LI-FRAUMENI SYNDROME : UPDATE ON MOLECULAR BASIS AND CLINICAL MANAGEMENT

Thierry Frebourg
Department of Genetics, University Hospital
Inserm U1079, Faculty of Medicine
Institute for Research and Innovation in Biomedicine
Rouen, Normandy, France
and French LFS working group

I. THE HISTORICAL LFS DEFINITION

1988

Li and Fraumeni, Annals of Internal Medicine 1969
Li et al., Cancer Research 1988

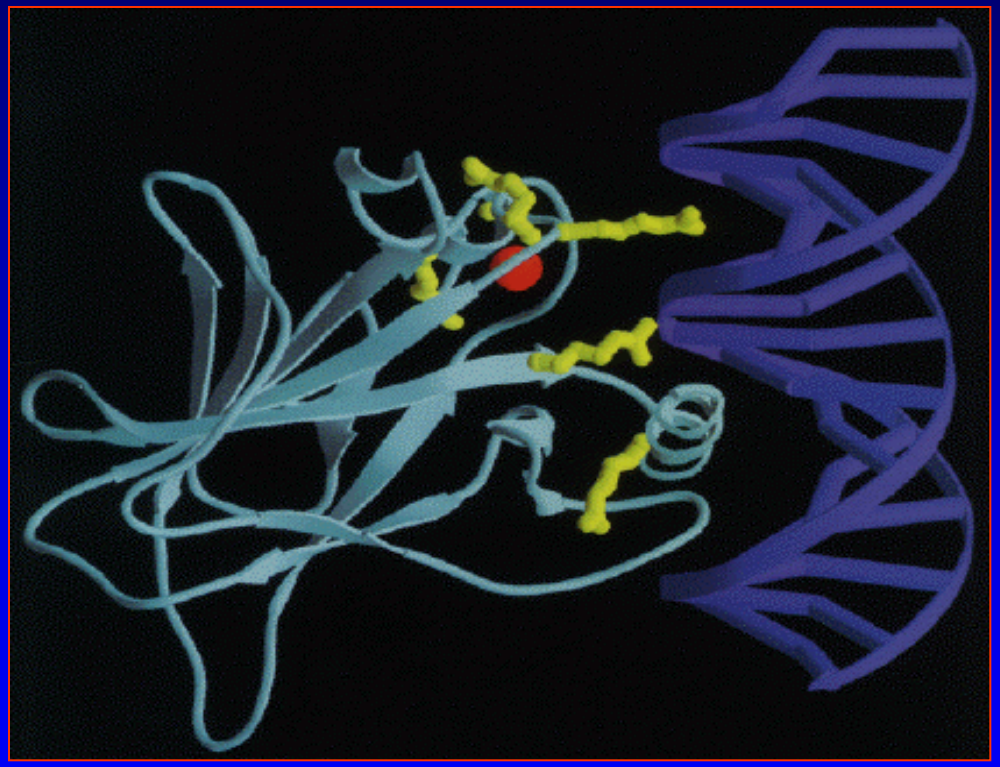
641 children with rhabdomyosarcoma

1. A proband aged under 45 years with a sarcoma *and*
2. A first degree relative under 45 years with any cancer *and*
3. Another first- or second-degree relative in the same lineage with any cancer under 45 years or a sarcoma at any age

II. THE MOLECULAR LFS DEFINITION

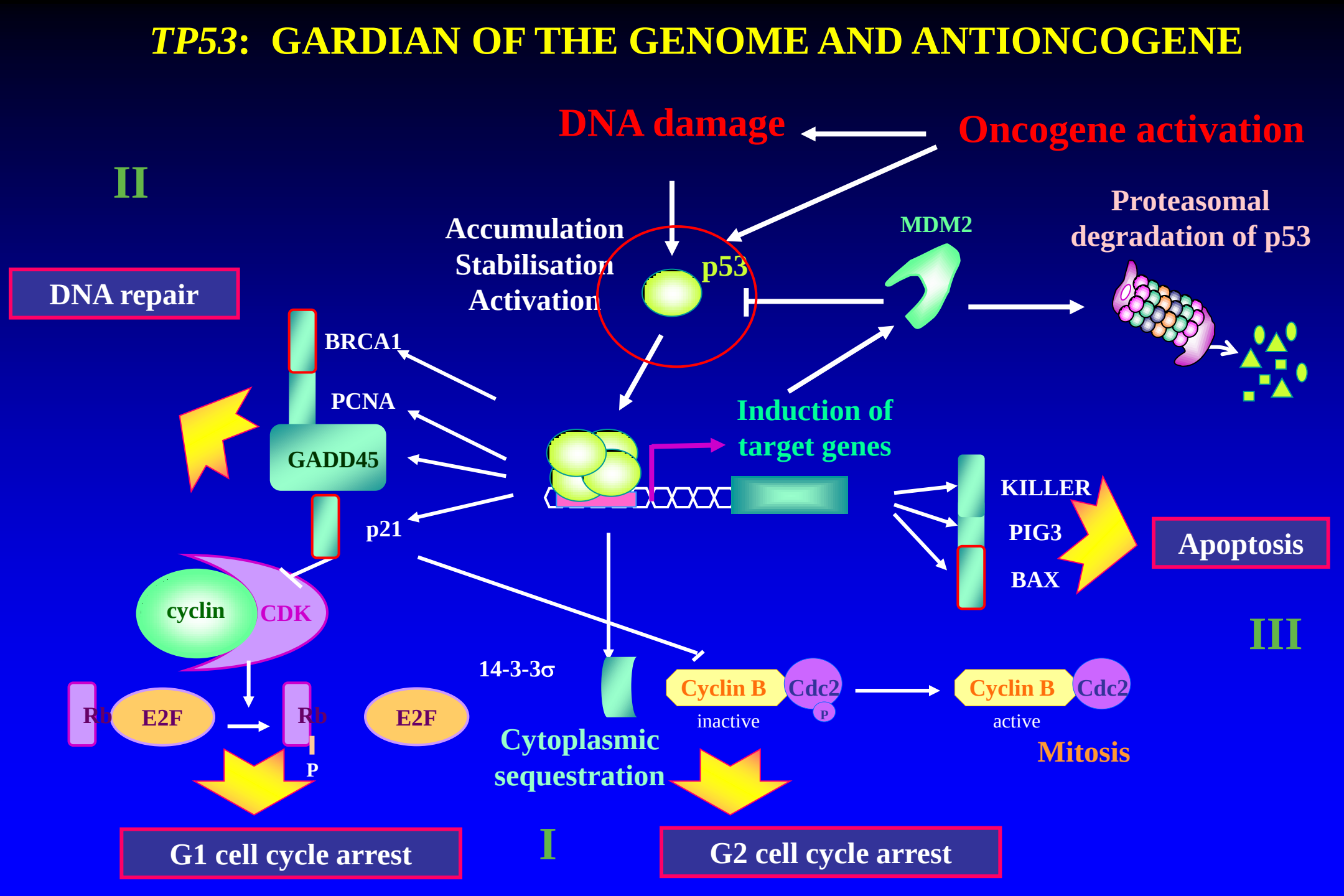
1990

TP53



Malkin et al., Science 1990; Strivastava et al., Science 1990

TP53: GARDIAN OF THE GENOME AND ANTIONCOGENE



III. THE CHOMPRET CRITERIA FOR THE LI-FRAUMENI SYNDROME

I. A proband with a LFS tumour
(soft-tissue sarcoma, osteosarcoma, brain tumour, adrenocortical carcinoma, breast cancer, leukaemia, bronchoalveolar lung cancer)
under 46 years
and
One first- or second- degree relative with a LFS tumour (except breast cancer if the proband has a breast cancer) under 56 years or with multiple tumours

II. A proband with multiple primary tumours (except multiple primary breast cancers), two of which belonging to the narrow LFS spectrum, the first being developed before 46 years

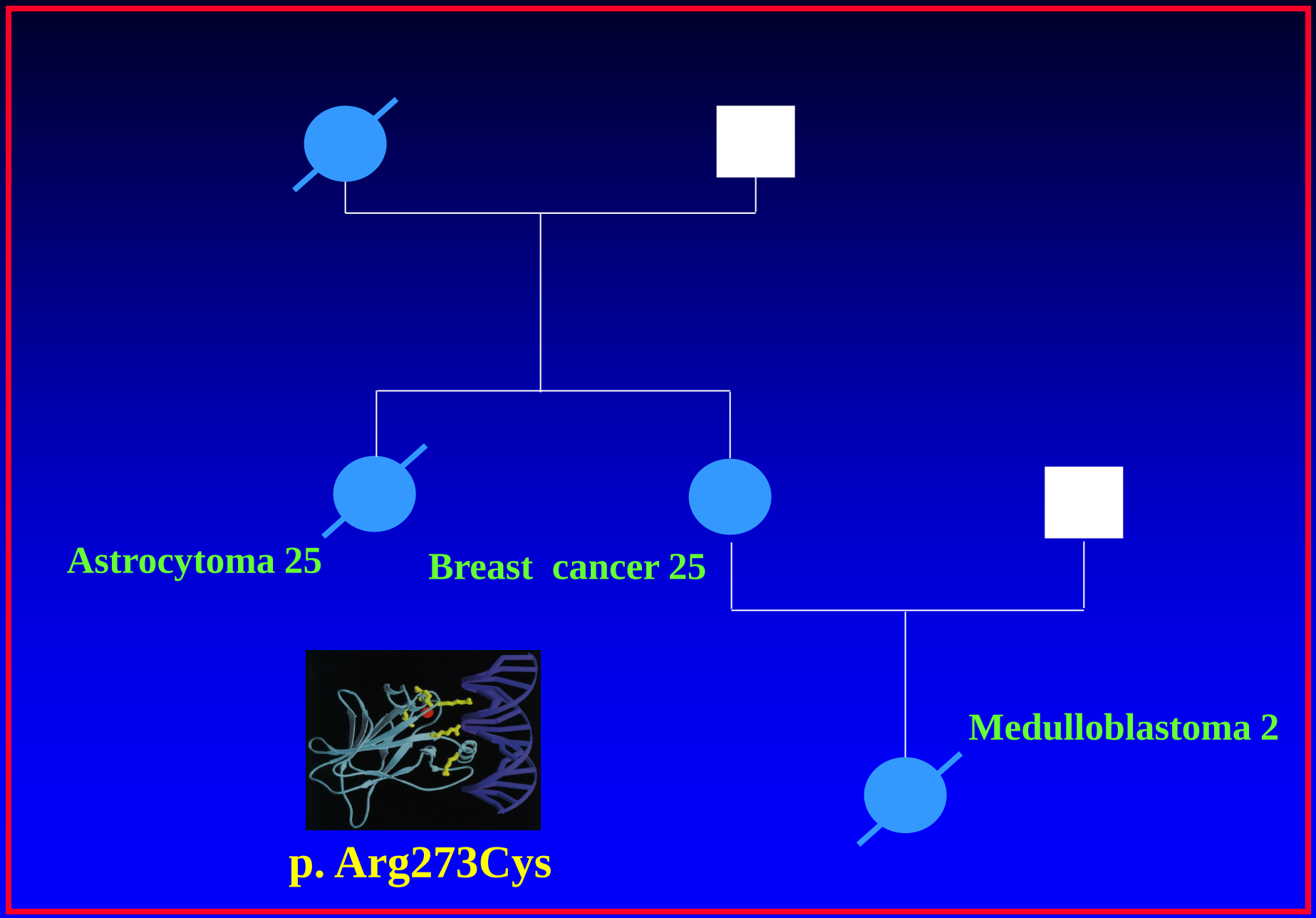
III. A proband with adrenocortical carcinoma or choroïd plexus cancer irrespective of the family history

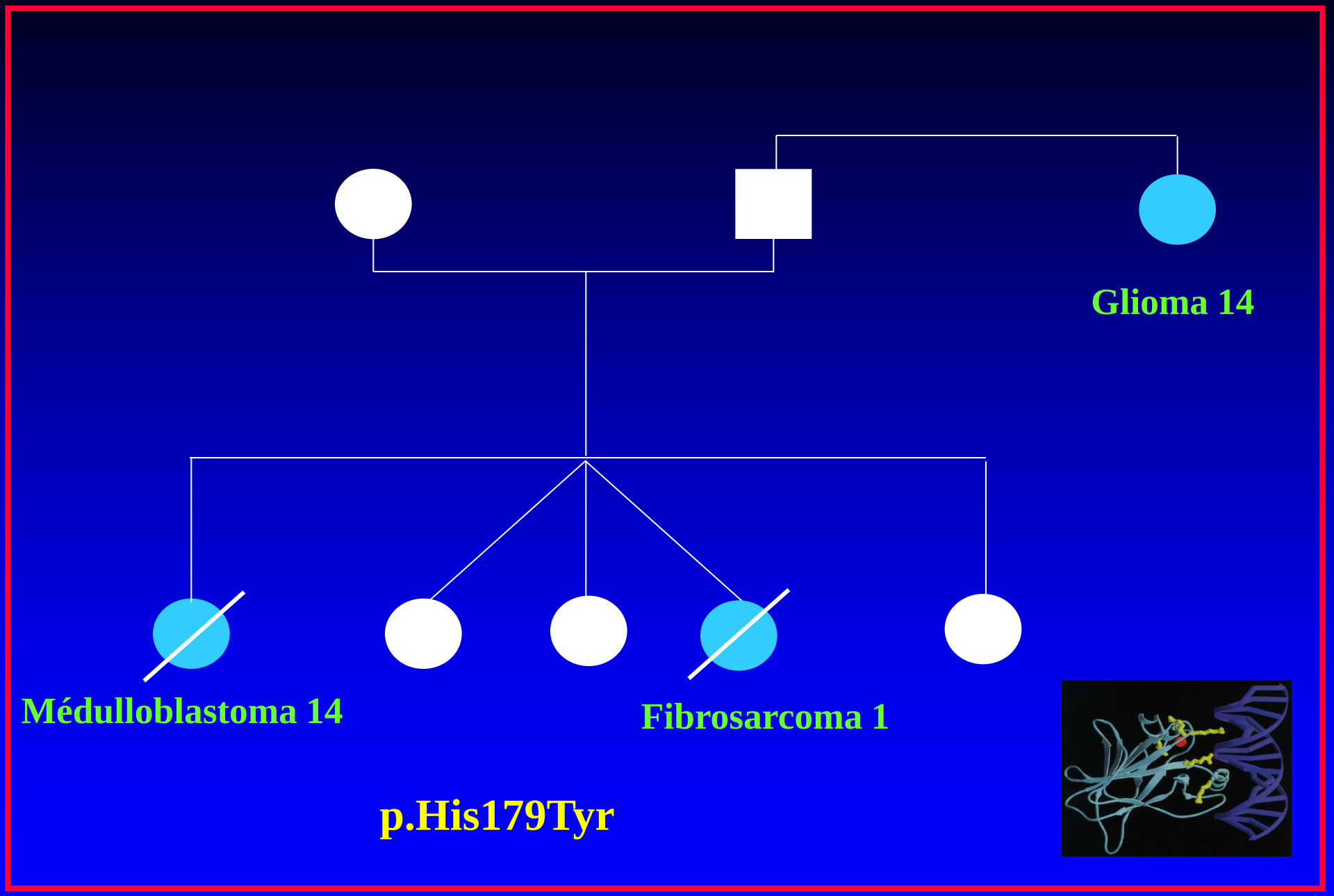
Mutation detection rate = 29%
(Sensitivity = 82%)
(Specificity = 58%)

VOLUME 27 · NUMBER 26 · SEPTEMBER 10 2009
JOURNAL OF CLINICAL ONCOLOGY

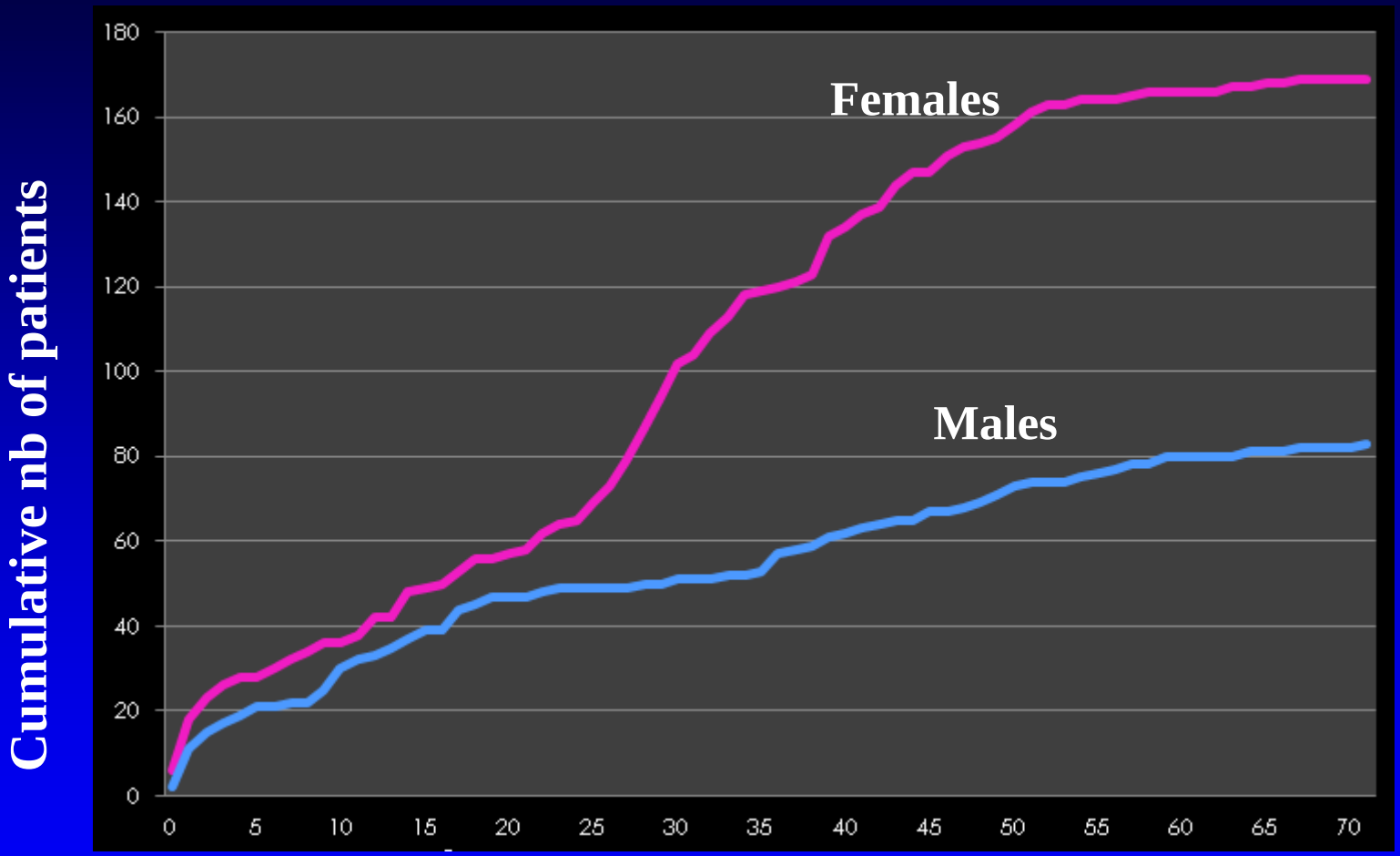
2009 Version of the Chompret Criteria for Li Fraumeni Syndrome

Tinat J, Bougeard G, Baert-Desurmont S, Vasseur S, Martin C, Bouvignies E, Caron O, Bressac-de Paillerets B, Berthet P, Dugast C, Bonaïti-Pellié C, Stoppa-Lyonnet D, Frébourg T.


Astrocytoma 25
Breast cancer 25
Medulloblastoma 2
p. Arg273Cys


Glioma 14
Médulloblastoma 14
Fibrosarcoma 1
p.His179Tyr

IV. AGE OF FIRST TUMOUR ONSET IN MALES AND FEMALES



252 affected *TP53* mutation carriers

French LFS consortium, 2012

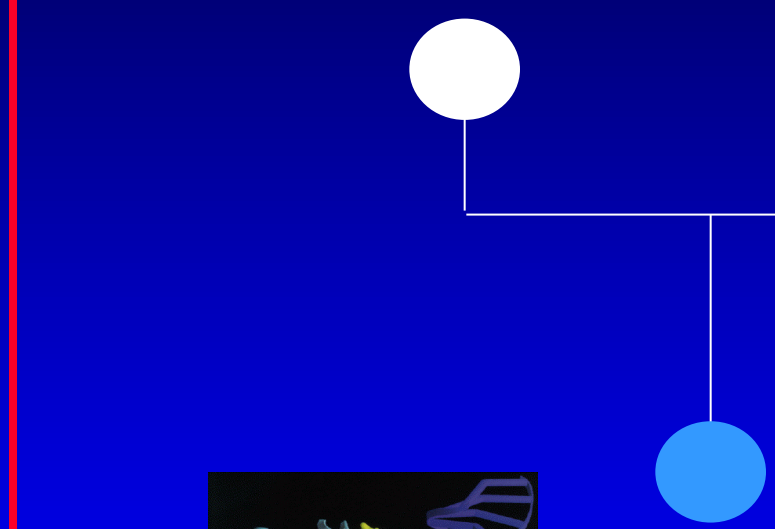
IV. MEAN AGE OF TUMOUR ONSET

	Number of tumours	Mean age (years)	Age range (years)
Breast cancer	**143**	**34**	**20-69**
Soft-tissue sarcoma	**75**	**31**	**<1-70**
Osteo/chondrosarcoma	**47**	**20**	**6-55**
Brain tumour	**36**	**15**	**<1-67**
Adrenocortical carcinoma	**31**	**6**	**<1-32**

252 affected *TP53* mutation carriers

French LFS consortium, 2012

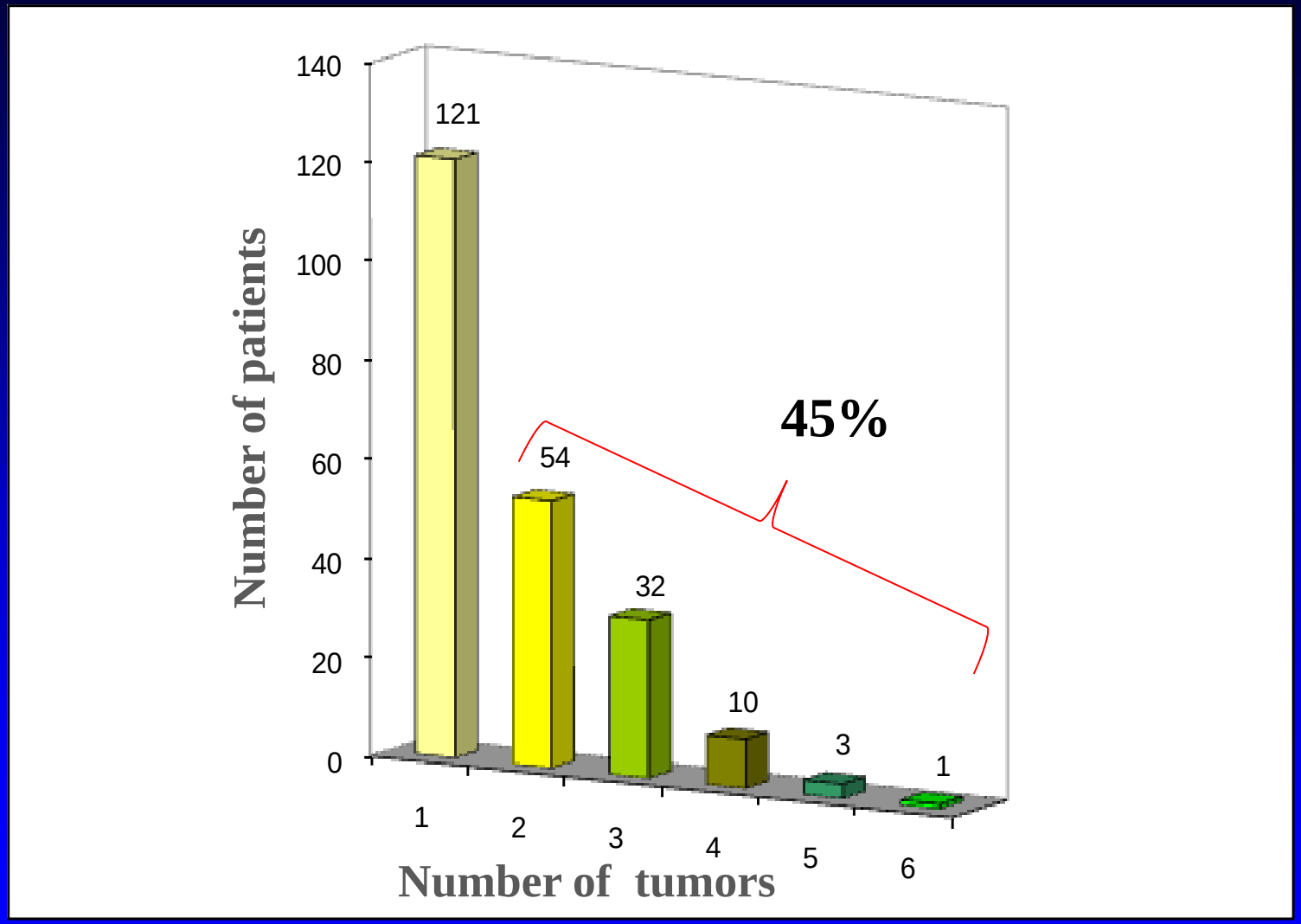
V. FREQUENCY OF MULTIPLE PRIMARY TUMOURS IN LFS



Sarcoma 2
Adrenocortical carcinoma 6
Osteosarcoma 14
Left breast cancer 22
Right breast cancer 25

p.Pro152Leu

V. FREQUENCY OF MULTIPLE PRIMARY TUMOURS IN LFS



252 affected *TP53* mutation carriers

French LFS consortium, 2012

VI. RISK OF RADIOTHERAPY IN LFS PATIENTS

Int. J. Cancer (Radiat. Oncol. Invest): **96,** 238–242 (2001)
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Publication of the International Union Against Cancer

Two Metachronous Tumors in the Radiotherapy Fields of a Patient with Li-Fraumeni Syndrome

Jean-Marc Limacher, M.D.,[1*] Thierry Frebourg, M.D., Ph.D.,[2]
Shanti Natarajan-Ame, M.D.,[1] and Jean-Pierre Bergerat, M.D.,[1]

Heymann *et al. Radiation Oncology* 2010, **5**:104
http://www.ro-journal.com/content/5/1/104

RADIATION ONCOLOGY

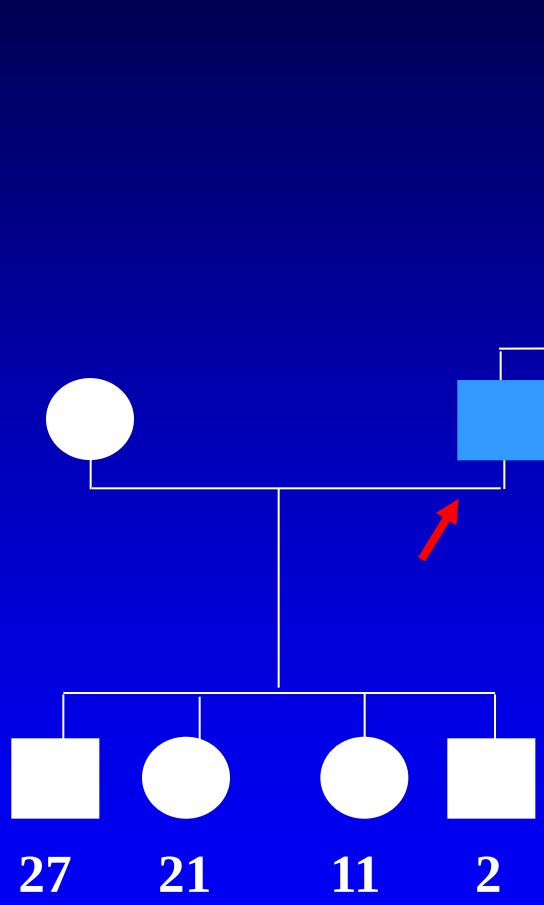
RESEARCH Open Access

Radio-induced malignancies after breast cancer postoperative radiotherapy in patients with Li-Fraumeni syndrome

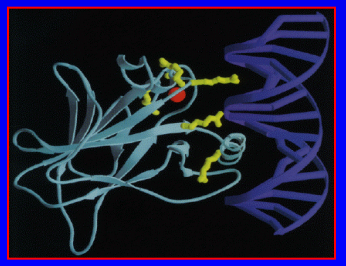
Steve Heymann[1*], Suzette Delaloge[2], Arslane Rahal[2], Olivier Caron[3], Thierry Frebourg[4], Lise Barreau[5], Corinne Pachet[5], Marie-Christine Mathieu[6], Hugo Marsiglia[1,7], Céline Bourgier[1]

Avoid radiations if possible

VII. LATE ONSET LFS ASSOCIATED TO *TP53* NULL MUTATION



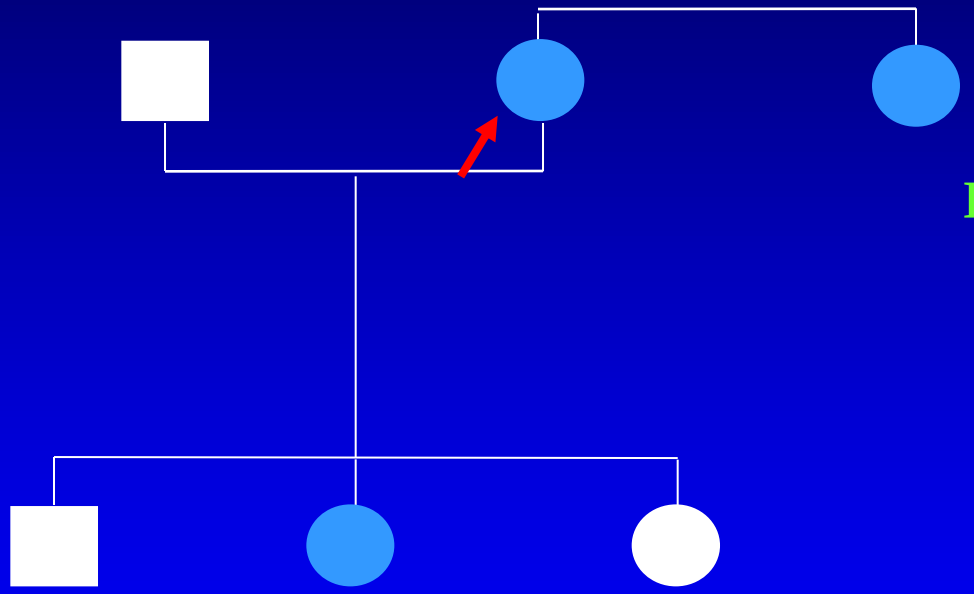
Renal cell carcinoma 41
Sarcoma 48
Liposarcoma
Leiomyosarcoma 51
Rectal adenocarcinoma 53



c.991>T, p.Gln331X, exon 9

VII. LATE ONSET LFS ASSOCIATED TO *TP53* NULL MUTATION

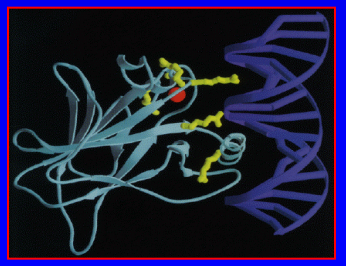
Uterus leiomyosarcoma 44
Renal cell adenocarcinoma 68
Colon leiomyosarcoma 69



Liposarcoma 57

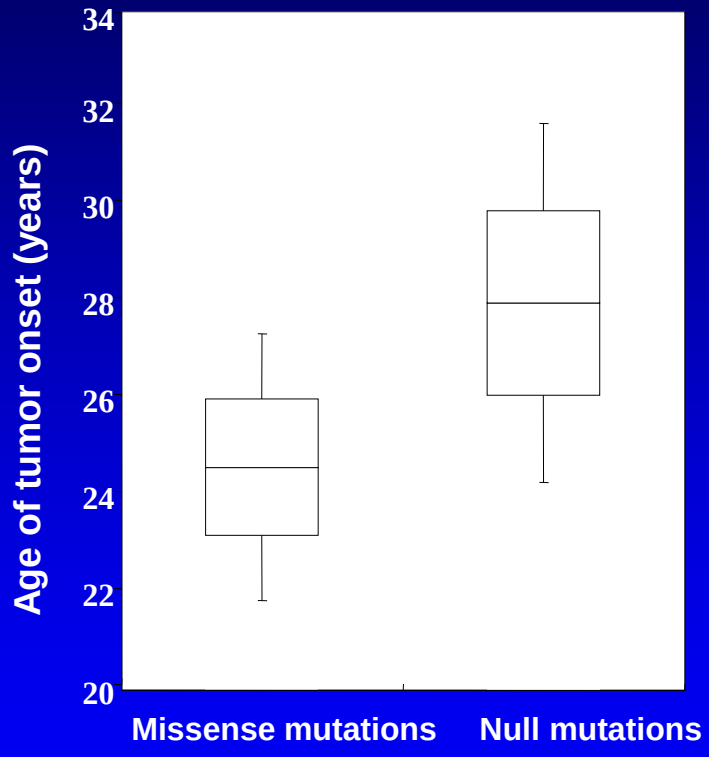
Leiomyosarcoma 32

c.375G>A, splicing mutation

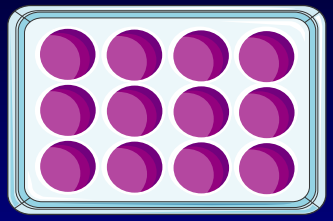


VII. IMPACT OF THE TYPE OF *TP53* ALTERATION ON THE AGE OF FIRST TUMOUR ONSET

Type of mutation	Nb of mutation carriers (n=252)	Median age of first tumour onset (years)
Missense	157	25
Null mutations	95	29

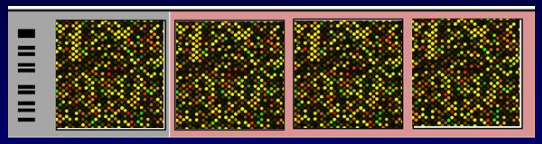


A NEW P53 FUNCTIONAL ASSAY TO ASSESS THE IMPACT OF GERMLINE HETEROZYGOUS *TP53* MUTATIONS



EBV- immortalized lymphocytes

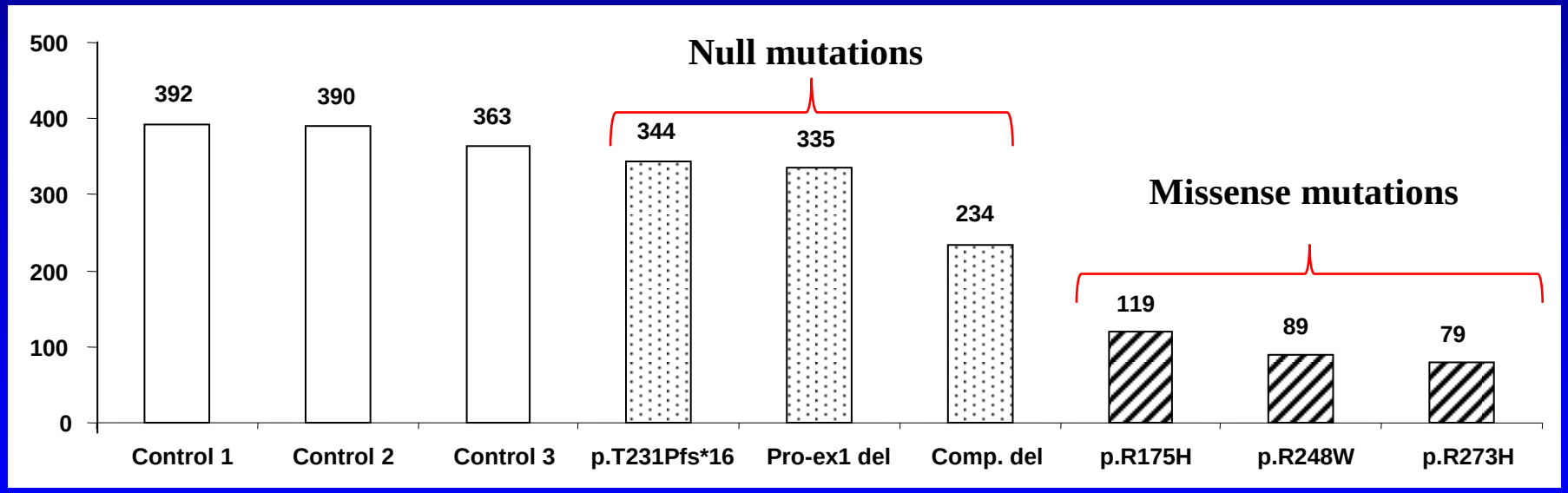
+/- Doxorubicine 8h at 37°C



41 000 probes - 19 596 RNA

Comparative transcriptomic analysis

+/- Doxorubicin

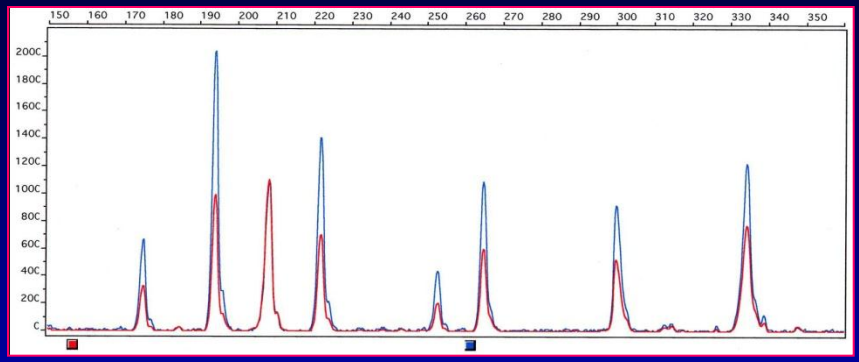


Drastic effect of the missense mutations on the p53 mediated response to DNA damage

VIII. MOLECULAR BASIS OF THE LI-FRAUMENI SYNDROME IN 2012

Functional analysis in yeast of mutant *TP53* cDNA :

Loss of transcriptional activity



QMPSF :

Detection of genomic deletions

LFS : Loss of p53 function

But the drastic effect of missense mutations on the response to DNA damage, probably resulting from the trans-dominant activity of the mutant over the wild-type, explains their predominance in LFS patients

IX. MEDICAL BENEFITS OF *TP53* TESTING IN LFS

- ✓**Avoid a delay** to the diagnosis of another tumour
- ✓**Annual clinical review** by an informed clinician
- ✓**Systematic MRI screening only for breast** from 20 years on an annual basis
- ✓**Avoid radiations (sarcoma and breast cancer)** if possible
- ✓**Prenatal diagnosis**

X. EVALUATION OF THE CLINICAL MANAGEMENT OF LFS

The Lifscreen Project (2012-2014)
Olivier Caron - Institut Gustave Roussy
11 French centers

100 *TP53* mutation carriers
Follow-up during 2 years

Efficiency and acceptance

Arm A
Every year

- ✓Clinical exam
- ✓Brain MRI
- ✓Abdominal ultrasound
- ✓Breast MRI and ultrasound

in women since 20 years

Arm B
Every year

- ✓Clinical exam
- ✓Brain MRI
- ✓Abdominal ultrasound
- ✓Breast MRI and ultrasound

in women since 20 years

- ✓ + Total body MRI

PRENATAL DIAGNOSIS IN LFS

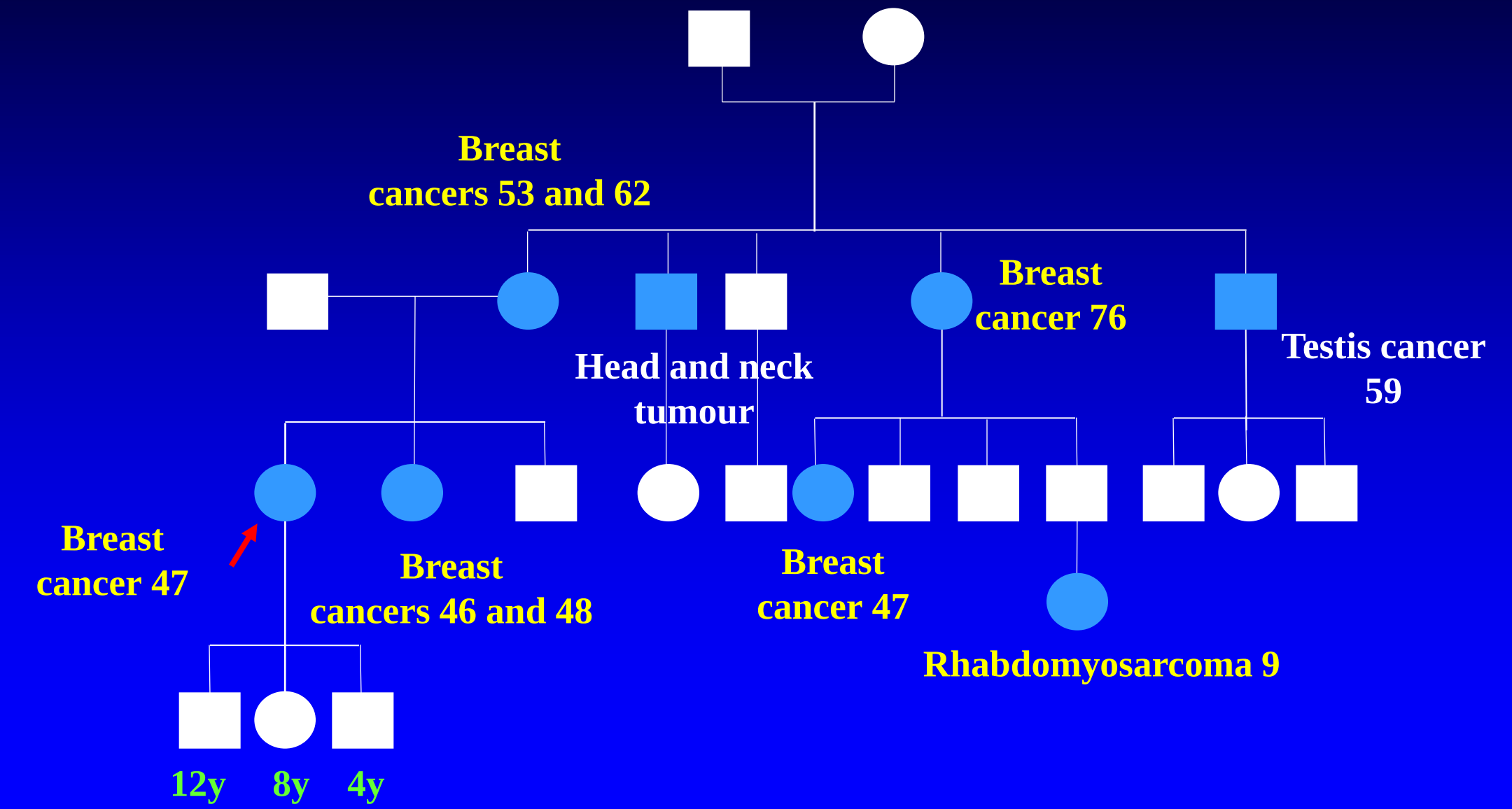
- **Young age of onset** of the LFS tumours
- **Prognosis** of some tumours
- **Impossibility to ensure an efficient early detection**
- Risk for mutation carriers to develop **multiple primary tumours**

Pre-implantation testing

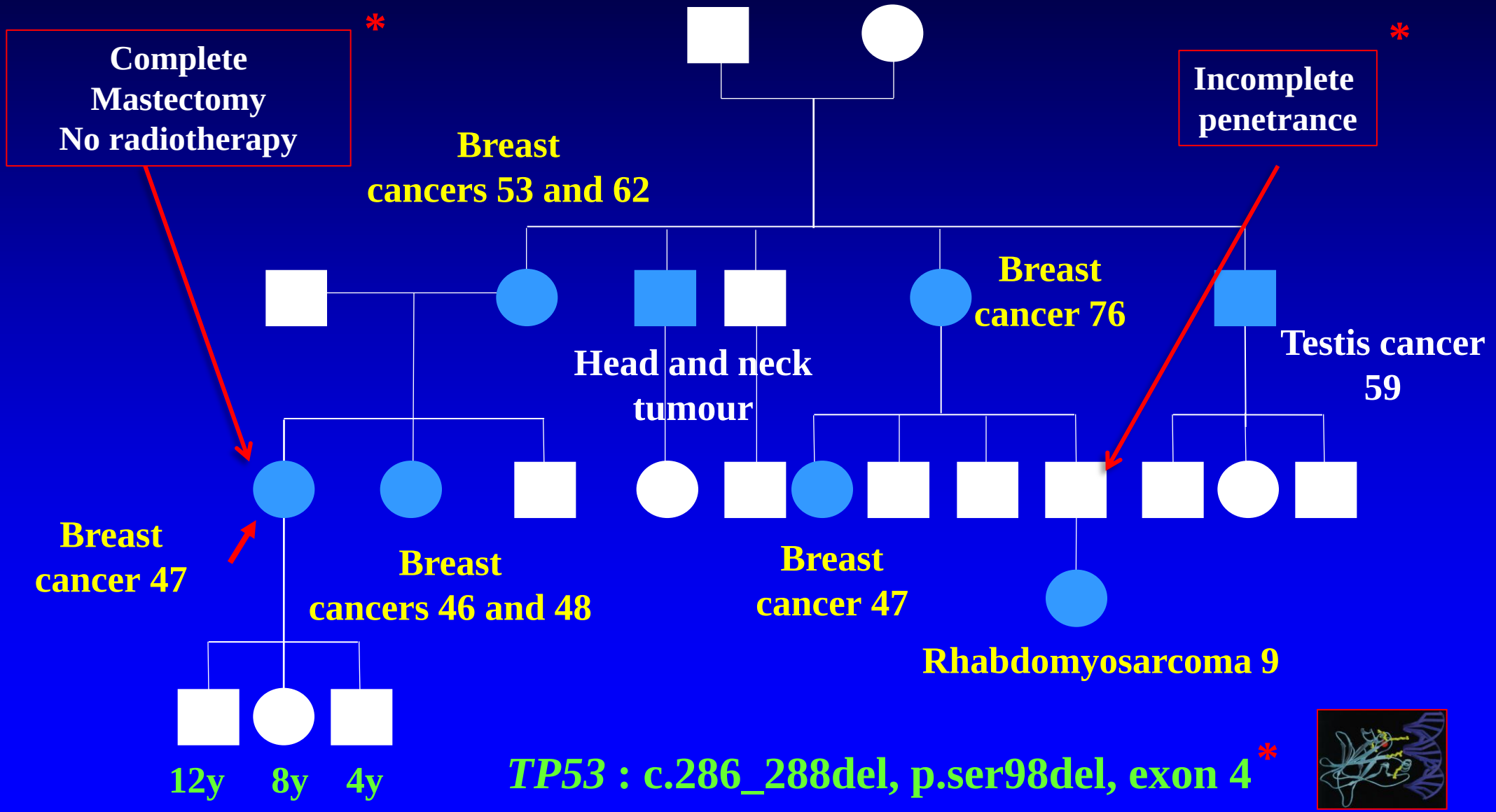
XI. *TP53* TESTING IN CHILDREN

	Adults	Children
Positive testing in affected subjects	Yes	Yes
Presymptomatic testing unaffected relatives	Yes	Must be very carefully considered

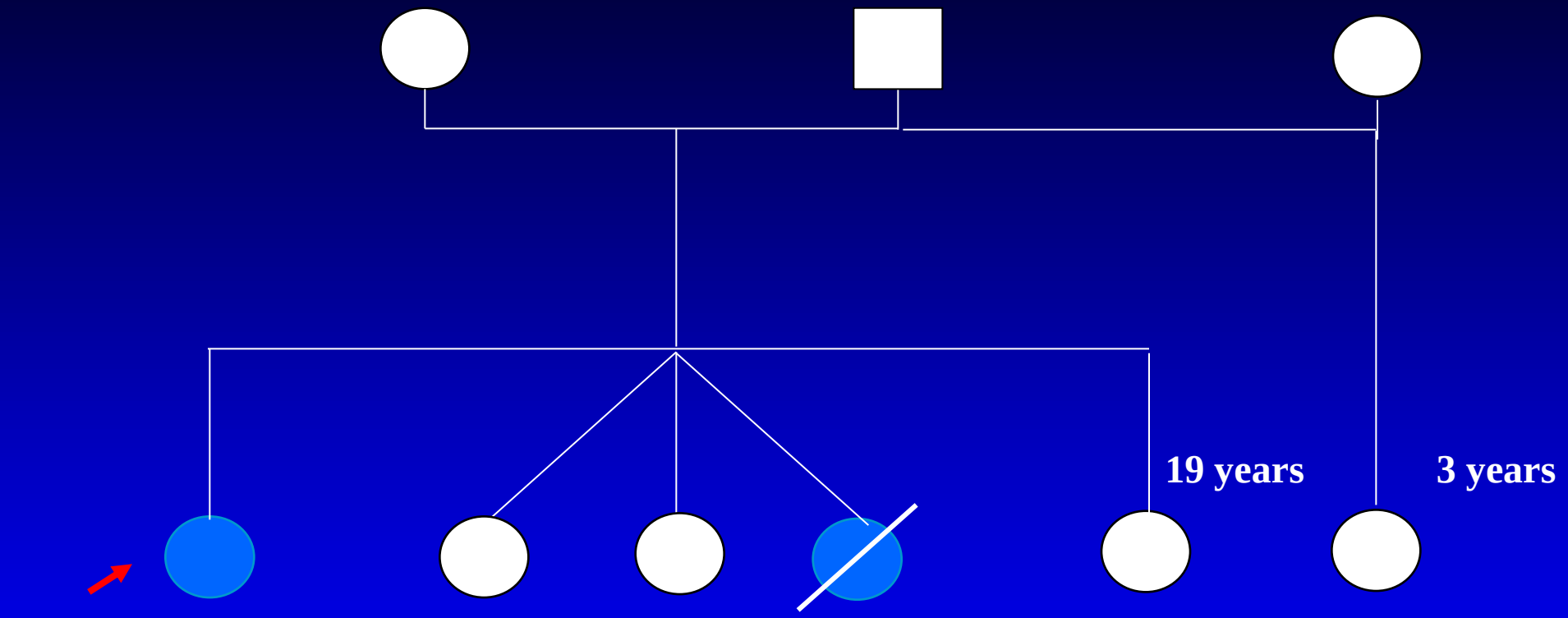
CASE 1 : *BRCA* OR *TP53* ?



CASE 1 : *BRCA* OR *TP53* ?

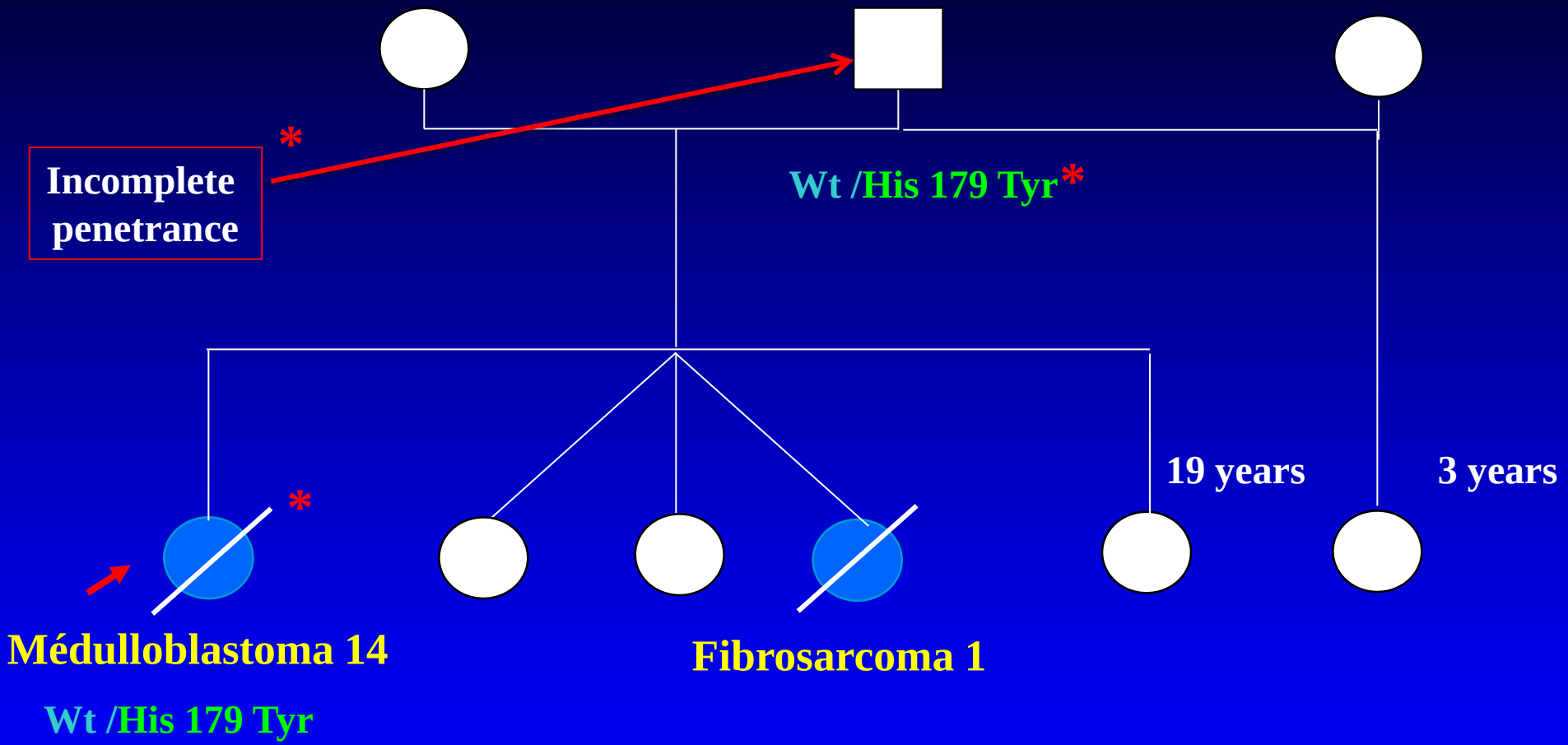


CASE 2 : *TP53* PRE-SYMPTOMATIC TESTING?



***TP53* : p.His179Tyr**

CASE 2 : *TP53* PRE-SYMPTOMATIC TESTING?



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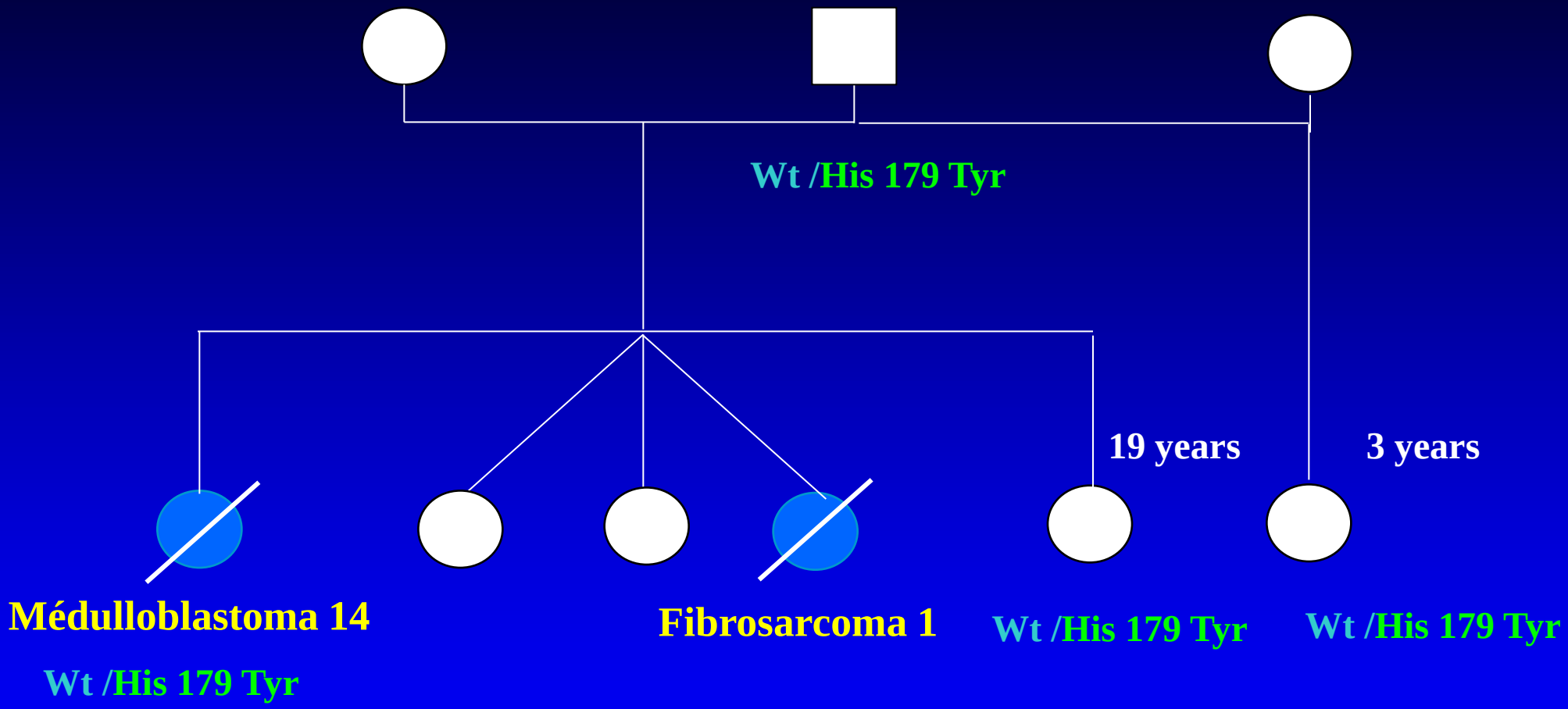
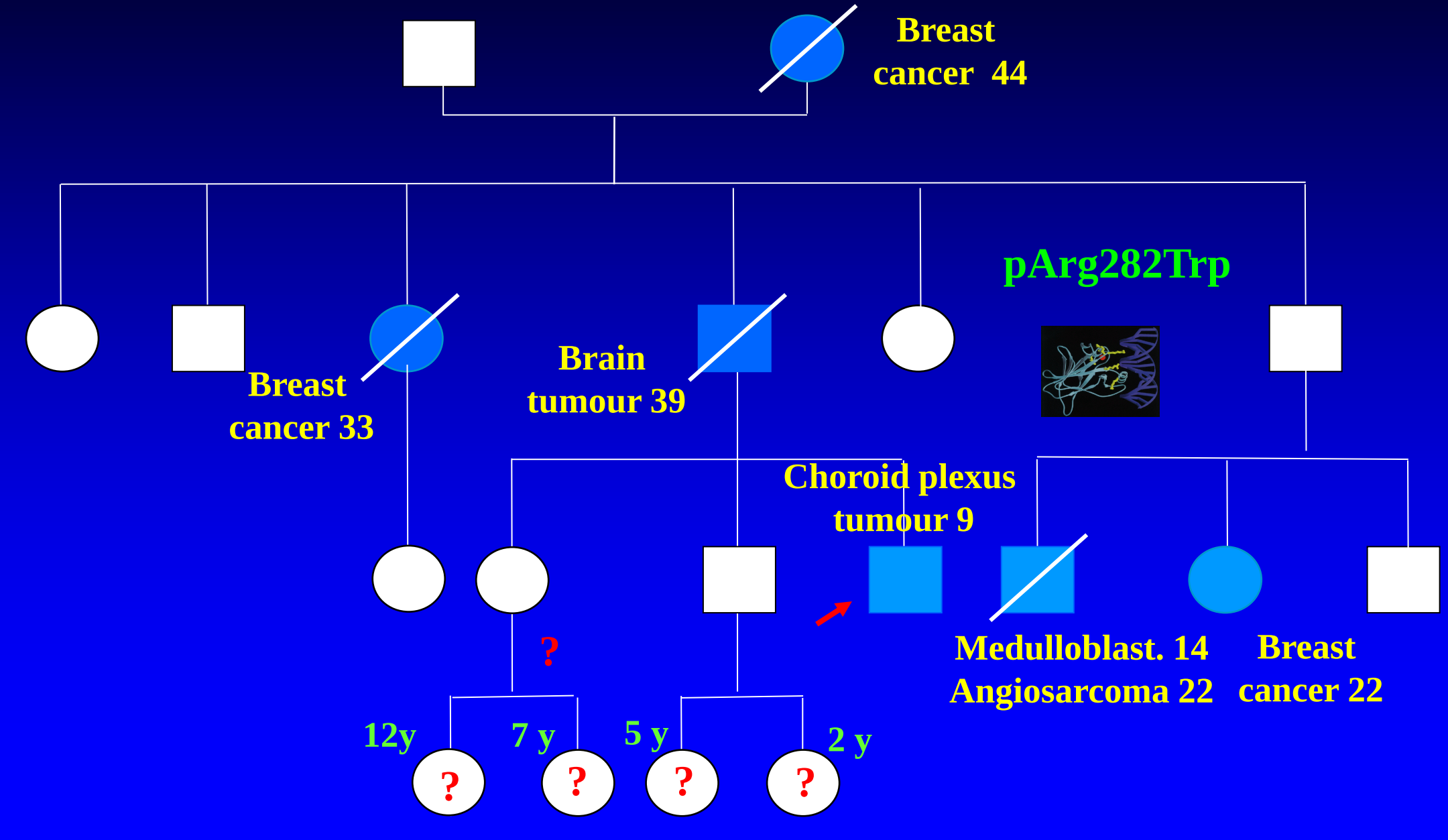
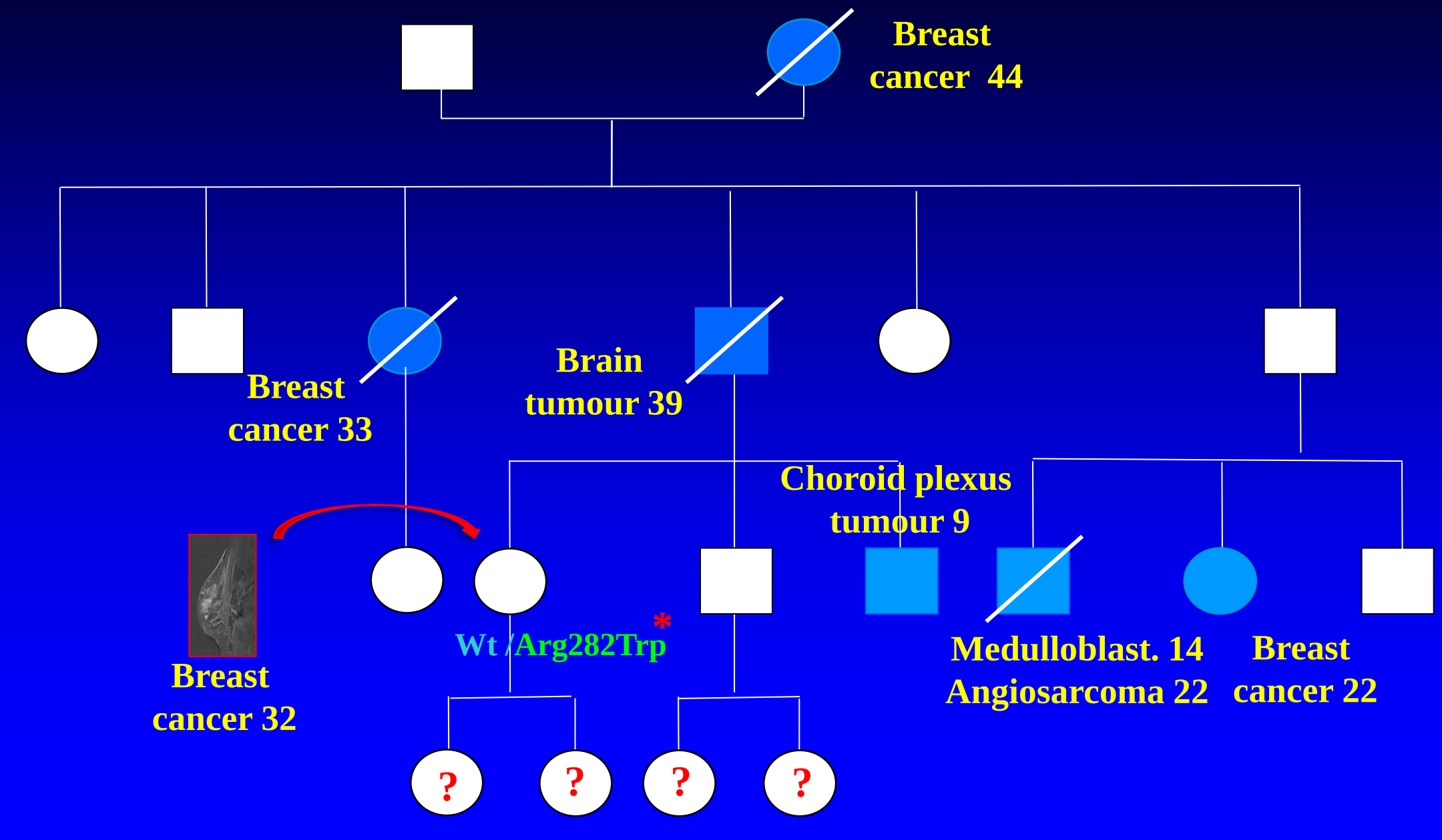


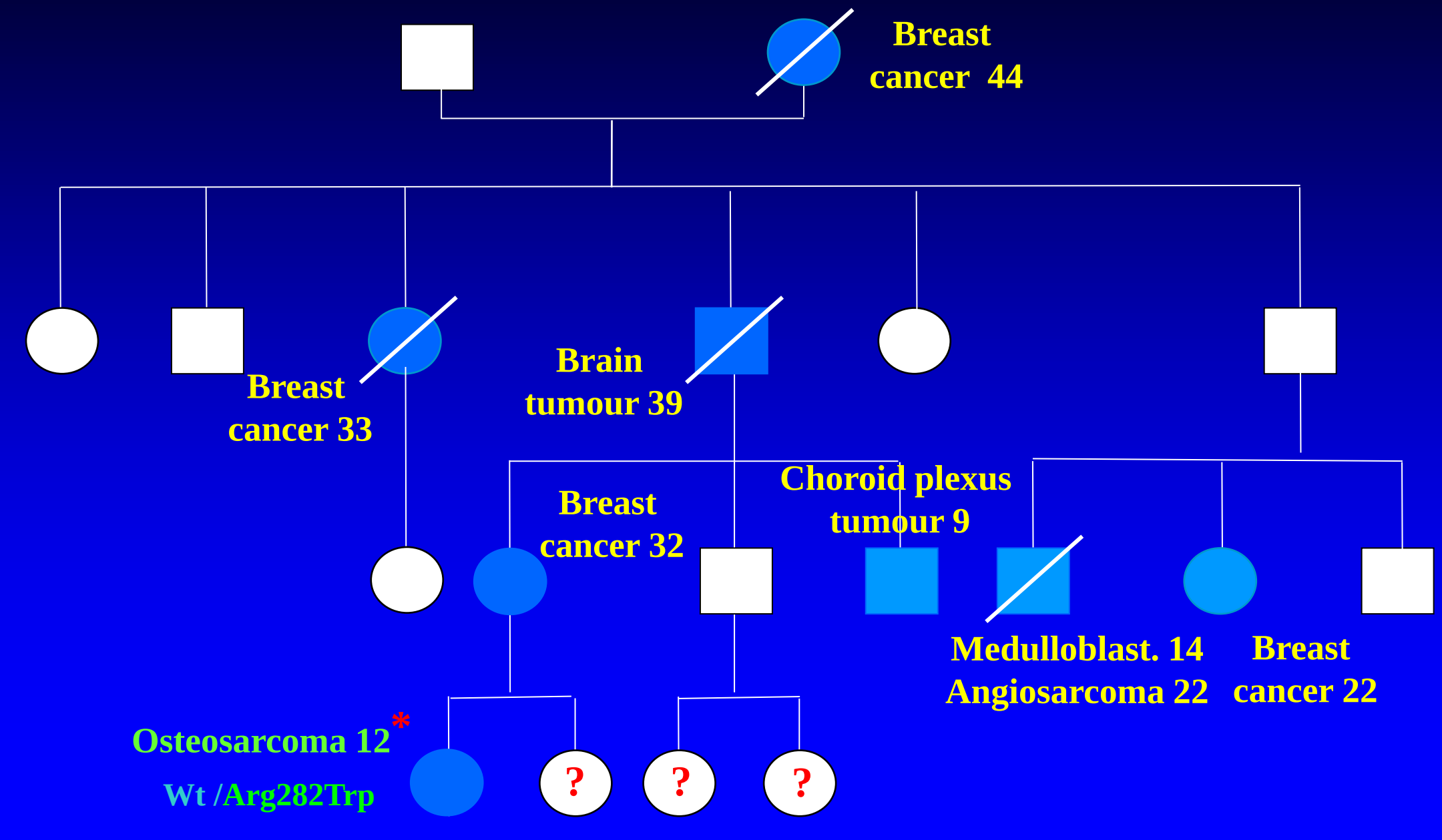
CASE 3 : *TP53* PRE-SYMPTOMATIC TESTING?



CASE 3 : *TP53* PRE-SYMPTOMATIC TESTING?



CASE 3 : *TP53* PRE-SYMPTOMATIC TESTING?



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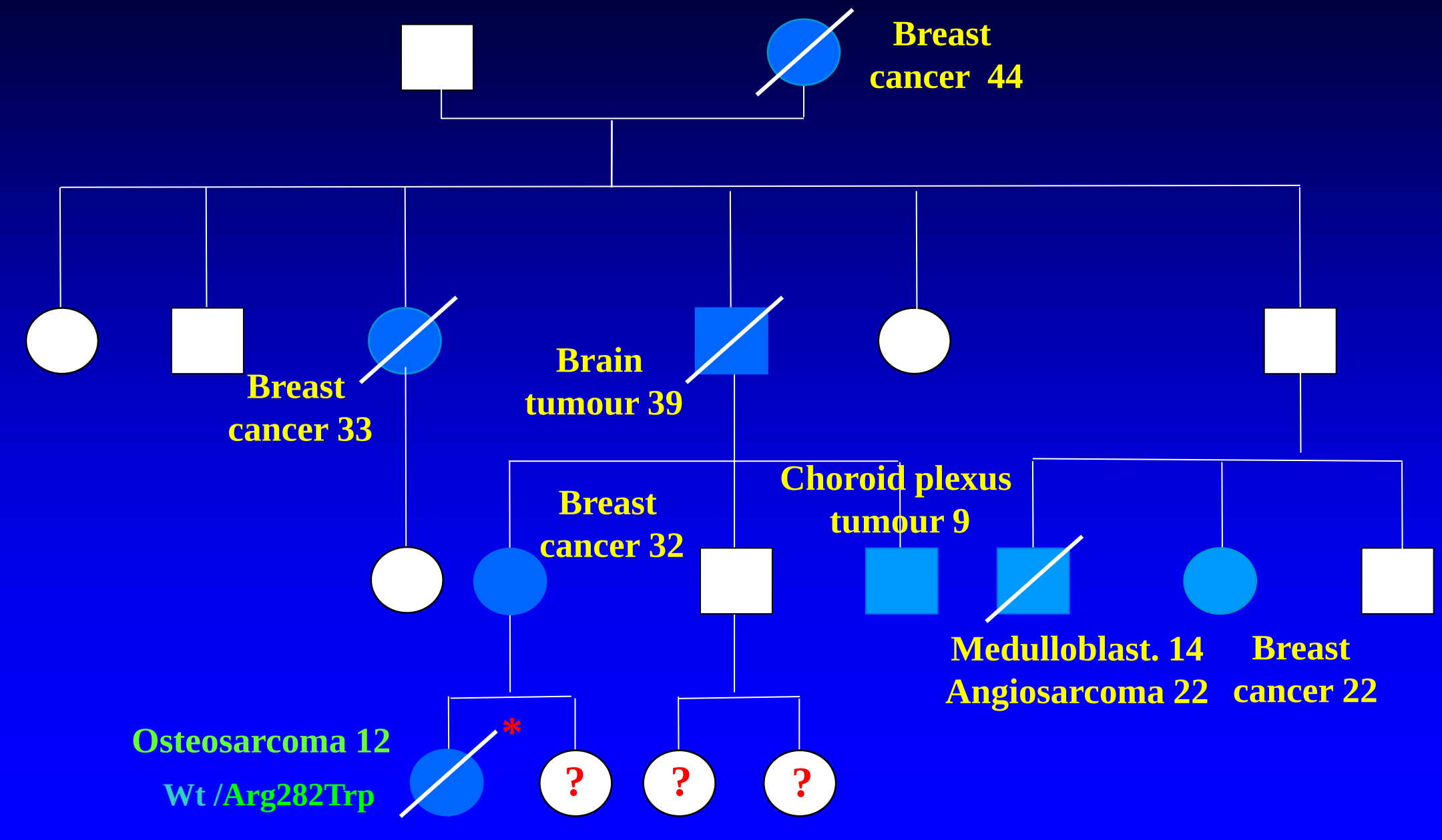

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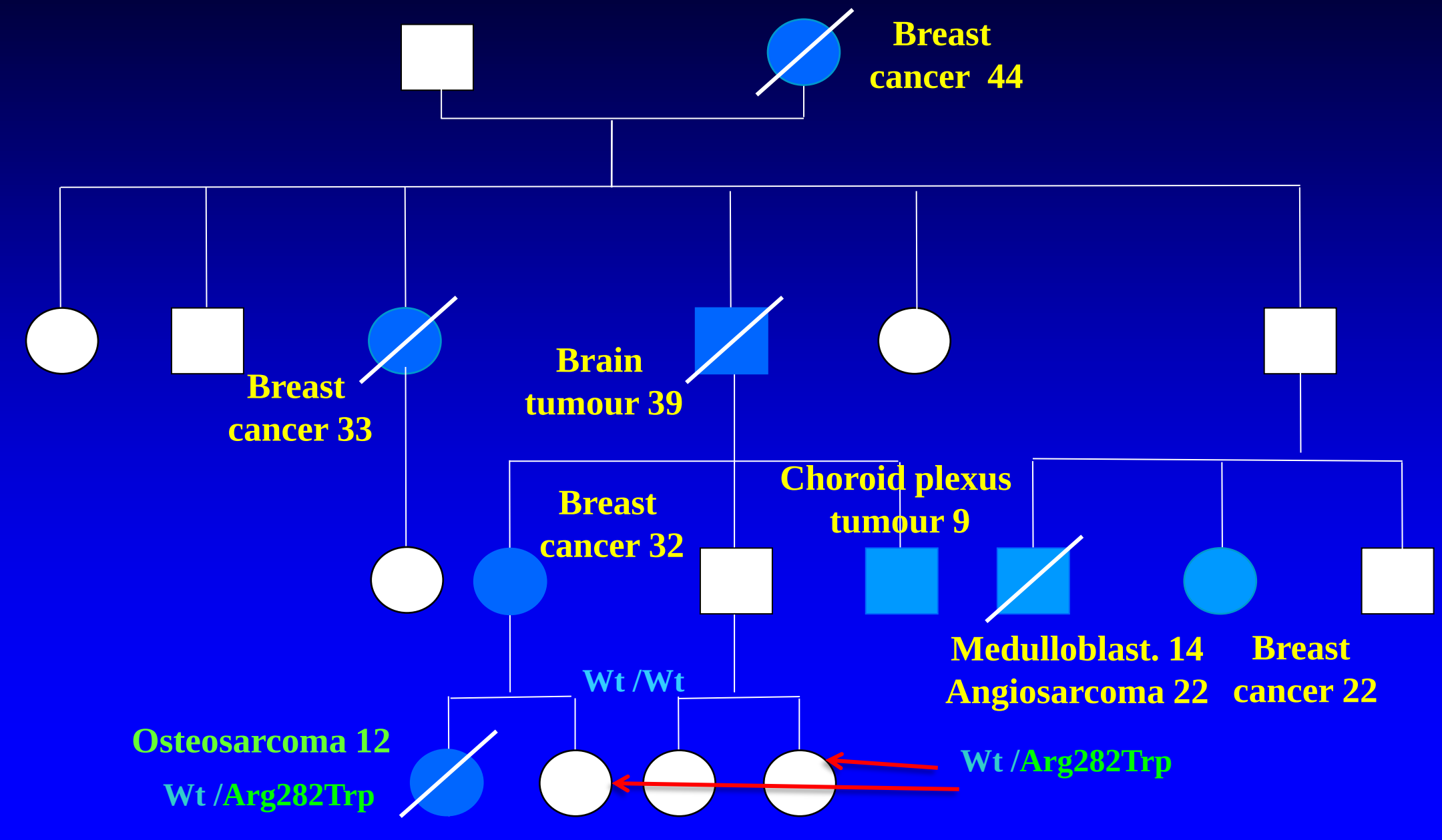
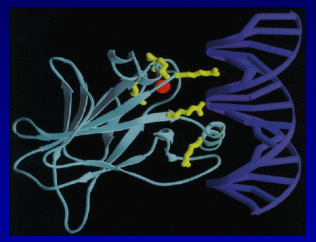


CASE 4 : *TP53* PRE-SYMPTOMATIC TESTING?



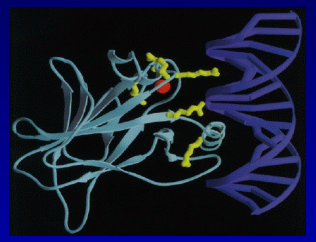
14 years

Adrenocortical tumour
3 years
Wt /Mt

Loss of weight
Inflammatory syndrome

***TP53* : c783-1G>A**

CASE 4 : *TP53* PRE-SYMPTOMATIC TESTING?



Incomplete penetrance *

Wt /Mt

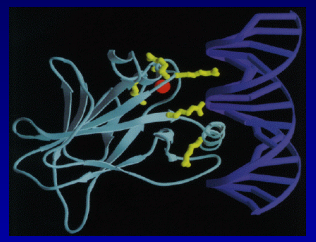
14 years

Adrenocortical tumour
3 years
Wt /Mt

Loss of weight
Inflammatory syndrome

***TP53* : c783-1G>A**

CASE 4 : *TP53* PRE-SYMPTOMATIC TESTING?



Wt /Mt

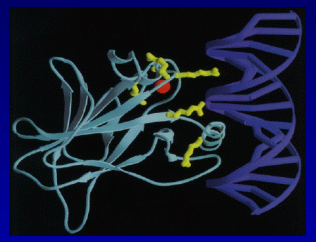
14 years

Adrenocortical tumour
3 years
Wt /Mt

Loss of weight
Inflammatory syndrome

Wt /Mt*

CASE 4 : *TP53* PRE-SYMPTOMATIC TESTING?



Wt /Mt

14 years

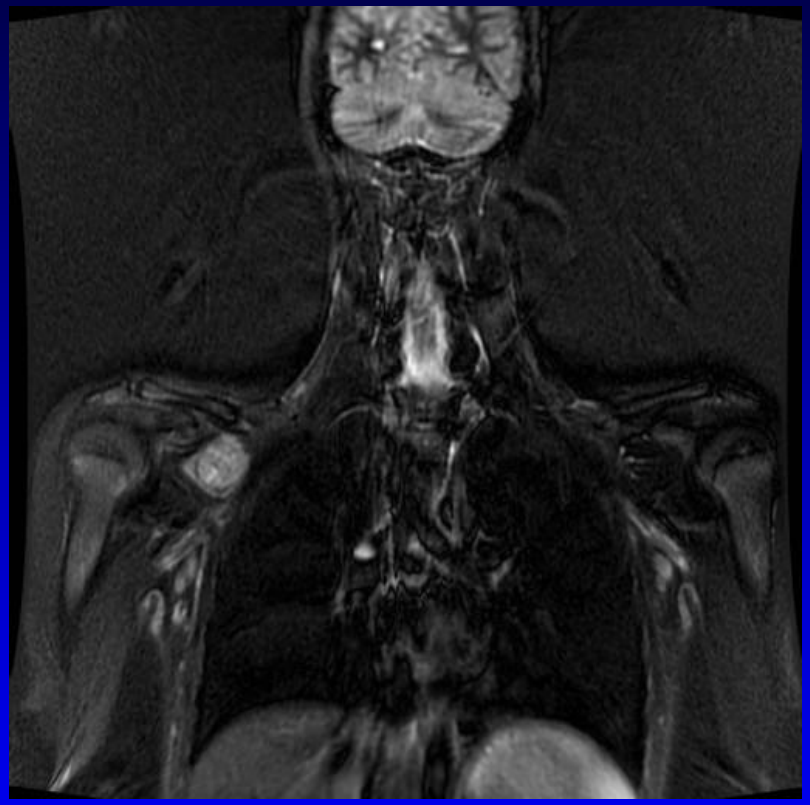
Adrenocortical tumour
3 years
Wt /Mt

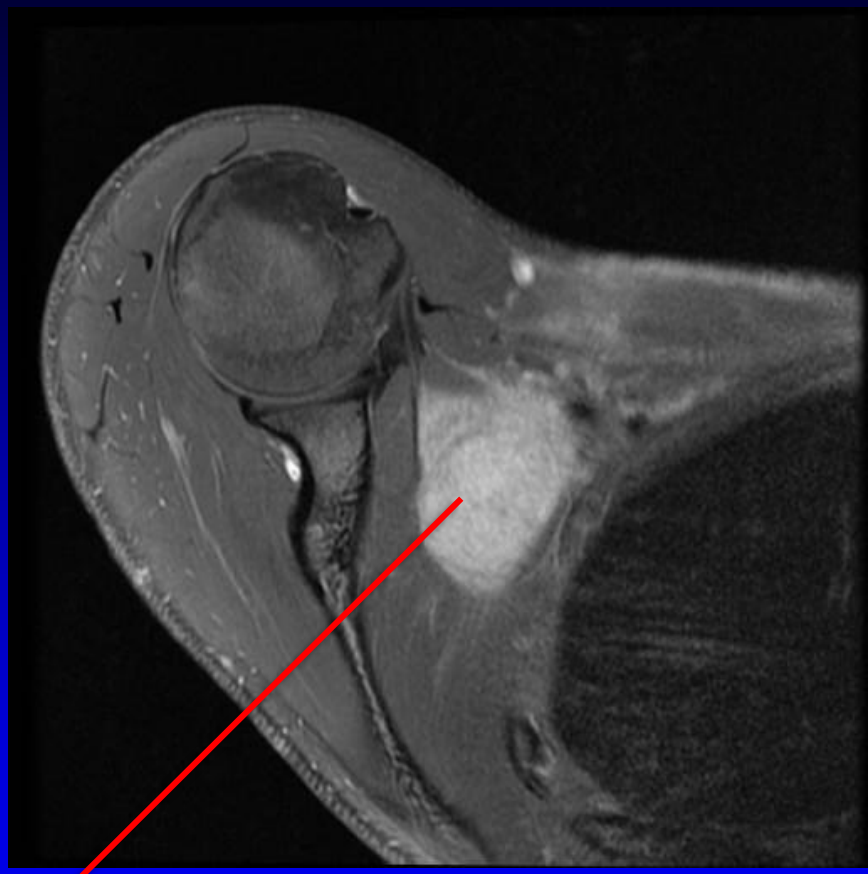
Loss of weight
Inflammatory syndrome

Wt /Mt

Total body MRI *

CASE 4 : *TP53* PRE-SYMPTOMATIC TESTING?





Angiomatoid fibrous histiocytoma

Surgical resection

TP53 TESTING IN LFS

- ✓**Annual clinical review** by an informed clinician
- ✓**Systematic annual MRI screening for breast** from 20 years
- ✓ Presymptomatic testing and evaluation of MRI-based follow-up
- ✓ Psychological supports
- ✓ Avoid radiations (sarcoma and breast cancer)
- ✓Prenatal diagnosis