Case presentation

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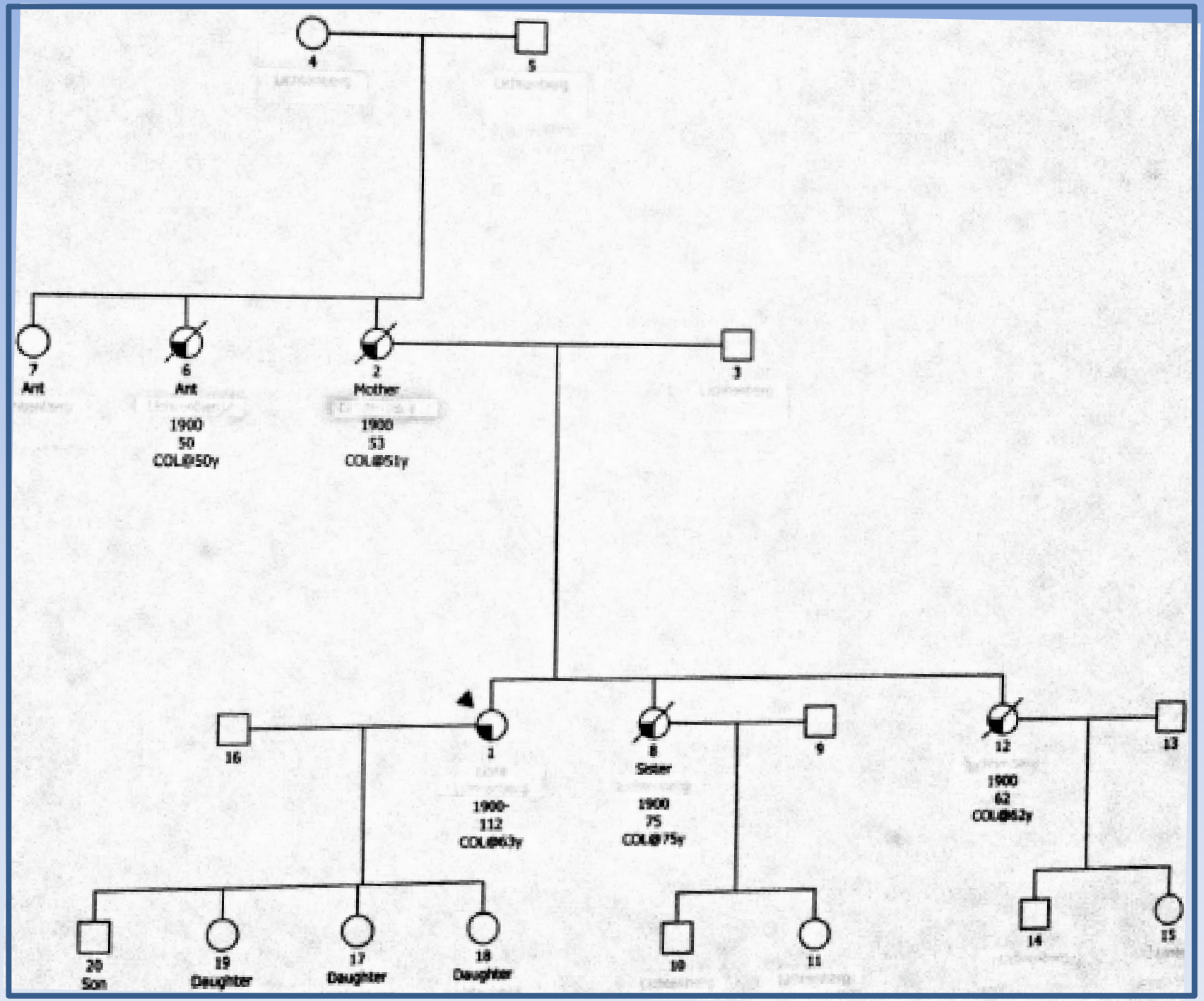
Case history

- 63 year old female patient
- Ashkenazi parents, no consanguinity
- Interval cancer (2 years after normal colonoscopy-) obstructing the descending colon
- Subtotal colectomy: mucinous carcinoma with Crohn's-like reaction with no TILS
- Staging: T3N0Mx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Mother
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COL@63y
8
Sister
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75
COL@75y
9
12
1900
62
COL@62y
13
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Son
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Daughter
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Daughter
18
Daughter
10
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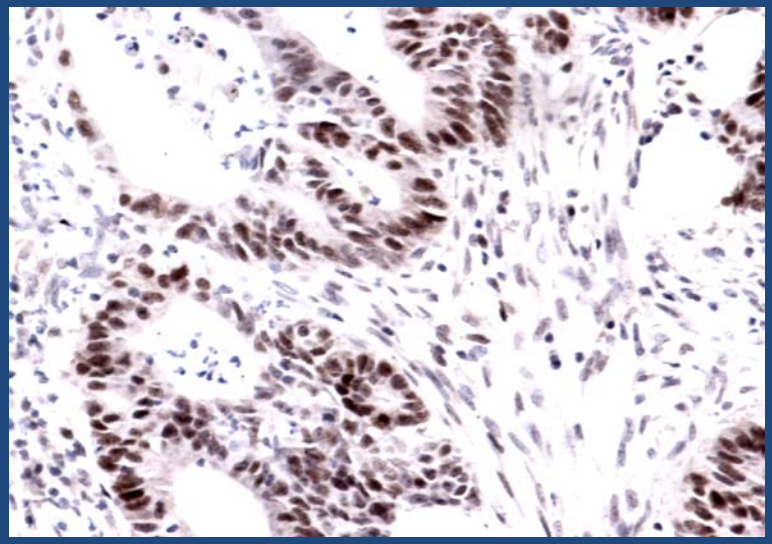
15

Family history

- No other family members evaluated (tumor or genetically)
- No known polyps in family
- No extracolonic malignancies described

Tumor analysis: Immunohistochemistry

MSH2



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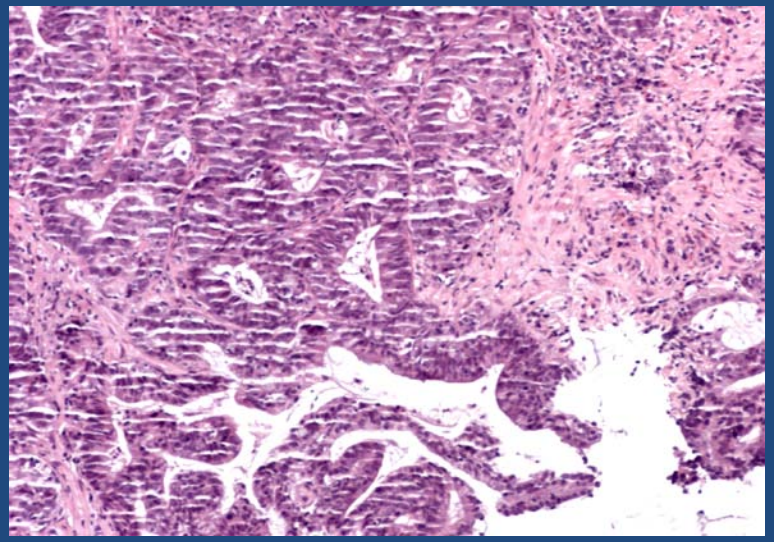
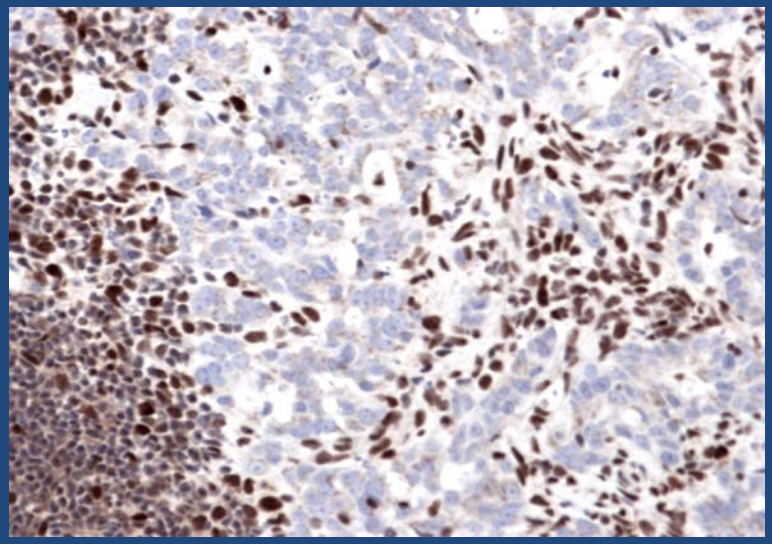


MLH1



MLH1/PMS2 negative
MSH2/MSH6 positive

Tumor analysis: Microsatellite Instability

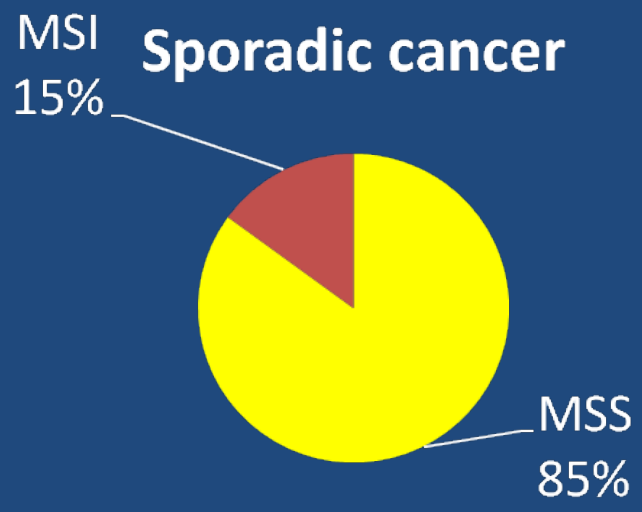
- MSI in 5/5 standard markers: unstable

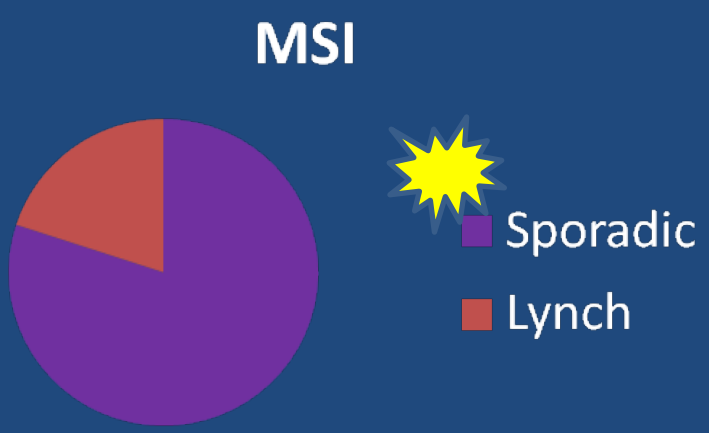
(BAT-25, BAT-26, NR-21, NR-21 and MONO-27)

Sequencing

- MLH1: no mutations
- MLH1 MLPA for insertions/deletions: normal
- PMS2: no mutations
- PMS2 MLPA: no evidence of deletion

Not every MSI tumor is Lynch





Inactivation of the MLH1 promoter by somatic methylation in the tumor

IHC will show MLH1 deficiency and MSI will be unstable

MSI sporadic vs. Lynch

- Methylation
- BRAF gene usually (not always) be mutated in these sporadic cancers, always WT in Lynch
- Rare cases of inherited constitutional methylated MLH1 (normal gene sequence) have been described

Back to the patient..

- Tumor MLH1 methylation- positive (methylation specific-MLPA, MRC-Holland)
- Constitutional MLH1 methylation (blood)- negative (0)
- **BRAF p.Val600Glu**: Wild type

What do we have?

- Suspected Lynch family, Amsterdam I criteria
- Proband tumor expression: MLH1 deficient
- MSI High
- No MMR germline mutation identified
- MLH1 promoter methylated in tumor
- No constitutional methylation
- BRAF wild type

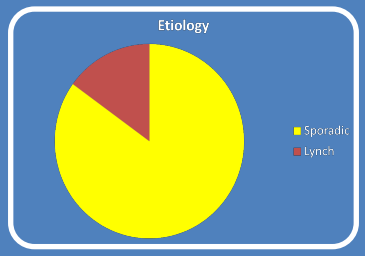
Differential Diagnosis

Lynch syndrome

- Unknown mutation
- Co-existing methylation

Different genetic syndrome

- X??/MYH
- With sporadic methylation causing MSI



Proband has sporadic cancer and is not a carrier

- Family has Lynch syndrome/X
- Tumor analysis in the family pending

Lynch phenotype with no mutation

- Approach to management-
  - meanwhile, no discounts for family members, f/u for gynecological malignancies
- Prevalence
- Further evaluation

Lynch Syndrome (Hereditary Nonpolyposis Colorectal Cancer) Diagnostics

Kristina Lagerstedt Robinson

J Natl Cancer Inst 2007;99:291–9

Table 1. Hereditary nonpolyposis colorectal cancer screening of patients from 285 families*

Criteria	MSI status	No. of patients with MMR mutation/total	MMR gene mutation type	
			Pathogenic	Unknown
Amsterdam family	Positive	43/43	38	5
	Negative	8/17	5	3
	Total	51/60	43	8
Non-Amsterdam family	Positive	10/17	9	1
	Negative	2/171†	1	1
	Total	12/188	10	2
Single patients	Positive	5/5	4	1
	Negative	0/32	0	0
	Total	5/37	4	1
All patients		68/285	57	11

Further evaluation

- Test family members- tumor gene expression, MSI, methylation
- Alternative genetic syndromes: MYH, BRCA, syndrome X
- Refine genetic analysis for Lynch syndrome beyond exome sequencing:

- Analyze flanking genes
- Analyze cDNA
- Perform long range PCR
- Modifier genes and miRNAs

Table 2. *TGFBR1* Exon 1 Genotypes by MMR Gene Mutation Status

MMR Status	*9A/*9A	*9A/*6A	*6A/*6A	*6A Allelic Frequency
MMR positive (n = 144)	115	28	1	0.104
MMR negative (n = 64)	43	17	4*	0.195†

Abbreviations: MMR, mismatch repair; *9A, *TGFBR1*; *6A, *TGFBR1**6A.
*$P = 0.032$ (Fisher's exact test, two sided).
†$P = 0.011$ (χ^2 test of independence).

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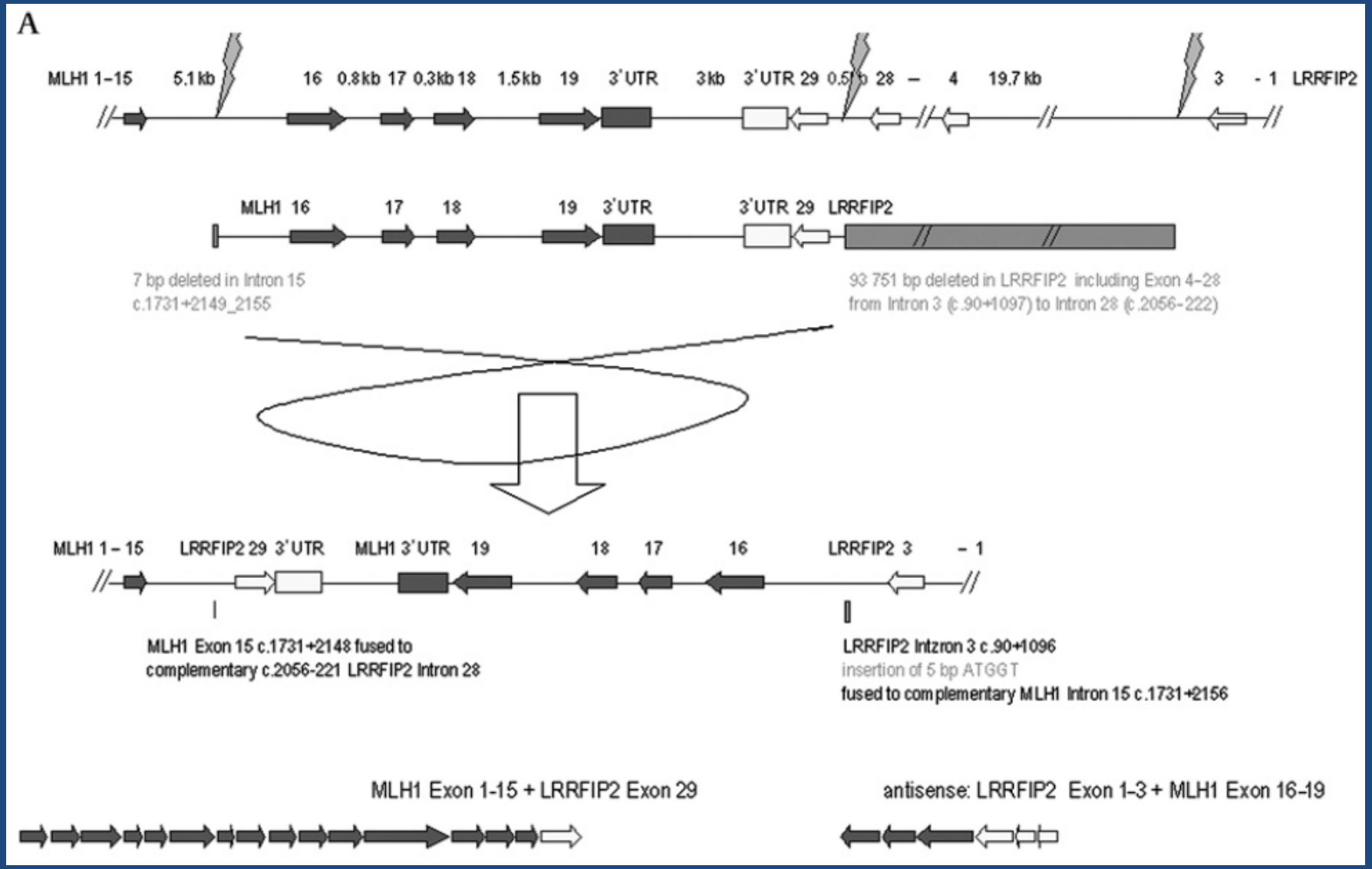
VOLUME 23 · NUMBER 13 · MAY 1 2005
JOURNAL OF CLINICAL ONCOLOGY



J Med Genet 2011;**48**:513–519.