Molecular pathogenesis in granulosa cell tumor is not only due to somatic *FOXL2* mutation

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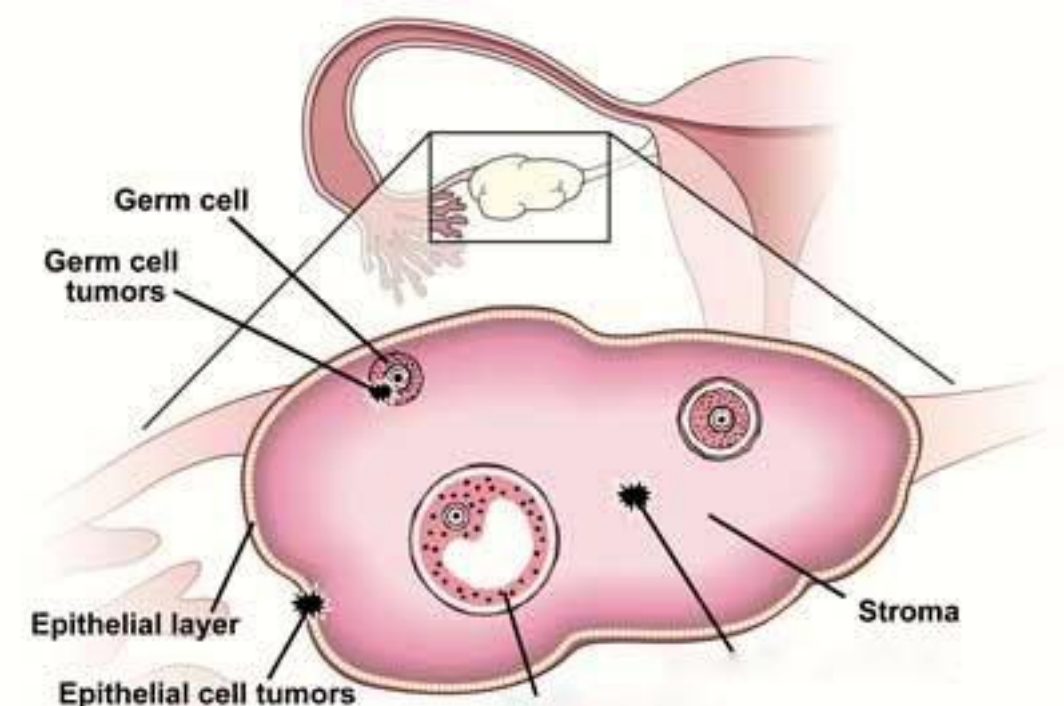
Types of Ovarian Cancer

- Sex Cord-Stromal
  - 5-10%
- Epithelial
  - 65-70%
- Germ Cell
  - 15-20%
- Metastasis
  - 5%



Sex Cord-Stromal

Sex Cord-Stromal Tumors

- Develop from the gonadal stroma
- Account for 5-10% of all ovarian neoplasms
- The most common types
  - Granulosa cell tumor
  - Theca cell tumor
  - Sertoli-Leydig cell tumor
  - Fibroma

estrogen-producing

Hormonal effects

Granulosa Cell Tumor

- Clinical presentation and histopathologic differences
- Adult Granulosa Cell Tumor
  - ~95% of GCT
  - perimenopausal or postmenopausal women
- Juvenile Granulosa Cell Tumor
  - Much more rare
  - premenarchal and premenopausal women

FOXL2 gene mutation 402C>G (C134W)

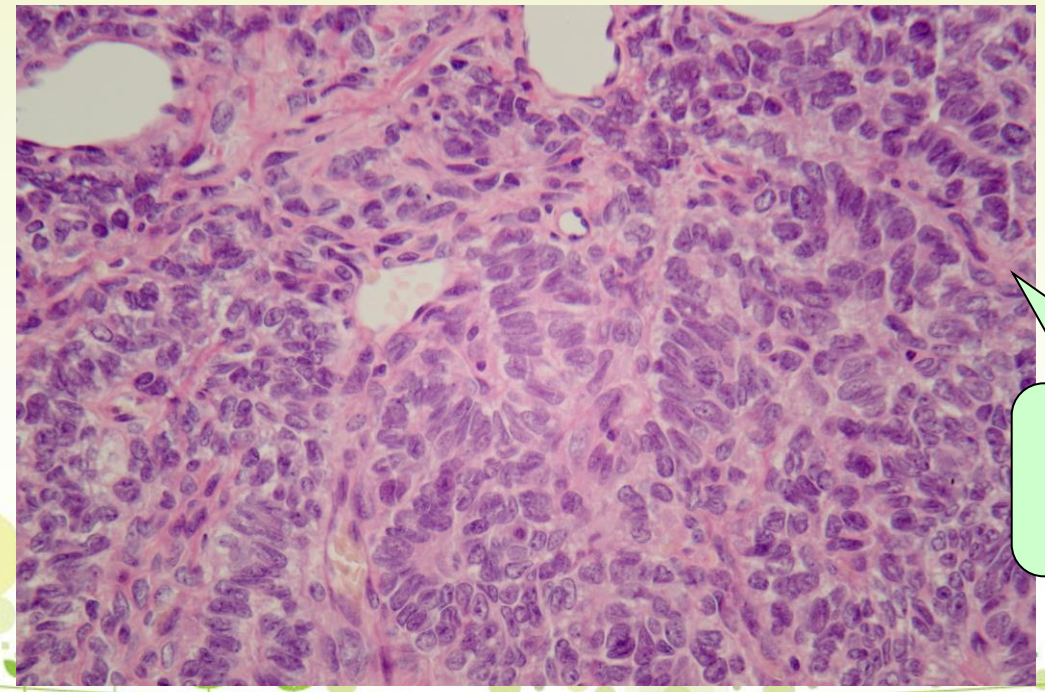
- Mutation of *FOXL2* in Granulosa-Cell Tumors of the Ovary
  - N Engl J Med 2009; 360:2719-2729
- Adult-type granulosa cell tumors and *FOXL2* mutation
  - Cancer Res. **2009** Dec 15;69(24):9160-2
- The role of *FOXL2* in the pathogenesis of adult ovarian granulosa cell tumours
  - Gynecol Oncol. **2014** May;133(2):382-7

Granulosa cell tumor
a case report

- An 80-year-old woman
  - clinically detectable pelvic mass
  - laparotomy for total hysterectomy and bilateral salpingo-oophorectomy
- An ovarian mass
  - with attached fallopian tube
  - 11.0 × 8.0 × 7.0 cm
  - brownish in color and elastic
  - On cut, the ovary was yellowish in color and soft.

Figure 1 Granulosa cell tumor

Histological cross-section after hematoxylin and eosin staining shows the adult granulosa cell tumor component



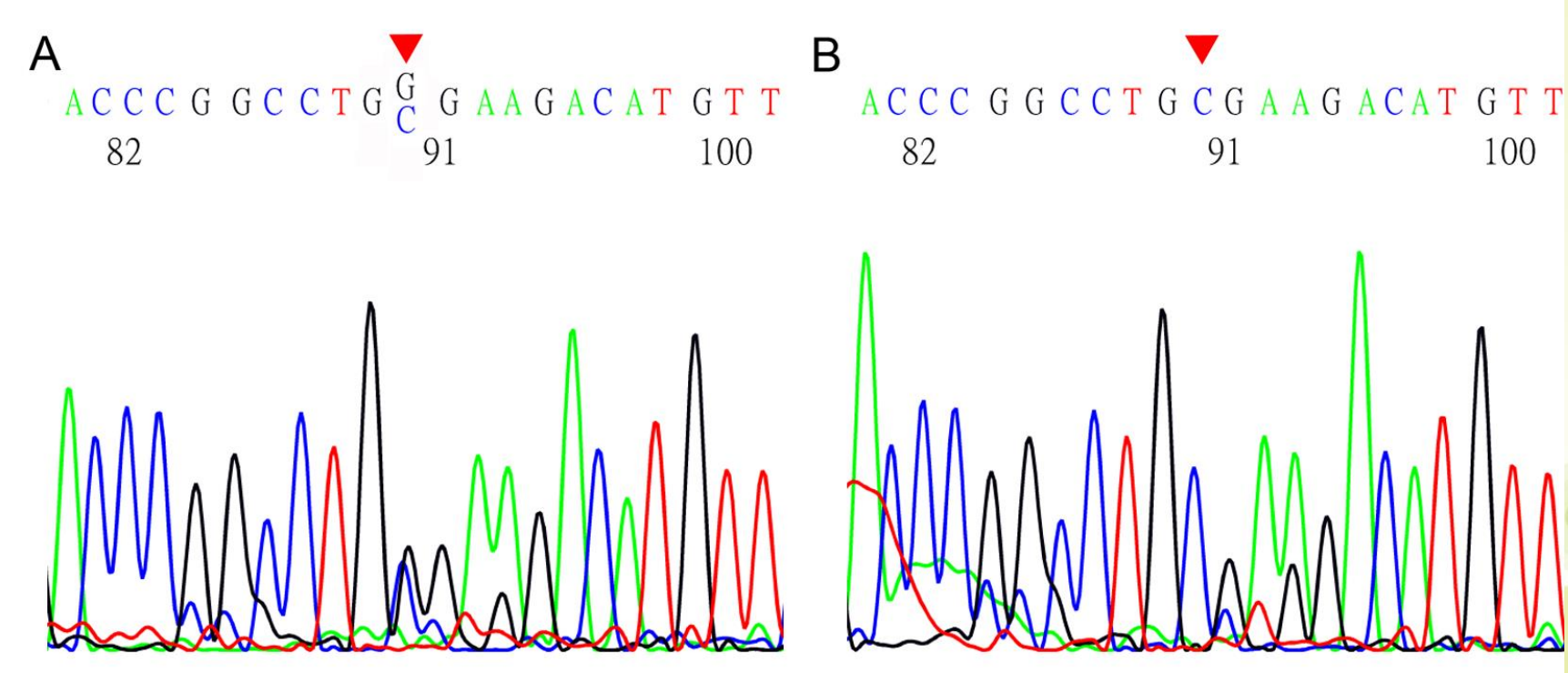
In this case of granulosa cell tumor

- Tumor marker of granulosa cell tumor

	immediately after operation	**one month post-operation**
Inhibin A	47.208	15.533
Inhibin B	92.473	22.331

- No recurrent disease was noted during 3-year post-operation follow-up period.

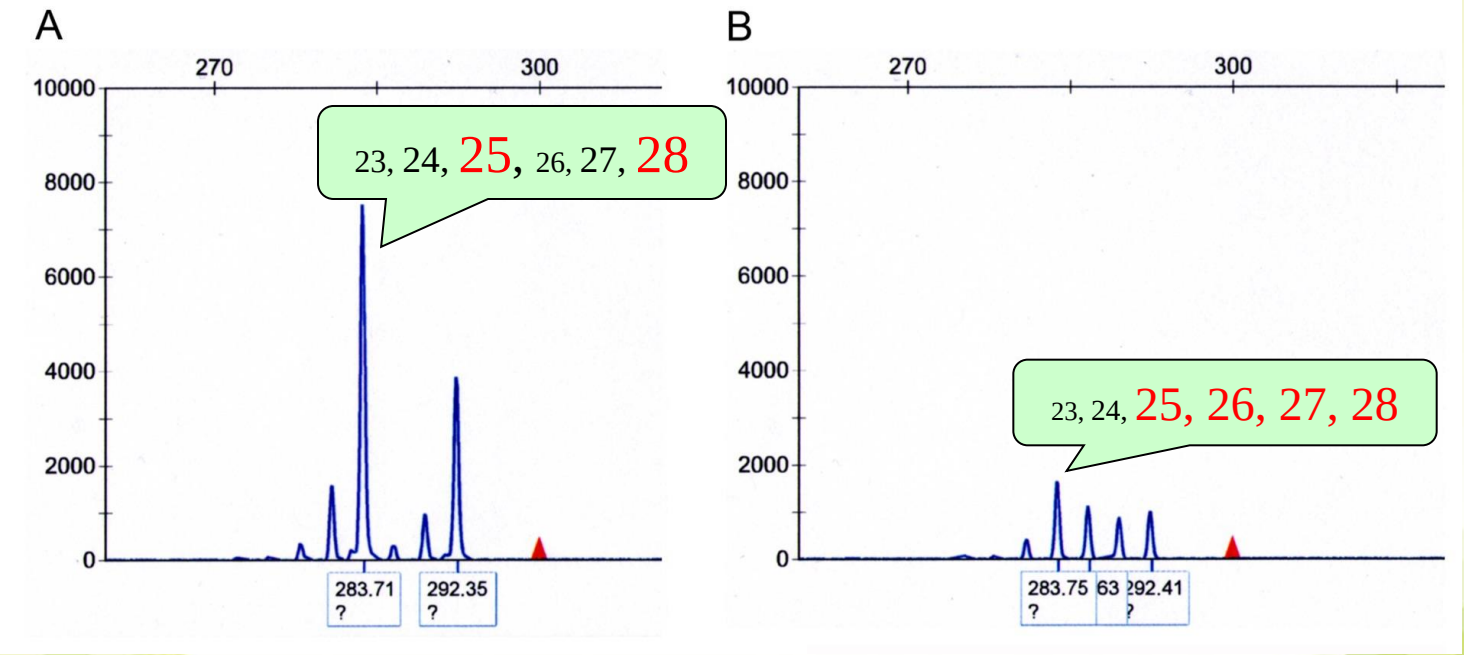
The granulosa cell tumor section revealed heterozygous *FOXL2* 402C>G mutation



(A) DNA from tumor

(B) DNA from normal cell

Figure 2 Replication error was detected on analysis of the lengths of CAG repeats in androgen receptor



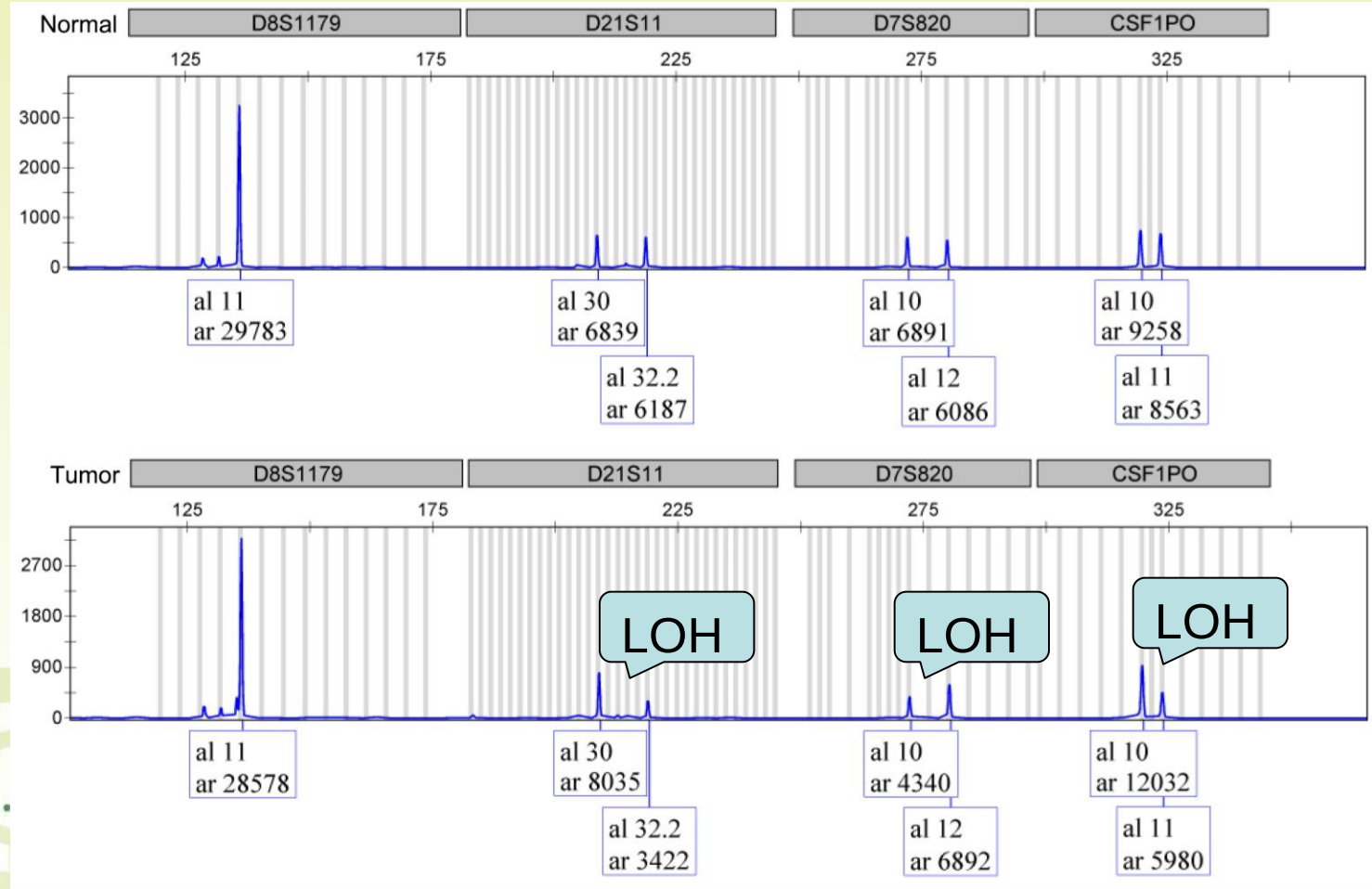
(A) DNA from normal cell (B) DNA from tumor

This result is consistent with a previous study

DNA replication error is frequent in ovarian granulosa cell tumors.

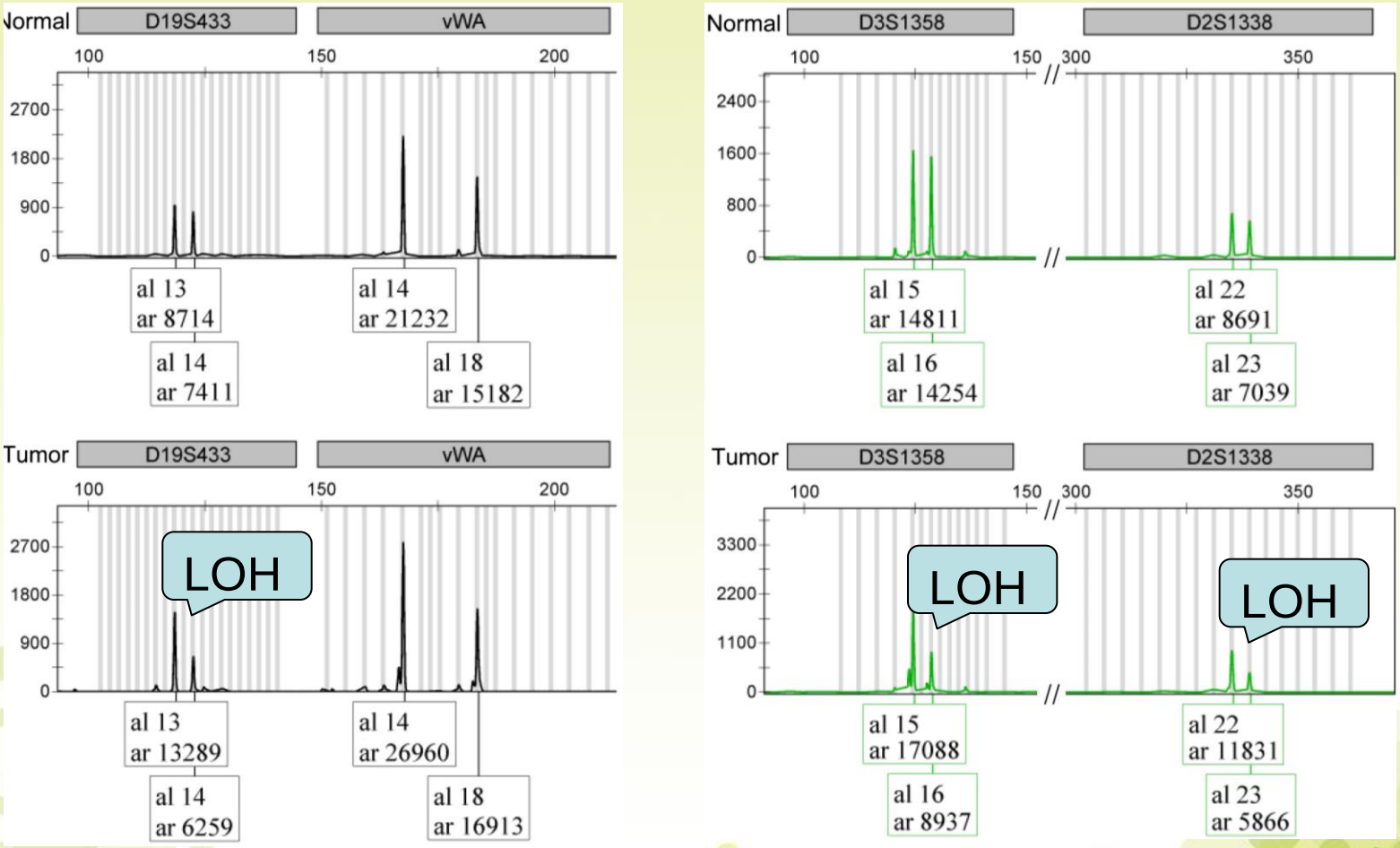
Suzuki M et al. Cancer Genet Cytogenet. (2000)

Figure 3 LOH (Loss of heterozygosity) for a number of STR markers



STR analysis with AmpFlSTR SGM Plus PCR amplification kit

Figure 3 LOH (Loss of heterozygosity) for a number of STR markers



STR analysis with AmpFlSTR SGM Plus PCR amplification kit

Table 1 Loss of heterozygosity in 15 STR loci of the granulosa cell tumor

STR Loci	Location	Alleles	R[a]
TPOX	2p23-2per	8, 8	ND
D2S1338	2q35-37.1	22, 23	1.63[b]
D3S1358	3p21.31	15, 16	1.84[b]
FGA	4q28	22, 23	1.01
D5S818	5q21-31	11, 11	ND
CSF1PO	5q33.3-34	10, 11	1.86[b]
D7S820	7q11.21-22	10, 12	0.56[b]
D8S1179	8q24.1-24.2	11, 11	ND
TH01	11p15.5	9, 9	ND
vWA	12p12-pter	14, 18	1.14
D13S317	13q22-31	10, 13	0.94
D16S539	16q24-qter	9, 11	1.11
D18S51	18q21.3	14, 18	1.06
D19S433	19q12-13.1	13, 14	1.81[b]
D21S11	21q11.2-q21	30, 31.2	2.12[b]

R = area $(T_1/T_2)/(N_1/N_2)$

LOH is positive when R ≥ 1.25 or ≤ 0.8 (ie., 20% change)

Figure 4 Array comparative genomic hybridization (aCGH) analysis

(B) DNA from tumor

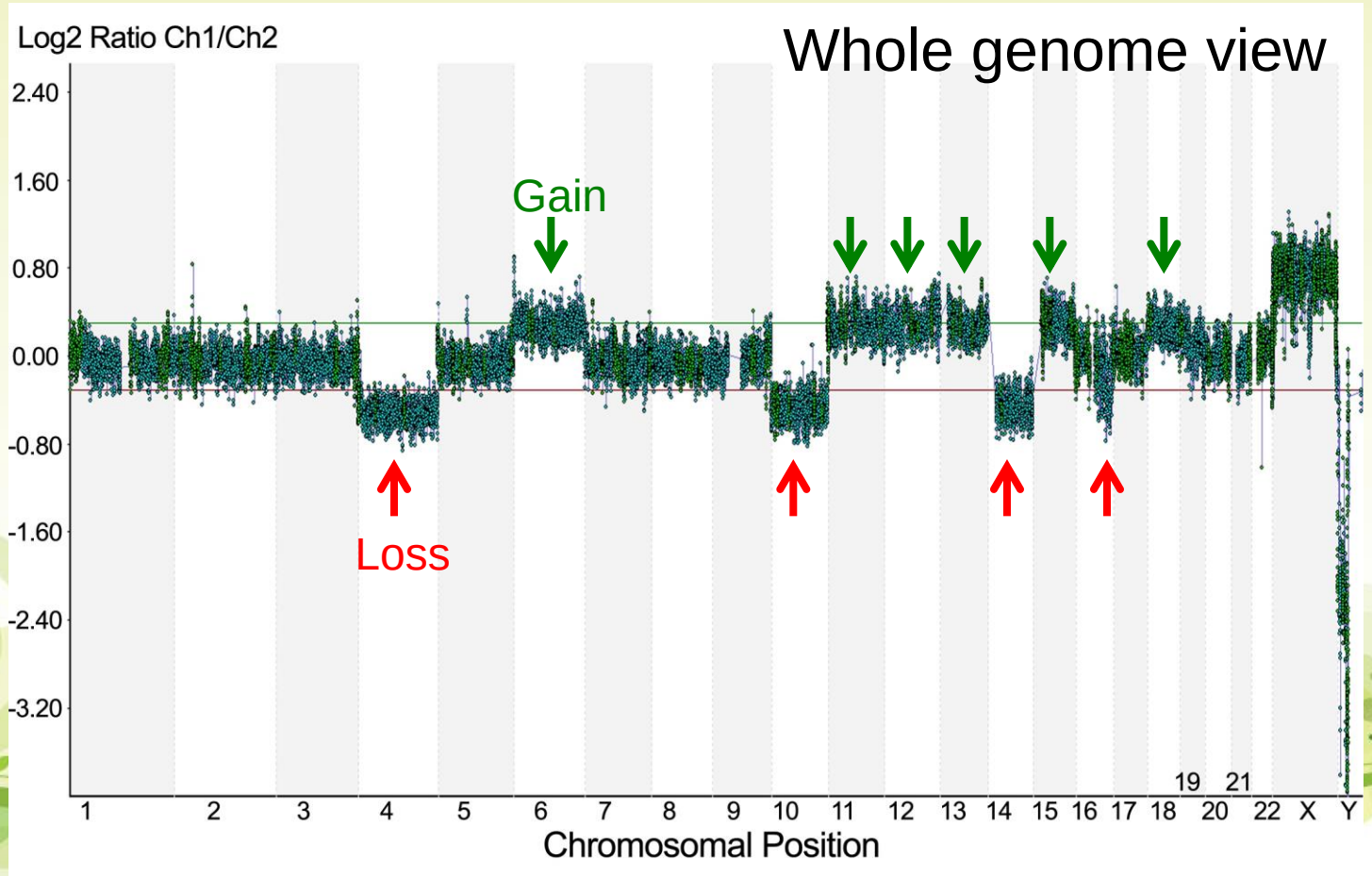


Table 2 The deleted or duplicated clones and their physical location in the granulosa cell tumor

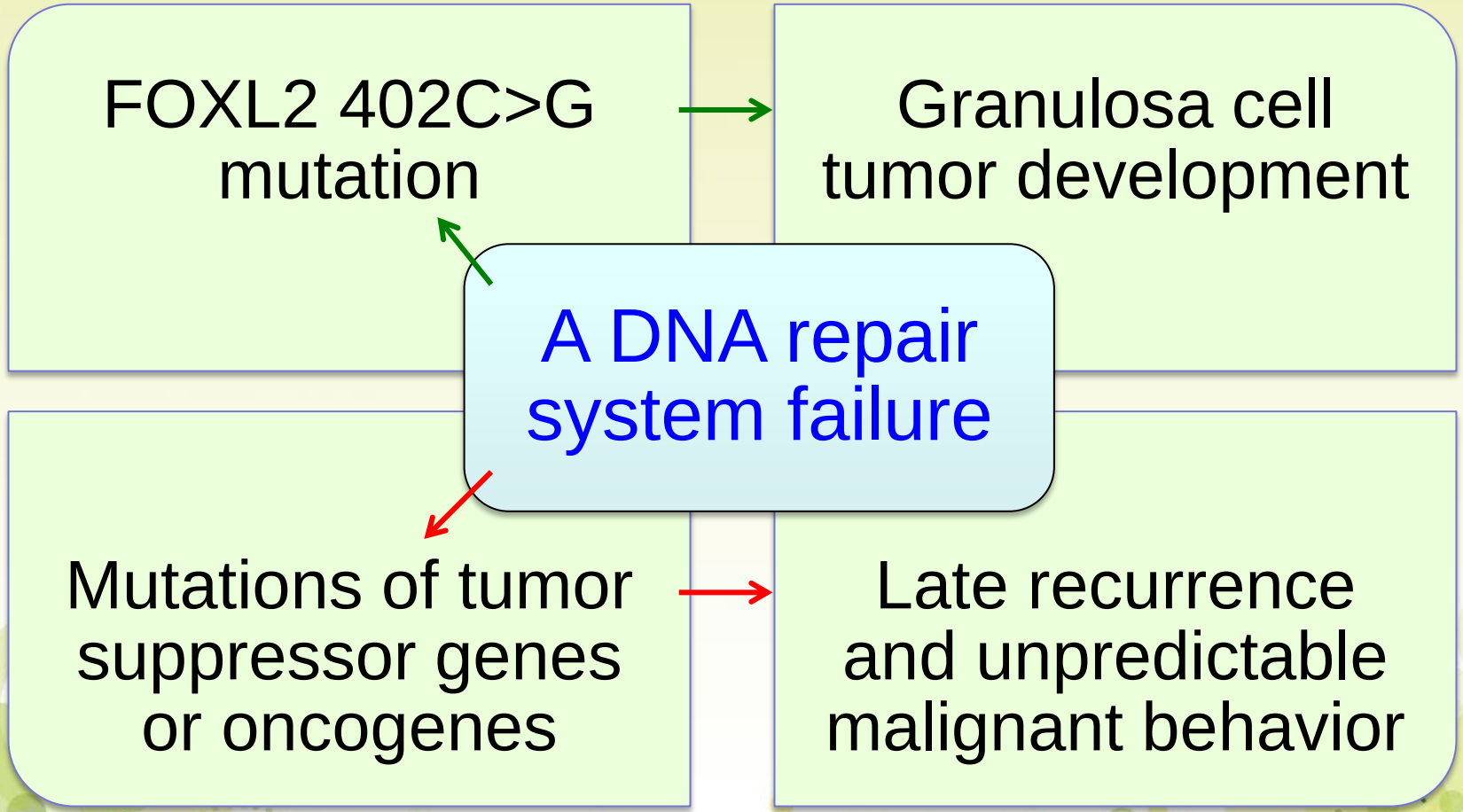
1	arr 4p16.3q35.2(37,152-190,896,645)×1	LOSS	190,859,493
2	arr 6p25.3q27(163,113-170,921,060)×2 ~ 3	GAIN	170,757,947
3	arr 10p15.3q26.3(136,391-135,434,149)×1	LOSS	135,297,758
4	arr 11p15.5q25(196,990-134,868,378)×2 ~ 3	GAIN	134,671,388
5	arr 12p13.33q24.33(230,451-133,773,499)×2 ~ 3	GAIN	133,543,048
6	arr 13q12.11q34(20,407,324-115,092,619)×2 ~ 3	GAIN	94,685,295
7	arr 14q11.2q32.33(20,608,246-107,287,476)×1	LOSS	86,679,230
8	arr 15q11.1q26.3(20,686,219-102,383,444)×2 ~ 3	GAIN	81,697,225
9	arr 16q11.2q24.3(46,500,771-90,148,364)×1 ~ 2	LOSS	43,647,593

These results imply that

A defective upstream regulatory gene is involved in this condition

DNA mismatch repair system failure appears likely in this patient

Our Hypothesis



Conclusions

- In addition to the FOXL2 402C>G mutation, we found DNA replication error and loss of heterozygosity in an adult-type granulosa cell tumor.

- DNA mismatch repair system failure appears likely in this patient.

Conclusions

It does suggest the need to incorporate DNA mismatch repair system examination into the clinical management of patients with granulosa cell tumor.

Wang and Lai *Journal of Ovarian Research* 2014, **7**:88
http://www.ovarianresearch.com/content/7/1/88

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CASE REPORT **Open Access**

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Wen-Chung Wang[1] and Yen-Chein Lai[2*]

Thanks for your attention

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Near MLH1

R = area $(T_1/T_2)/(N_1/N_2)$

LOH is positive when R ≥ 1.25 or ≤ 0.8 (ie., 20% change)

DNA mismatch repair system

Human	Bacterial	Function	Chromosome	Start	End
MSH2	MutS	Single mismatch, loop repair	2p21	47403067	47512577
MSH3	MutS	Loop repair	5q11-12	8065648	80876815
MSH4	MutS	Meiosis	1p31	75796871	75913238
MSH5	MutS	Meiosis	6p21.3	31739948	31762678
MSH6/GTBP	MutS	Single mismatch	2p16	47783082	47806953
MLH1	MutL	Mismatch repair	3p21.3	36993350	37050846
PMS2	MutL	Mismatch repair	7p22.2	5973239	6009106
PMS1	MutL	Mismatch repair	2q31.1	189784085	189877629

- These four genes were tested negative for somatic mutations.