>0.35

※MAPD>0.35以上のサンプルは、解析から除外することが推奨されている。
（同一ラボで取得されたサンプルの場合、MAPD>0.30で除外）

MAPD: the Median of the Absolute values of all Pairwise Differences between log2 ratios for a given chip

QC report（表7）

Sample: BRCA1女性84人、Normal女性49人、Sporadic ov.ca.女性42人
Software: Affymetrix Genotyping Console 4.0
Reference: HapMap 270 samples (male & female, 不死化リンパ球由来DNA)

	IN	OUT
BRCA1	45	39
Normal	22	27
Sporadic	0	42

"Bounds: out" ・・・ MAPD>0.35

※MAPD>0.35以上のサンプルは、解析から除外することが推奨されている。
（同一ラボで取得されたサンプルの場合、MAPD>0.30で除外）

QC report（表8）

Sample: BRCA1女性84人、Normal女性49人、Sporadic ov.ca.女性42人
Software: Affymetrix Genotyping Console 4.0
Reference: Endometriosis 406 samples（同一labでデータ取得）

	IN	OUT
BRCA1	78	6
Normal	49	0
Sporadic	38	4

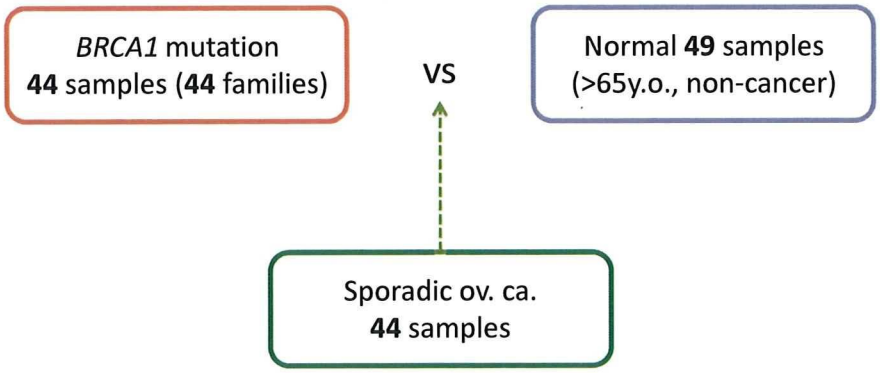
"Bounds: out" ・・・ MAPD>0.30

Endometriosis 406 samplesをRef.として
Copy Number Analysis へ

（表9）BRCA1変異陽性症例に特異的なコピー数変化の同定

1. Software: Partek Genomic Suite v6.4
2. Reference (Baseline): HapMap JPT female 21 samples
3. アルゴリズム: Hidden Markov Model
   (genomic marker >3、Copy Number Variation > 1kb　Nature Rev Genet 2006)

【1家系に対し1サンプル】



BRCA1 vs Sporadic vs Normal（表10）

chr.	Start (Mb)	Length (Kb)	Genomic marker	p-value	*BRCA1* (n = 44)		Sporadic (n = 44)		Normal (n = 49)	
					Amp.	Del.	Amp.	Del.	Amp.	Del.
2	132.1	4.70	3	0.0000000000030	7 (15.9%)	0 (0%)	39 (88.6%)	0 (0%)	15 (30.6%)	0 (0%)
2	132.1	588.31	216	0.000000000010	8 (18.2%)	0 (0%)	39 (88.6%)	0 (0%)	15 (30.6%)	0 (0%)
20	28.1	716.75	59	0.000000000054	4 (9.1%)	0 (0%)	33 (75.0%)	0 (0%)	11 (22.4%)	0 (0%)
18	14.1	39.75	12	0.000000000087	10 (22.7%)	0 (0%)	39 (88.6%)	0 (0%)	15 (30.6%)	0 (0%)
20	26.3	1811.78	9	0.00000000011	4 (9.1%)	0 (0%)	33 (75.0%)	0 (0%)	12 (24.5%)	0 (0%)
3	126.9	19.27	4	0.00000000014	8 (18.2%)	0 (0%)	36 (81.8%)	0 (0%)	12 (24.5%)	0 (0%)
3	126.9	184.88	75	0.00000000014	8 (18.2%)	0 (0%)	36 (81.8%)	0 (0%)	12 (24.5%)	0 (0%)
4	191.0	12.81	4	0.00000000015	11 (25.0%)	0 (0%)	41 (93.2%)	0 (0%)	20 (40.8%)	0 (0%)
18	14.2	9.84	3	0.00000000017	10 (22.7%)	0 (0%)	39 (88.6%)	0 (0%)	16 (32.7%)	0 (0%)
2	97.6	16.63	5	0.00000000023	0 (0%)	0 (0%)	22 (50.0%)	0 (0%)	3 (6.1%)	0 (0%)
18	14.2	343.06	99	0.00000000030	10 (22.7%)	0 (0%)	39 (88.6%)	0 (0%)	17 (34.7%)	0 (0%)
21	14.2	41.07	18	0.00000000047	6 (13.6%)	0 (0%)	30 (68.1%)	0 (0%)	6 (8.2%)	0 (0%)
20	25.7	230.87	62	0.00000000049	4 (9.1%)	0 (0%)	32 (72.7%)	0 (0%)	12 (24.5%)	0 (0%)
20	25.9	336.79	132	0.00000000049	4 (9.1%)	0 (0%)	32 (72.7%)	0 (0%)	12 (24.5%)	0 (0%)
2	97.2	76.92	36	0.00000000060	0 (0%)	0 (0%)	26 (59.1%)	0 (0%)	9 (18.4%)	0 (0%)
3	131.2	47.12	18	0.00000000095	1 (2.3%)	0 (0%)	20 (45.5%)	0 (0%)	1 (2.0%)	0 (0%)
3	131.3	89.34	35	0.00000000095	1 (2.3%)	0 (0%)	20 (45.5%)	0 (0%)	1 (2.0%)	0 (0%)

*BRCA1*変異陽性卵巣癌症例に特異的なコピー数変化の同定（表11）

Software: Partek Genomic Suite v6.4

Reference (Baseline): HapMap JPT female 21 samples

Algorithm: Hidden Markov Model　(genomic marker >3)

「Copy Number Variation > 1kb」（Nature Rev Genet 2006)

BRCA1卵巣癌発症
51 samples (**39** families)*

Normal **49** samples
(>65y.o., non-cancer)

VS

BRCA1卵巣癌未発症
30 samples (**16** families)*

Sporadic ov. ca.
44 samples

＊家系数：重複有り

BRCA1-related germline CNV（表12）

chr.	Start (Mb)	Lengths (Kb)	Genomic markers	*BRCA1* (n = 81)		Sporadic (n = 44)		Normal (n = 49)	
				Amp.	Del.	Amp.	Del.	Amp.	Del.
3	138.5	1.58	7	17 (21.0%)	0 (0%)	14 (31.8%)	0 (0%)	0 (0%)	0 (0%)
12	36.5	91.75	4	11 (13.6%)	0 (0%)	8 (18.2%)	0 (0%)	0 (0%)	0 (0%)
14	21.5	63.00	63	0 (0%)	8 (9.9%)	1 (2.3%)	1 (2.3%)	0 (0%)	0 (0%)
4	8.7	159.20	41	8 (9.9%)	0 (0%)	6 (13.6%)	0 (0%)	0 (0%)	0 (0%)
19	61.0	2.23	3	0 (0%)	7 (8.6%)	0 (0%)	2 (4.5%)	0 (0%)	0 (0%)
3	127.1	56.24	54	6 (7.4%)	0 (0%)	8 (18.2%)	0 (0%)	0 (0%)	0 (0%)
4	145.0	55.42	10	6 (7.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
9	103.8	10.57	3	0 (0%)	6 (7.4%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
X	16.9	734.54	217	5 (6.2%)	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	0 (0%)
5	0.9	30.48	7	4 (4.9%)	0 (0%)	3 (6.8%)	0 (0%)	0 (0%)	0 (0%)
X	28.7	109.16	100	4 (4.9%)	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	0 (0%)

BRCA1 ovarian cancer-related CNV（表13）

chr.	Start (Mb)	Lengths (Kb)	Genomic markers	*BRCA1* affected unchanged	*BRCA1* affected Amp.	*BRCA1* affected Deletion	*BRCA1* unaffected changed	Normal changed	Sporadic changed
3	138.5	1.58	7	38	13	0	4	0	14
19	61.0	2.23	3	44	0	7	0	0	2
12	36.5	91.75	4	46	5	0	6	0	8
3	127.1	2.50	4	46	5	0	2	0	8
4	145.0	55.42	10	46	5	0	1	0	0
9	103.8	10.57	3	47	0	4	2	0	0
3	127.1	56.24	54	47	4	0	2	0	7
5	0.9	30.48	7	47	4	0	0	0	3
14	21.5	63.00	63	47	0	4	4	0	1/1
4	8.7	159.20	41	47	4	0	4	0	6
X	16.9	734.54	217	47	4	0	1	0	1
X	28.7	109.16	100	47	4	0	0	0	1

Deletion at 19q13.42（表14）

Family No.	BRCA1 mutation	19q13.42 CNV (+)	CNV (-)
17	3834-3836del3,insC	260T*	263N
31	2730-2731delCC	31-2T	31-1T†
33	L63X	33-1T	33-2N*, 33-5N, 33-6N, 33-10N
A18	L63X	A18-1T	
B3	L63X	B3-1T	B3-2N*, B3-3N
B11	L63X	B11-1T, B11-2T	

発症者：赤，未発症：青

*: >65 y.o.

†: undifferentiated type

Deletion at 9q31.1（表15）

Family No.	BRCA1 mutation	9q31.1 CNV (+)	CNV (-)
1	241delA	16T, 15N	
26	3516-3517delTT	26-1T	26-2T†, 26-3N, 26-6N
55	Q934X	55-1T	
65	L63X	65-1T	

発症者：赤，未発症：青

*: >65 y.o.

†:endometrioid type

Amplification at Xp21.3（表16）

Family No.	BRCA1 mutation	Xp22.13 CNV (+)	CNV (-)
14	2080delA	230T, 231T	235N, 238N
B11	L63X	B11-1T, B11-2T	-

発症者:赤, 未発症:青

*: >65 y.o.

only female

Amplification at Xp22.13（表17）

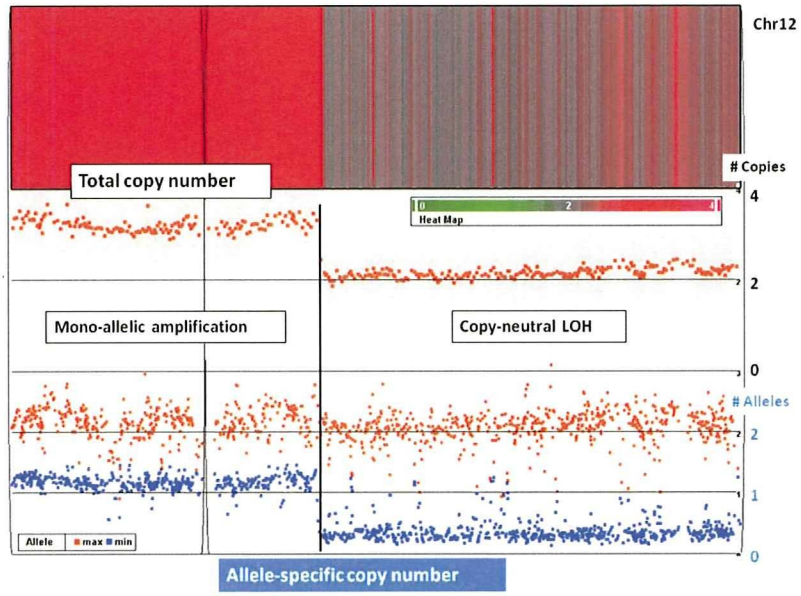
Family No.	BRCA1 mutation	Xp22.13 CNV (+)	CNV (-)
14	2080delA	230T, 231T, 238N	235N
B11	L63X	B11-1T, B11-2T	-

発症者:赤, 未発症:青

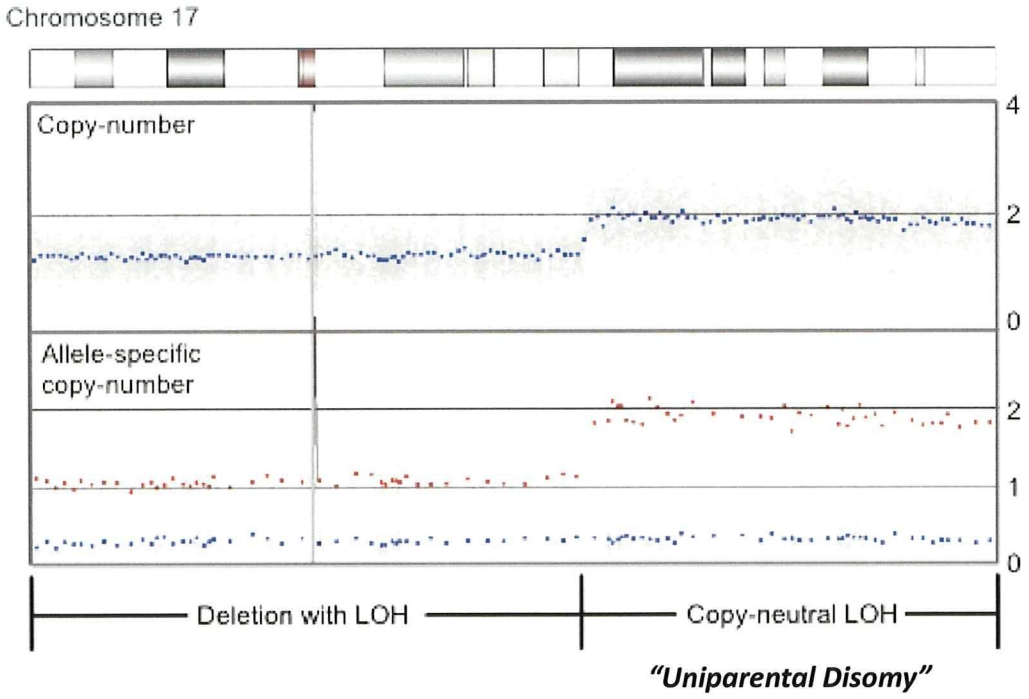
*: >65 y.o.

only female

図 1

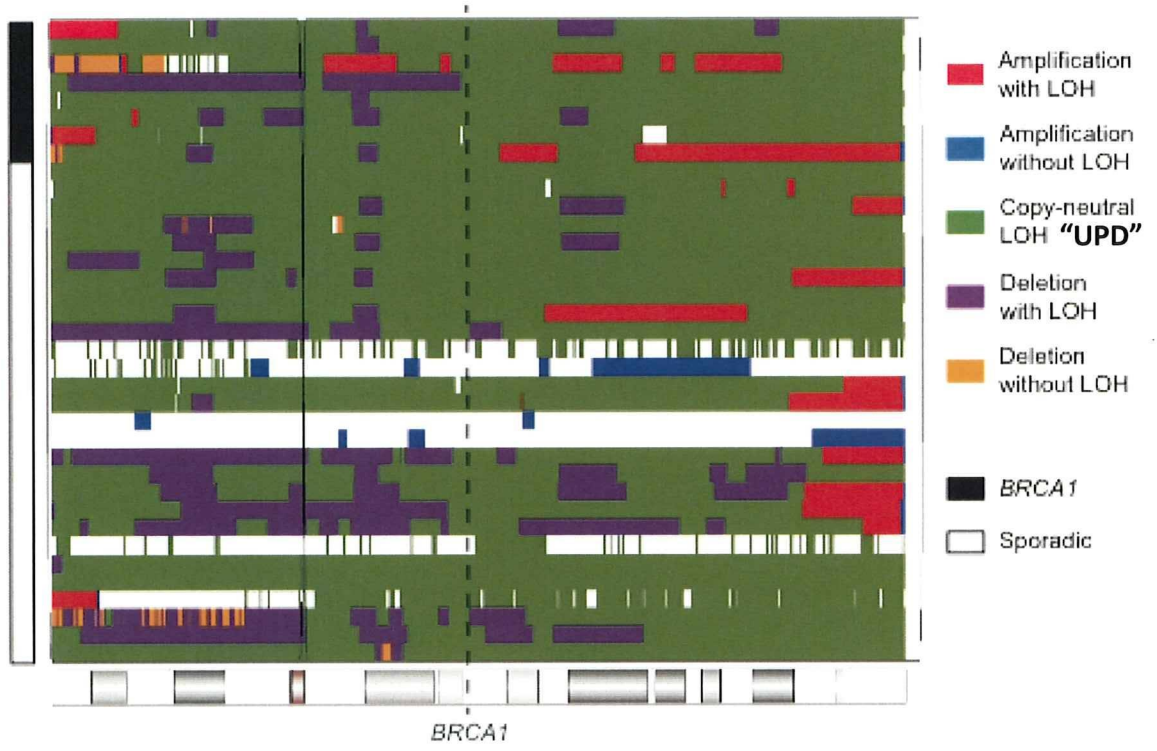

Chr12
Total copy number
Copies
4
2
0
Heat Map
Mono-allelic amplification
Copy-neutral LOH
Alleles
2
1
0
Allele
max
min
Allele-specific copy number

片親性ダイソミー（図2）
（Uniparental Disomy: UPD, copy-neutral LOH)

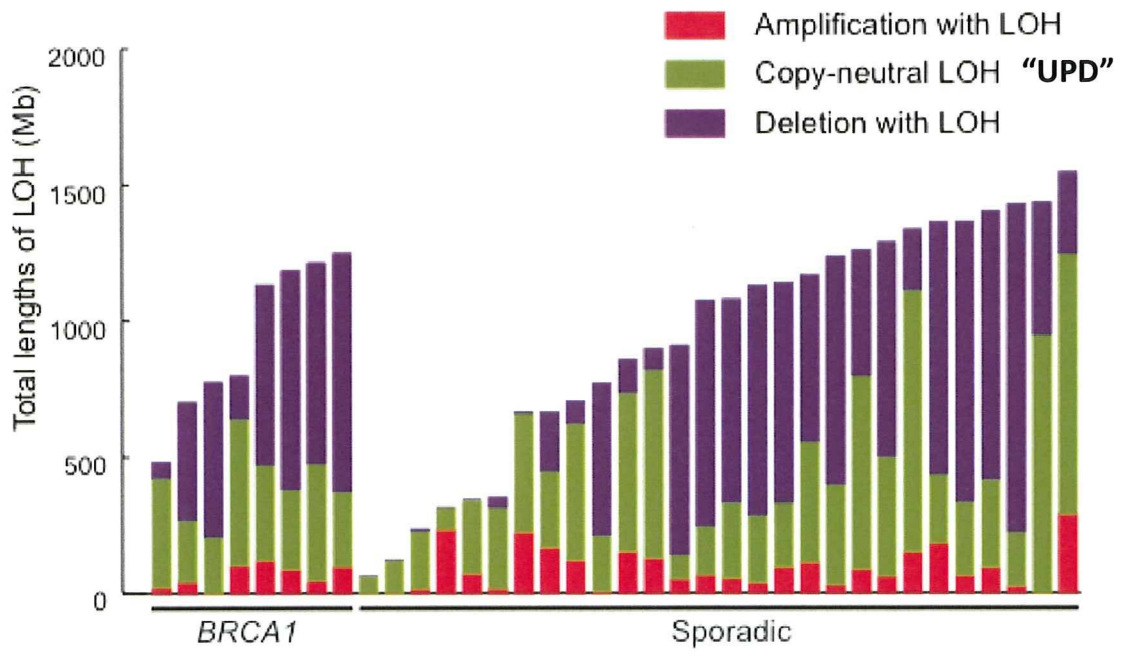


"Uniparental Disomy"

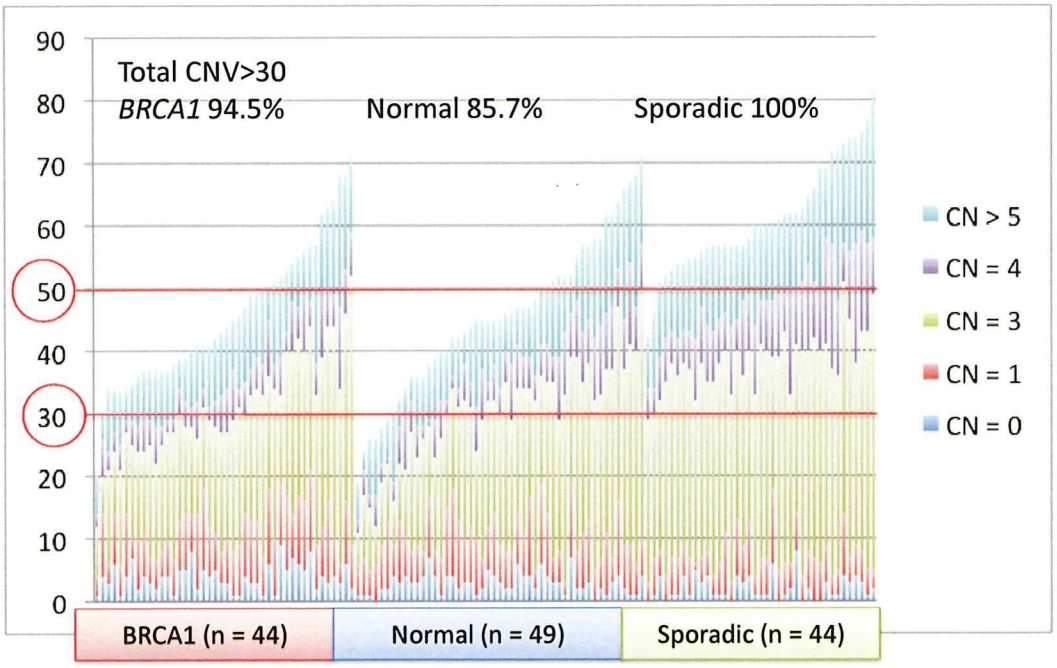
Chromosome 17（図3）



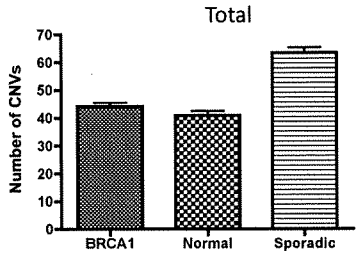
片親性ダイソミーの頻度（図4）



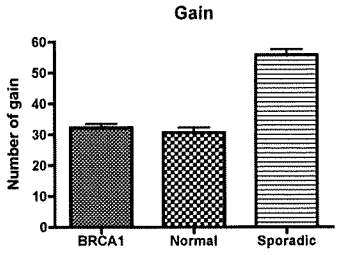
Total number of CNV(図5)



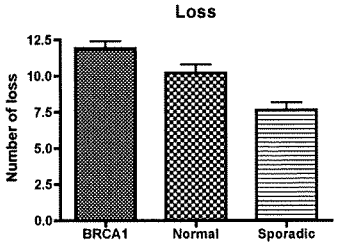
CNV frequency（図6）



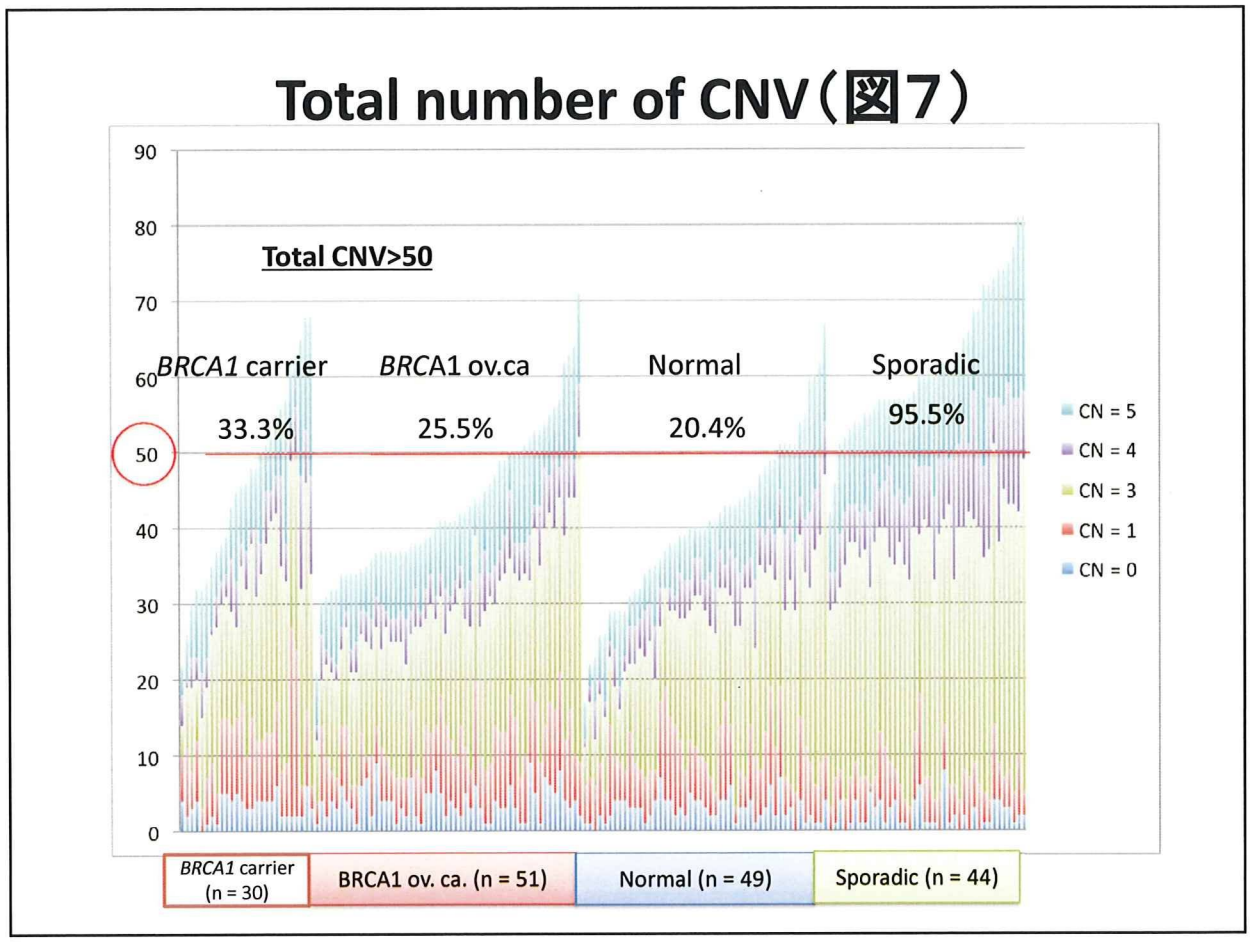
Kruskal-Wallis test: p<0.0001
Dunn's Multiple Comparison Test
BRCA1 vs Normal: p>0.05
BRCA1 vs Sporadic: p<0.001
Sporadic vs Normal: p<0.001



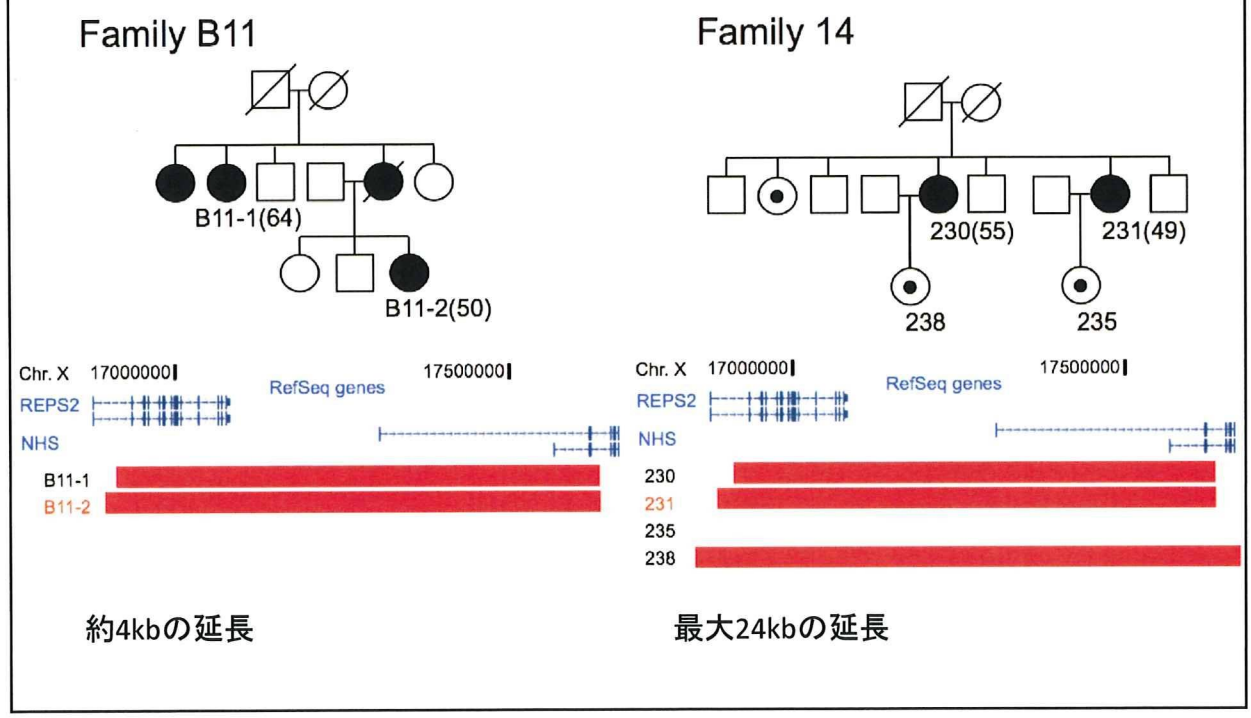
Kruskal-Wallis test: p<0.0001
Dunn's Multiple Comparison Test
BRCA1 vs Normal: p>0.05
BRCA1 vs Sporadic: p<0.001
Sporadic vs Normal: p<0.01



Kruskal-Wallis test: p<0.0001
Dunn's Multiple Comparison Test
BRCA1 vs Normal: p>0.05
BRCA1 vs Sporadic: p<0.001
Sporadic vs Normal: p<0.01


Total number of CNV（図7）
Total CNV>50
BRCA1 carrier
BRCA1 ov.ca
Normal
Sporadic
33.3%
25.5%
20.4%
95.5%
90
80
70
60
50
40
30
20
10
0
CN = 5
CN = 4
CN = 3
CN = 1
CN = 0
BRCA1 carrier (n = 30)
BRCA1 ov. ca. (n = 51)
Normal (n = 49)
Sporadic (n = 44)

Genetic anticipation（図8）



約4kbの延長

最大24kbの延長