What we know about Li-Fraumeni syndrome

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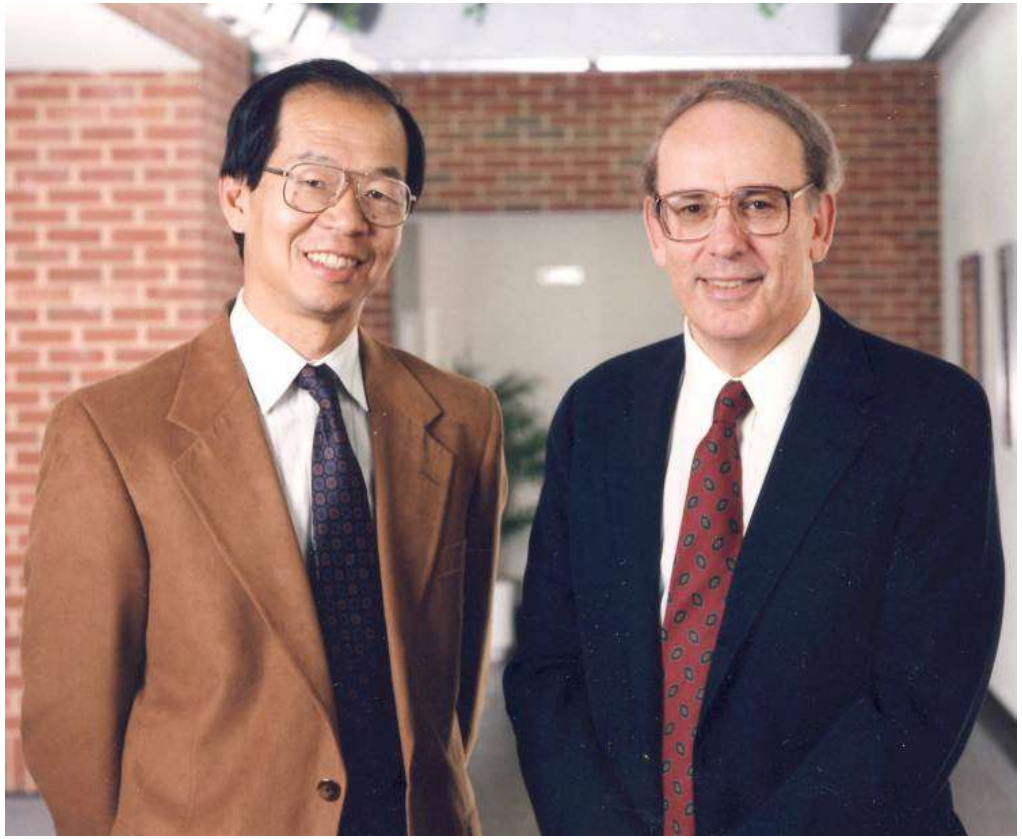
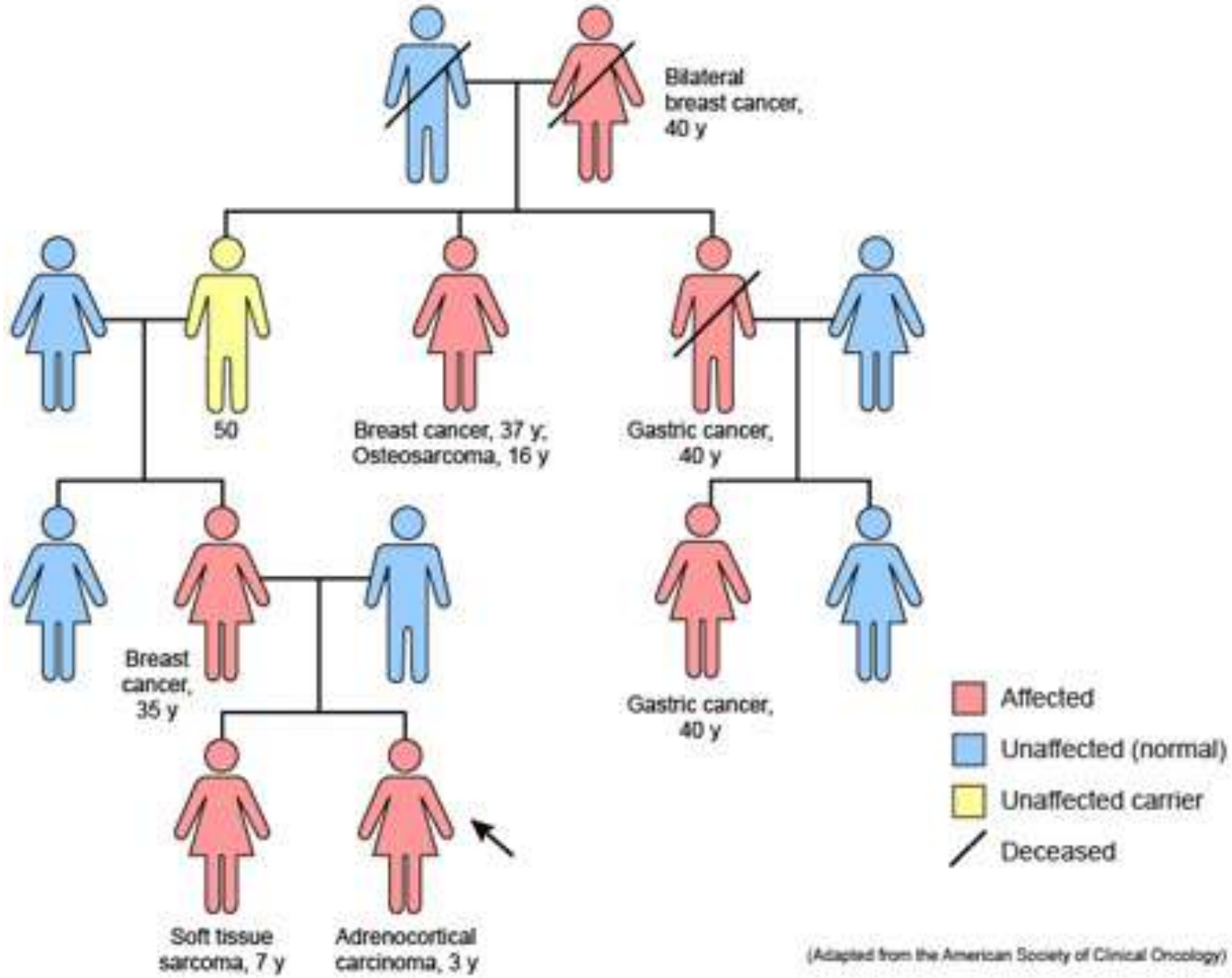
History of LFS

- 1969 Li and Fraumeni describe four families from their studies of childhood rhabdomyosarcoma
- They observe that these families have multiple early onset cancers
- Other clinicians report similar families
- 1982 the pattern of cancers is called Li-Fraumeni syndrome



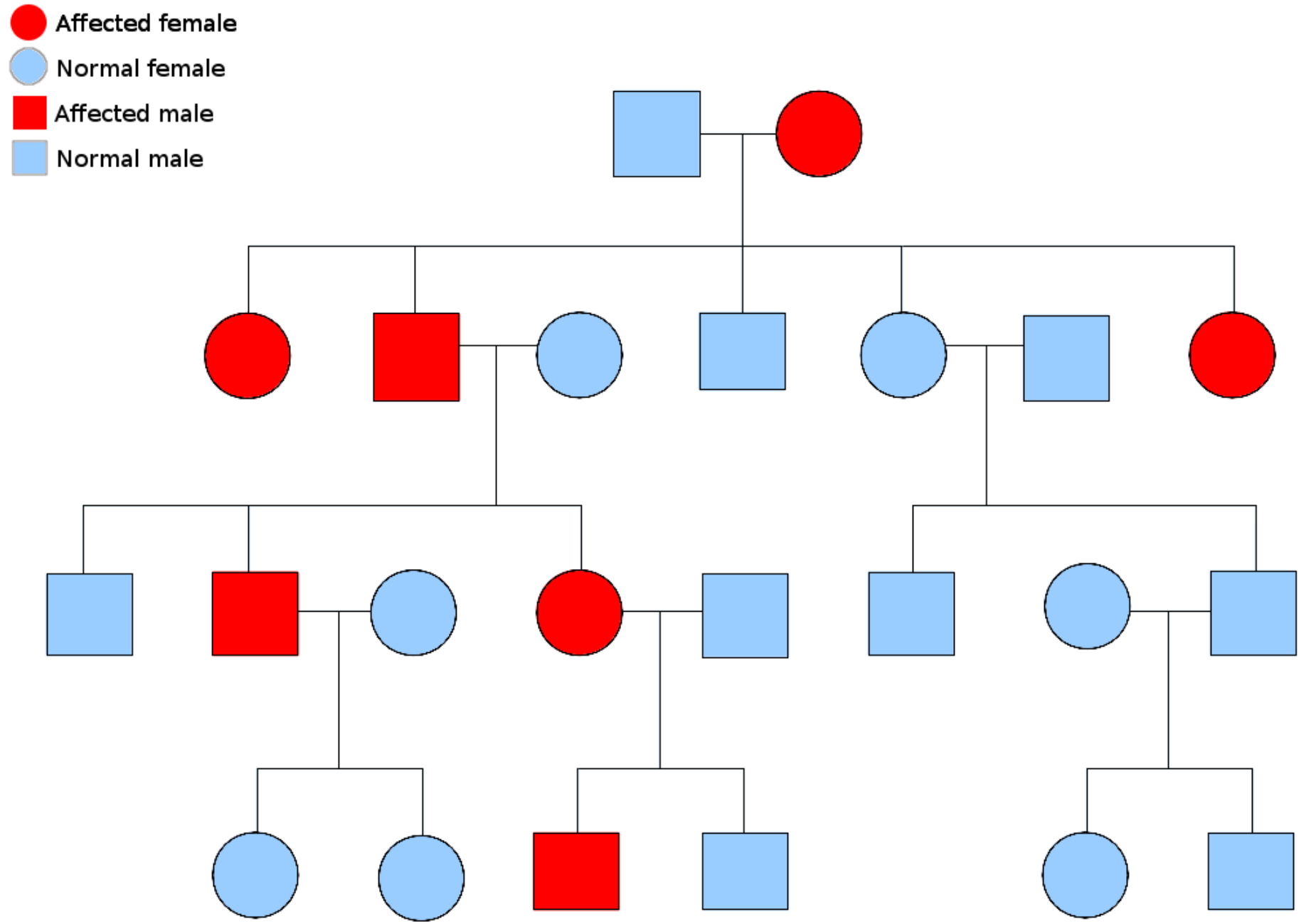
Li-Fraumeni Syndrome



(Adapted from the American Society of Clinical Oncology)

Classic LFS

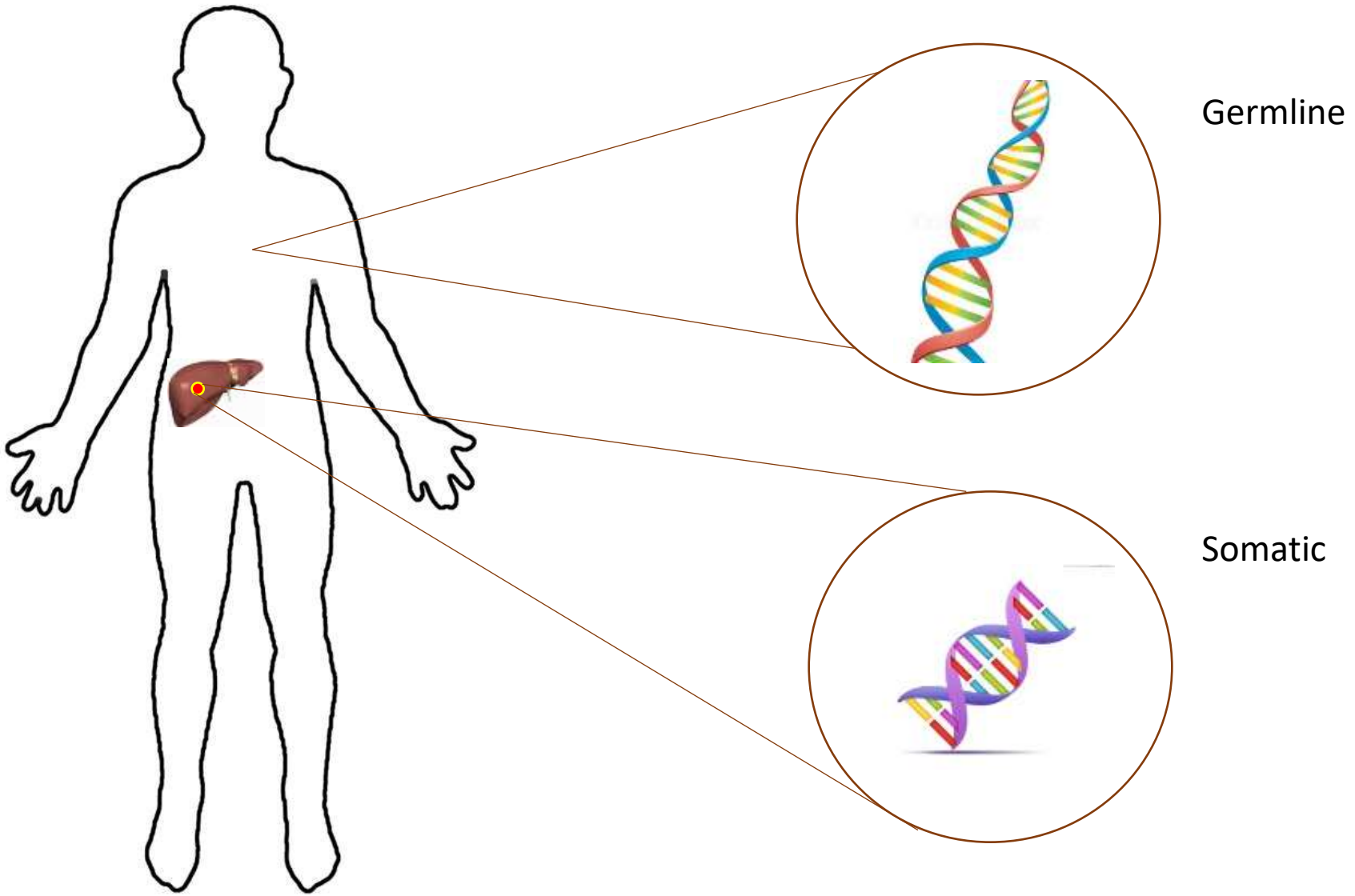
- 1988 Li and Fraumeni undertake a further study to further define the clinical features of this syndrome
- They select 24 families from the National Cancer institute according to strict clinical criteria “three close family members affected with cancer at a young age including at least one case of sarcoma”
- These criteria become known as the Classic LFS criteria
- Follow up studies of these families suggest key LFS associated cancers are sarcoma, breast, brain and adrenocortical cancer
- Appears that condition is inherited in an autosomal dominant pattern


Affected female
Normal female
Affected male
Normal male

Finding the cause of LFS

- TP53 gene was known to be a gene commonly mutated in human cancer

Cancer is a battle of two genomes

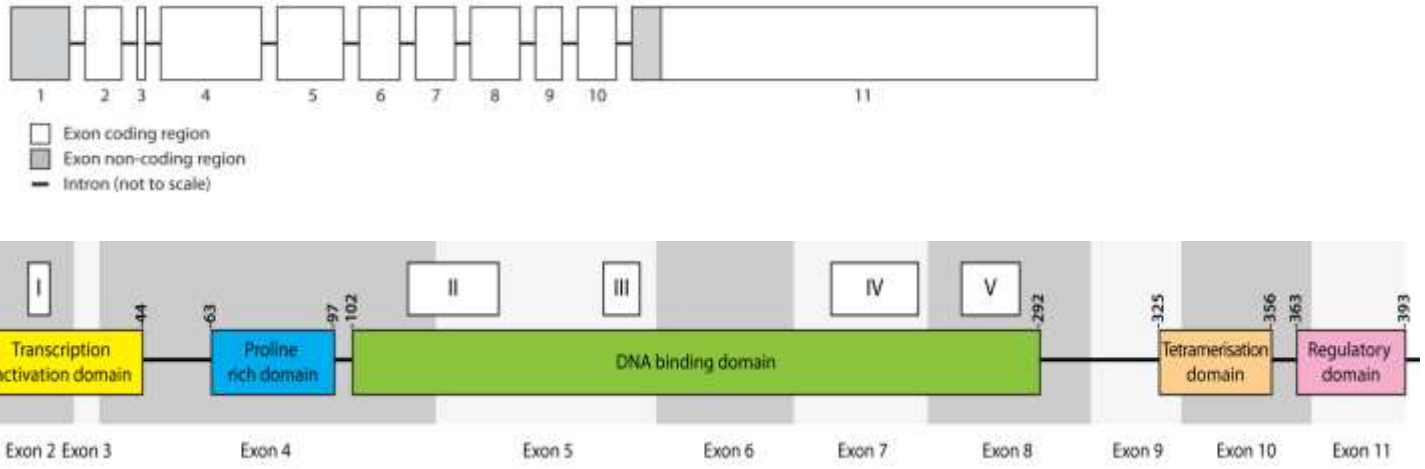


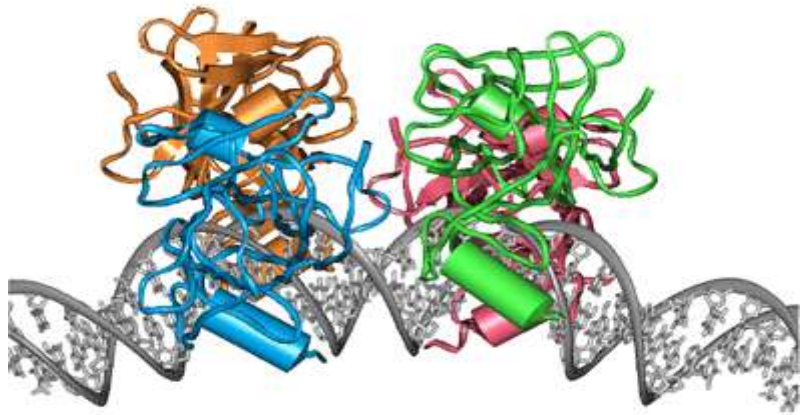
Finding the cause of LFS

- Researchers hypothesised that germline TP53 mutations could be the cause of LFS
- Genetic testing was undertaken in five families with features of classic LFS and mutations in TP53 identified in **all** families

TP53 Guardian of the genome

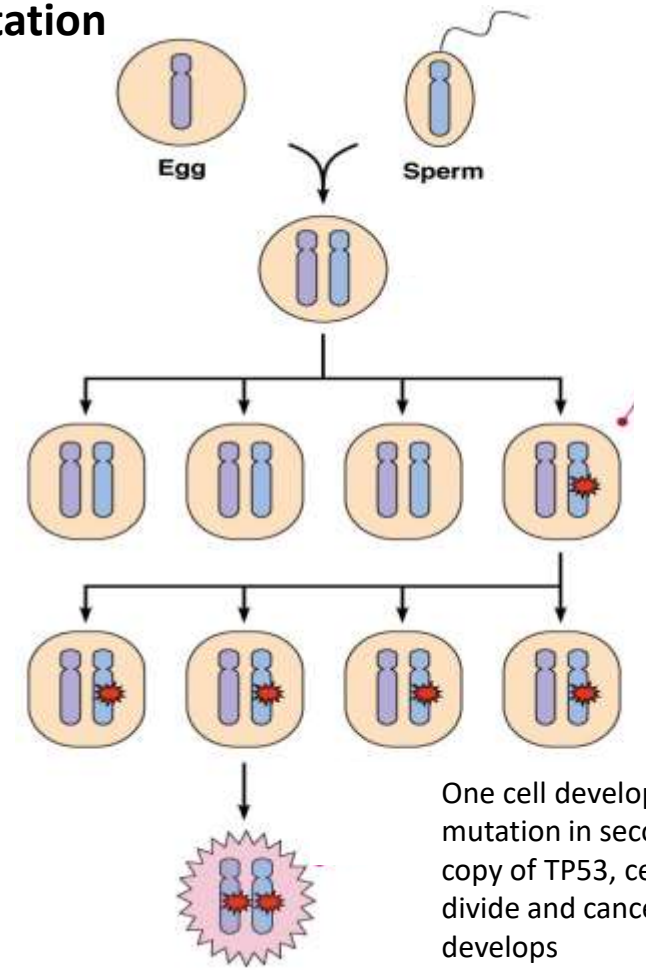
- Normal role is to preserve the genetic integrity of the cell
- If cell is damaged TP53 has the ability to activate hundreds of other genes to either repair damage to DNA, cause the cell to “self-destruct” or stop dividing
- These mechanisms prevent cancer developing





Tumour suppressor gene

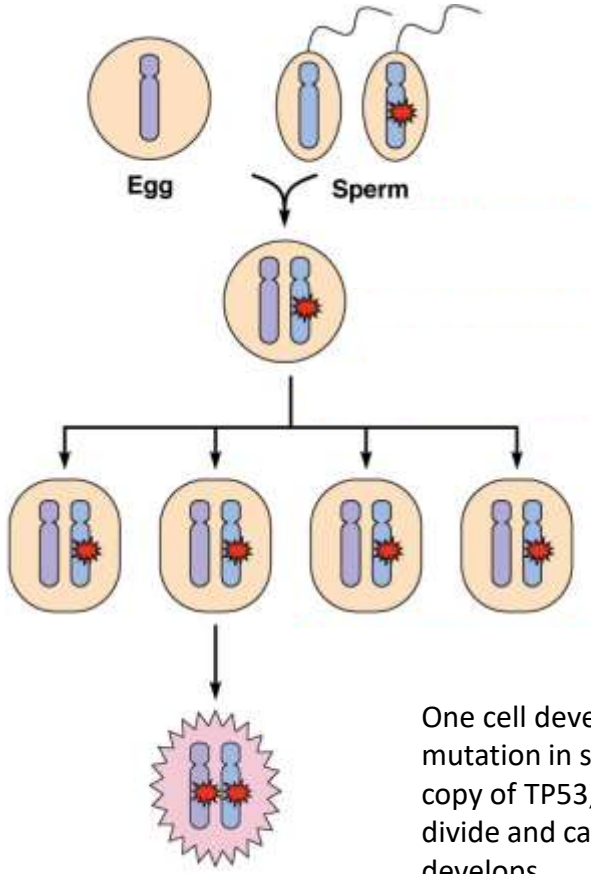
Cancer in general population –somatic mutation



Mutation in TP53 occurs as cells divide

One cell develops a mutation in second copy of TP53, cells divide and cancer develops

Cancer in TP53 carrier –hereditary mutation



All cells start off with mutation in one copy of TP53

One cell develops a mutation in second copy of TP53, cells divide and cancer develops

What is a mutation?

ATAAATGTATGAATACTCCATTTTTCTATTATCCTATATGGCCCCAGGTGTAATTGTATAGTATCTCTTT
TTACTGTTAAATGCTGCAATAAGACTCACATGCAAAAAGCTGTATCTCTAAGCACTTAATAATTTGTTTC
CCCAGGAGAGTGATTCGATGATGGTGGATCCAACCAATGACATCCGGATTATAGGCTCCATCACAGTGGT
GATTCTTCTAGGAATTTCAGTAGCTGGAATGGAATGGGAGGCAAAGGTAAATTTCTCAAAAATGATATTA
TCAACAGTGGCTGGTCAGGTCCTGAACAAATTGCAGGAGTAGAGGGAACTCCATATTCAAAAGGAATTGC
TGTTATTACCTGCTATGGTGAAATGAGCAGGCAAGTGCTAGGTGGAACACCAAGCCTGCAAAGCACGAAG
CCCAGGCAGTCATGATTCAGGGCTCACGAGTCACATGACTGCCGTATTTTGTCTCTCTGTGCTGTCACCA
AGGCGGCTGCCTTATGCACAGACCCCTTATGATCATAGCAGTGGTGCACGCTGGAAGCCTGGGTCTCTCA
ATCACAAACCCTGGTTCCTCTTTCAAGCTGCCTGTGGGTGCAAAAGCCCAAGAGAAATGGCAAGTGTGTT
GAGAACATAAGAGAGGCAAAAACTATCATTCTCATCTGAAAGCCAGTACTTCACCAGCAAATTTAGGCAC
ATCATAGGCTTTAGAACCAGAAAATCTCTGAGTTTAACTAGTGATAAAATGGATAGTAAATTTCCGAATG
ATGGGAAACATGTCTTTTGCCTCCTTTGTAATTCCCTCAAGTGACTGGTGCAATTGAAAATATTCCTACG
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ATAAGTCAATAGAAAACATTCCTACATGGCATTTATTTGTAGATTATGCATTCACACATTCAACAAAAAT
TAAGTTAGTGCCTACCACATGTTGAGCATTCTTCTCGGCACTGATATGGACCTGTGACCAAAACAGGCCT
AATCCCTATATATGGTCTATGAAGAGATCAATAATAAGCAAGCAAATAAAGAAATAAATATAAAAAGAGA
ATTTGTGAAAATTAGTATCAACAGGACACTGTGATGAAAAAACACAGAACCCTACTTTAGATAACTTTAT
TCCCTGAGTGAGGCAATGAAGTTTAGTTAGCAGTAGAGGGTAGCATTTAAAGCTCCAGCTCTGTAGTTAG
AGTGCCTGAATTTGAATCCAGCTTATATCTCTGCAGCCTTTAGTAAATTATTTAACCTCTCGGTGCTTCA
GTGTCTTTACCTTTAAAATGAGGATAATAATATTGCCTACTCCATAAGGTTGTCAGTTTGTTGGTGGTAT
TATTTACCTAAAAGAATGCAGGGAAAGTAAATCTGCAACTGCTCTATTGTAAGCCCTCAGTGAACAGATA
GCTGTTATTATTTAAATGGGCCAGGCACGGTGGCACATACCTGTAATCCCAGCACTTTGGGAGGCTGAGG
CGGGCAGATCACGAGGTCAGGAGTTCGAGGCCAGCCTGGCCAACATGGTCAAACCCTGTCTCTATTAAAA
ATATAAAATTAGCCAGGGTGGCGTATGCCTGTAATCCCAGCTACTCAGGAGGCTGAGGCAGGAGAATTGC
TTGAACCCAGGAGGTGGAGGTTGCAGTGAGCCGAGATCGTGCCATTGCATTCCAGCCTGGGCGACAGAGT
GAGACTCCATCTTGGGAAAACAAAATAAAATAAAAAAACATAAAAGATTAAATTTTCAAGAAAGGCCCTC
TGAGGAGGTAACTAAGACTTAAAGGATGAAAAGAAGGAAATAGCTATGCAAGAAGTAGAGTGAAGTGCTT

The genetic code is ‘read’ in 3-letter words…

TTCTCGGCACTGATATGGACC

TTC TCG GCA CTG ATA TGG ACC

Phe - Ser - Ala - Leu - Iso - Trp - Thr

TTCTCGGAGCTGATATGGACC

TTC TCG GAG CTG ATA TGG ACC

Phe – Ser – Glu – Leu – Iso – Trp - Thr

‘Missense’ mutation

TTCTCGGAGCTGATATGAACC

TTC TCG GAG CTG ATA TGA ACC

Phe – Ser – Glu – Leu – Iso – Stop

‘Nonsense’ mutation

TCTCGGCACTGATATGGACC

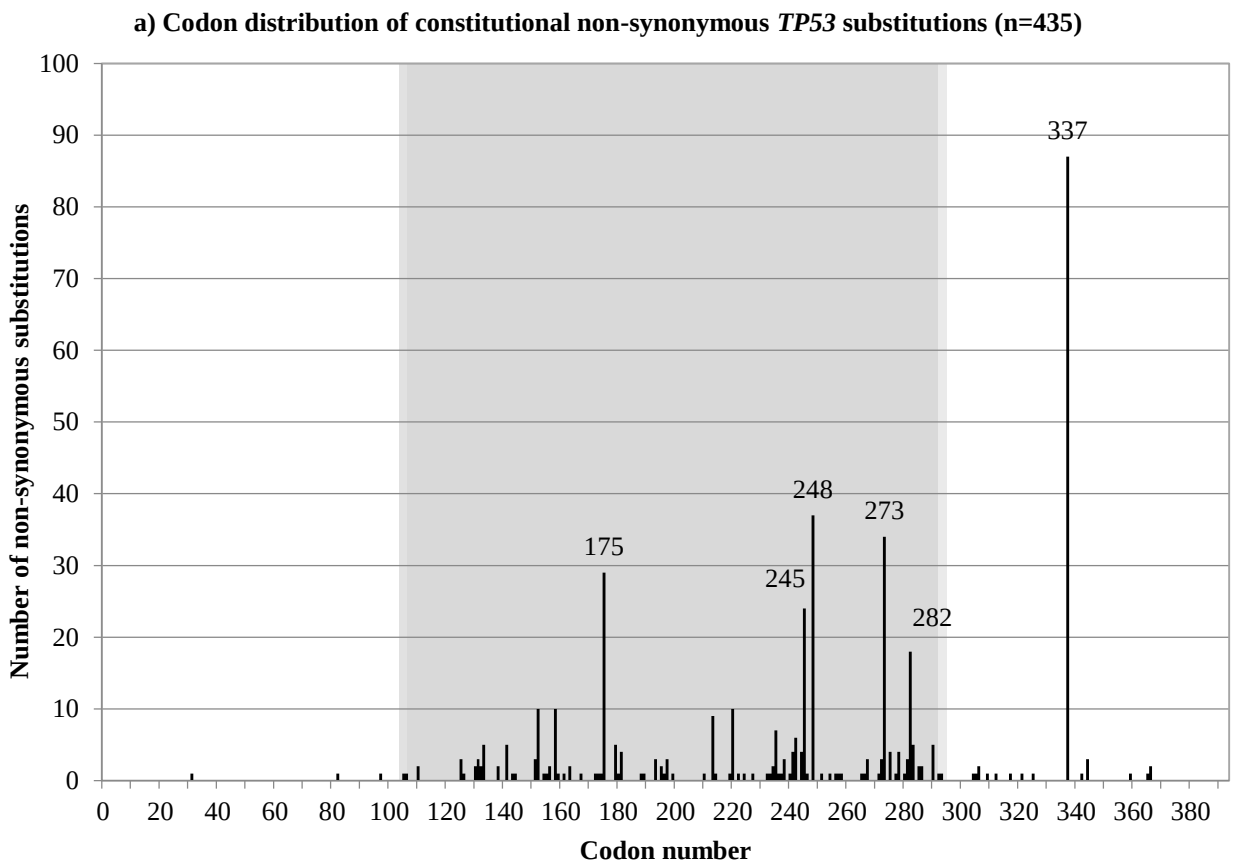
TTC CGG CAC TGA TAT CGA CCT

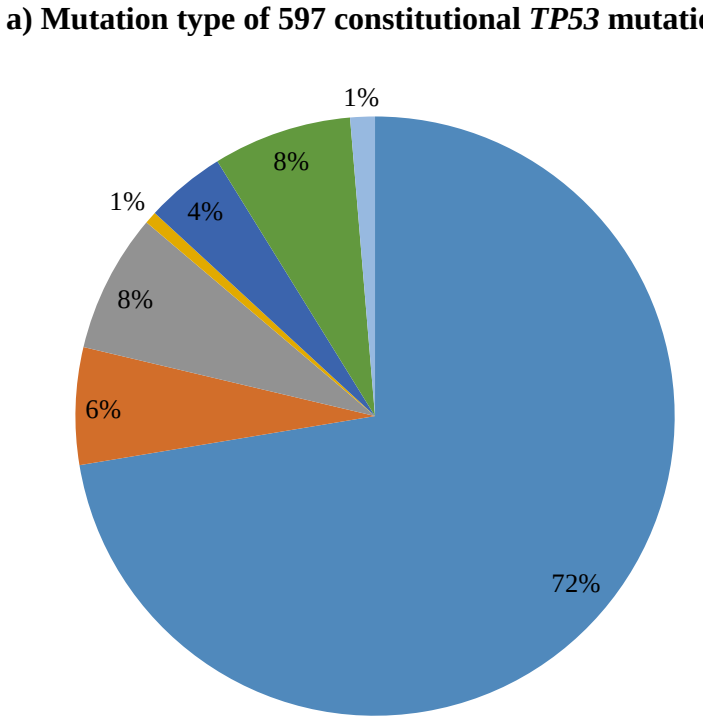
↓

Phe - Arg - His - Stop

‘Frameshift’ mutation

Mutation spectrum

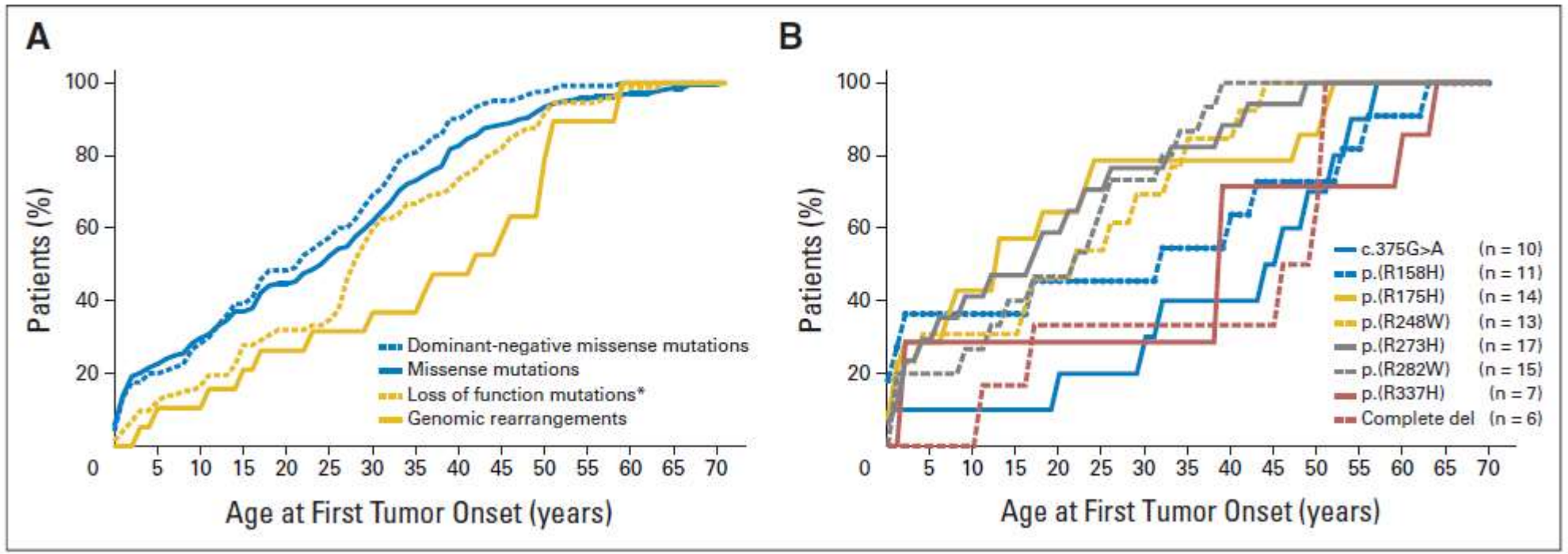




Type of mutation may affect cancer risk –further work needs to be done-

Revisiting Li-Fraumeni Syndrome From *TP53* Mutation Carriers

Gaëlle Bougeard, Mariette Renaux-Petel, Jean-Michel Flaman, Camille Charbonnier, Pierre Fermey, Muriel Belotti, Marion Gauthier-Villars, Dominique Stoppa-Lyonnet, Emilie Consolino, Laurence Brugières, Olivier Caron, Patrick R. Benusiglio, Brigitte Bressac-de Paillerets, Valérie Bonadona, Catherine Bonaïti-Pellié, Julie Tinat, Stéphanie Baert-Desurmont, and Thierry Frebourg



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ORIGINAL REPORT

Variants of unknown significance

- Genetic variation makes us unique
  - “polymorphisms”
- Is the basis for evolution

http://dee-annarogers.com

TTCTCGGAGCTGATATGGACC

TTC TCG GAG CTG ATA TGG ACC

Phe – Ser – Glu – Leu – Iso – Trp - Thr

Change in code– but does this affect the function of the gene?

TP53 variants of unknown significance

- We know there are normal variants in the TP53 gene R72P and P47S
- Found at significant frequency in control population
- Other variants may be rare
- Some variants are hard to classify on the available evidence and need to remain under review until further statistical evidence or functional studies are performed

Prevalence of LFS

- Hard to estimate
- Families have been highly selected for testing
- We know that TP53 mutations are identified in families who don’t meet LFS criteria –but probably many other patients and families have not been tested

Cancer risk

- Defined on classic LFS families
- Females have higher lifetime cancer risks due to risk of breast cancer
- Female carriers: Ages 20 (18%), 30 (49%), 40 (77%), and 50 (93%)
- Male carriers: Ages 20 (10%), 30 (21%), 40 (33%), and 50 (68%)

- Risk likely more variable
- Some mutations appear to be associated with lower or more specific cancer risks e.g R337H
- LFS is a clinical diagnosis –need to move to TP53 related risks –more research required

Spectrum of Cancers

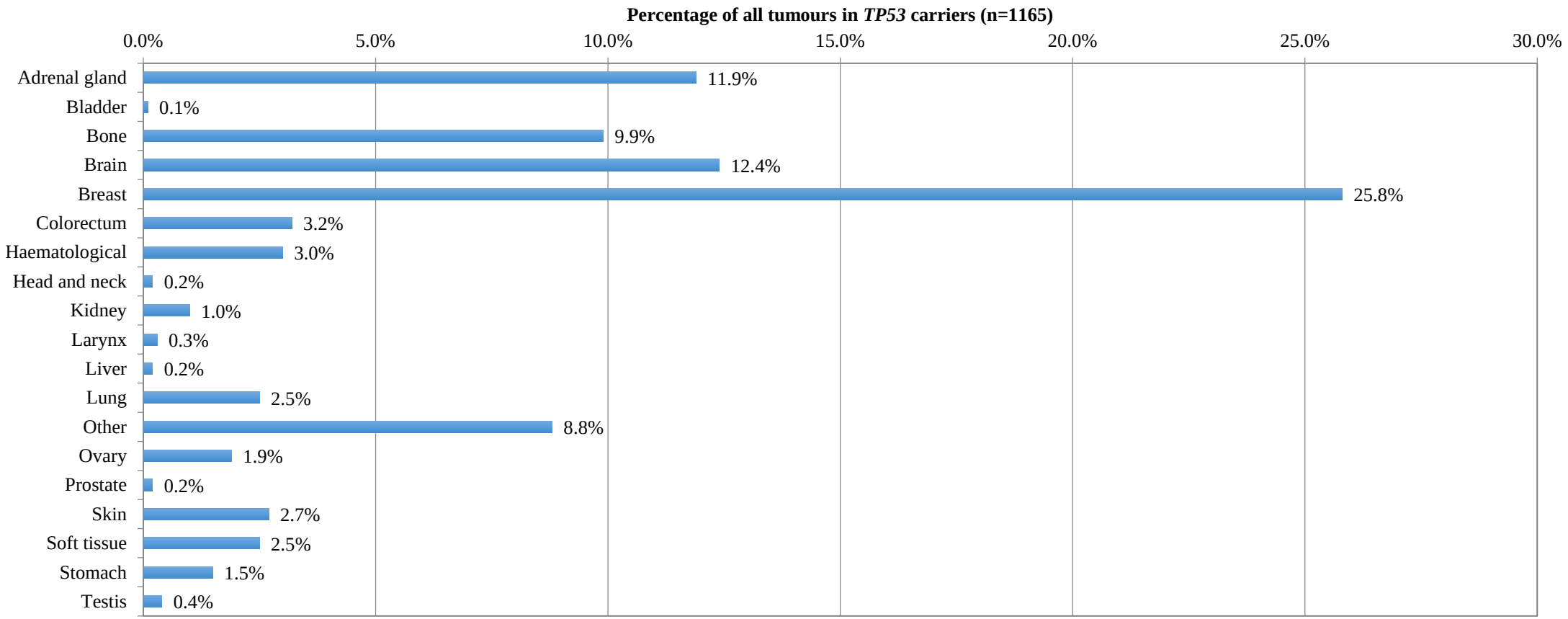


Table 1. Distribution of Tumors in Affected Germline *TP53* Mutation Carriers

Tumor	No. of Tumors	No. of Patients	% of Affected Mutation Carriers	Mean/Median Age at Tumor Onset, Years (range)*
		In All Patients (N = 322; 213†, 109‡)		
Breast carcinoma	172 (172†; 0‡)	127 (127†)	**60**†	35/33 (20-69†)
Soft tissue sarcoma	104 (54†; 50‡)	86 (46†; 40‡)	**27**	29/31 (0.5-67†; 0.5-70‡)
Osteosarcoma	53 (24†; 29‡)	50 (23†; 27‡)	**16**	18/16 (8-55†; 5-54‡)
CNS tumor	43 (25†; 18‡)	42 (25†; 17‡)	**13**	15/11 (0.3-67†; 1-33‡)
Adrenocortical carcinoma	43 (30†; 13‡)	42 (29†; 13‡)	**13**	6/1 (0.5-41†; 0.7-19‡)
Lung cancer	18 (8†; 10‡)	18 (8†; 10‡)	6	42/44 (14-58†; 37-54‡)
Leukemia	16 (9†; 7‡)	14 (7†; 7‡)	4	14/12 (6-35†; 2-16‡)
Prostate cancer	4 (4‡)	4 (4‡)	4‡	63/62 (57-71‡)
Colorectal cancer	12 (5†; 7‡)	11 (5†; 6‡)	3	40/40 (21-74†; 27-52‡)
Renal cancer	11 (4†; 7‡)	9 (3†; 6‡)	3	51/49 (34-68†; 41-70‡)
Melanoma	11 (9†; 2‡)	8 (6†; 2‡)	2	40/43 (25-65†; 15-55‡)
Lymphoma	7 (3†; 4‡)	7 (3†; 4‡)	2	18/13 (11-42†; 2-32‡)
Stomach carcinoma	7 (3†; 4‡)	7 (3†; 4‡)	2	41/44 (44-58†; 17-54‡)
Pancreas carcinoma	6 (2†; 4‡)	6 (2†; 4‡)	2	46/39 (32-64†; 37-66‡)
Head and neck cancer	6 (1†; 5‡)	6 (1†; 5‡)	2	41/42 (21†; 30-59‡)
Skin cancer	6 (4†; 2‡)	5 (3†; 2‡)	2	31/31 (29-39†; 19-ND‡)
Chondrosarcoma	5 (2†; 3‡)	5 (2†; 3‡)	2	32/31 (21-57†; 19-33‡)
Ovary carcinoma	3 (3†)	3 (3†)	1†	43/35 (26-69†)
Nephroblastoma	3 (0†; 3‡)	3 (0†; 3‡)	0.9	3/2 (1-6‡)
Thyroid carcinoma	3 (3†; 0‡)	3 (3†; 0‡)	0.9	42/40 (35-50†)
Endometrial carcinoma	2 (2†)	2 (2†)	0.9†	54/54 (31-77†)
Testis choriocarcinoma	1 (1‡)	1 (1‡)	0.9‡	17/17 (17‡)
Esophageal cancer	2 (0†; 2‡)	2 (0†; 2‡)	0.6	63/63 (59-67‡)
Bladder carcinoma	2 (1†; 1‡)	2 (1†; 1‡)	0.6	49/49 (66†; 31‡)
Cervical carcinoma	1 (1†)	1 (1†)	0.5†	ND†
Gestational choriocarcinoma	1 (1†)	1 (1†)	0.5†	30/30 (30†)
Neuroblastoma	1 (1†; 0‡)	1 (1†; 0‡)	0.3	0.5/0.5 (0.5†)
Mesothelioma	1 (1†; 0‡)	1 (1†; 0‡)	0.3	52/52 (52†)
Myeloma	1 (0†; 1‡)	1 (0†; 1‡)	0.3	43/43 (43‡)
Thymoma	1 (1†; 0‡)	1 (1†; 0‡)	0.3	33/33 (33†)
Appendix carcinoma	1 (1†; 0‡)	1 (1†; 0‡)	0.3	45/45 (45†)

Management for TP53 carriers

- Lyon working group 2007
- No evidence for surveillance other than breast cancer
- Breast MRI and discussion of risk reducing mastectomy

- Screening strategies under investigation

Inheritance

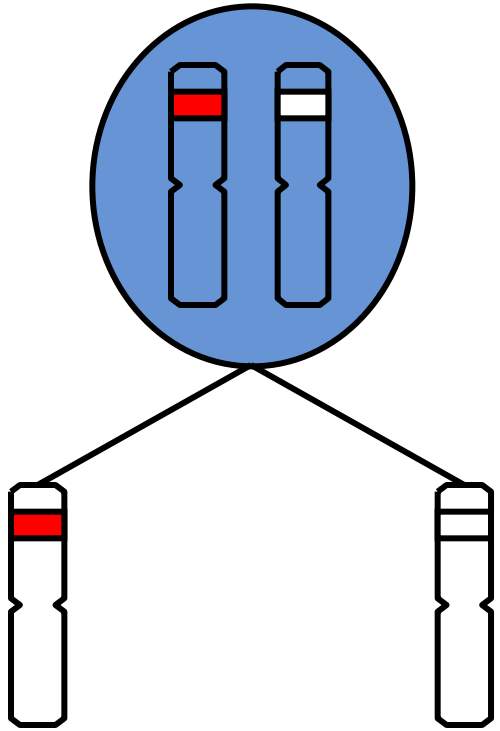
- Autosomal dominant
- De novo

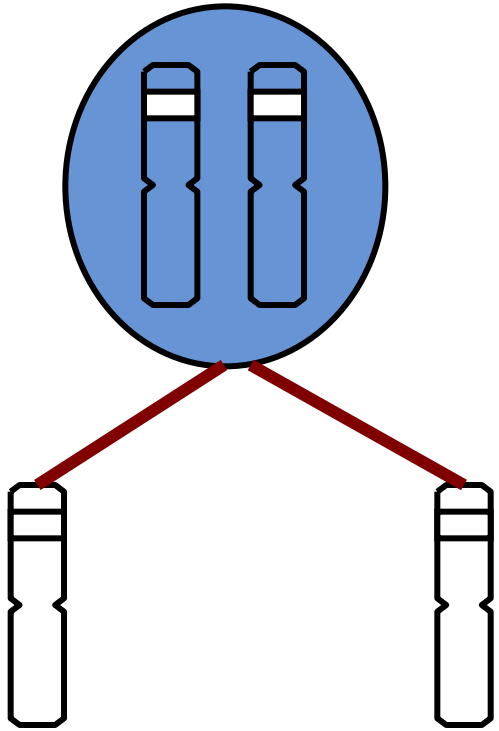
AUTOSOMAL DOMINANT INHERITANCE

Parents

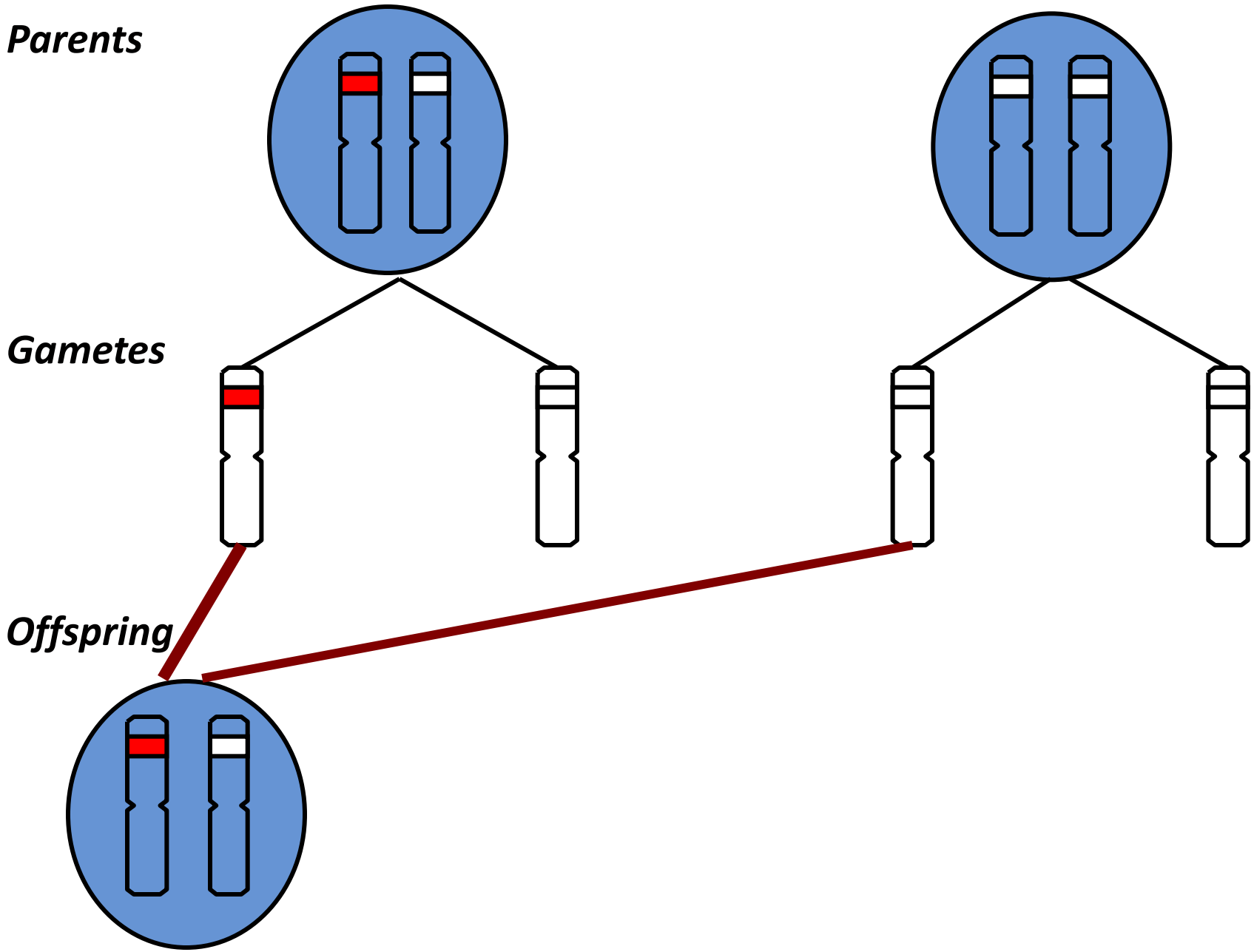
Gametes

egg/sperm





AUTOSOMAL DOMINANT INHERITANCE



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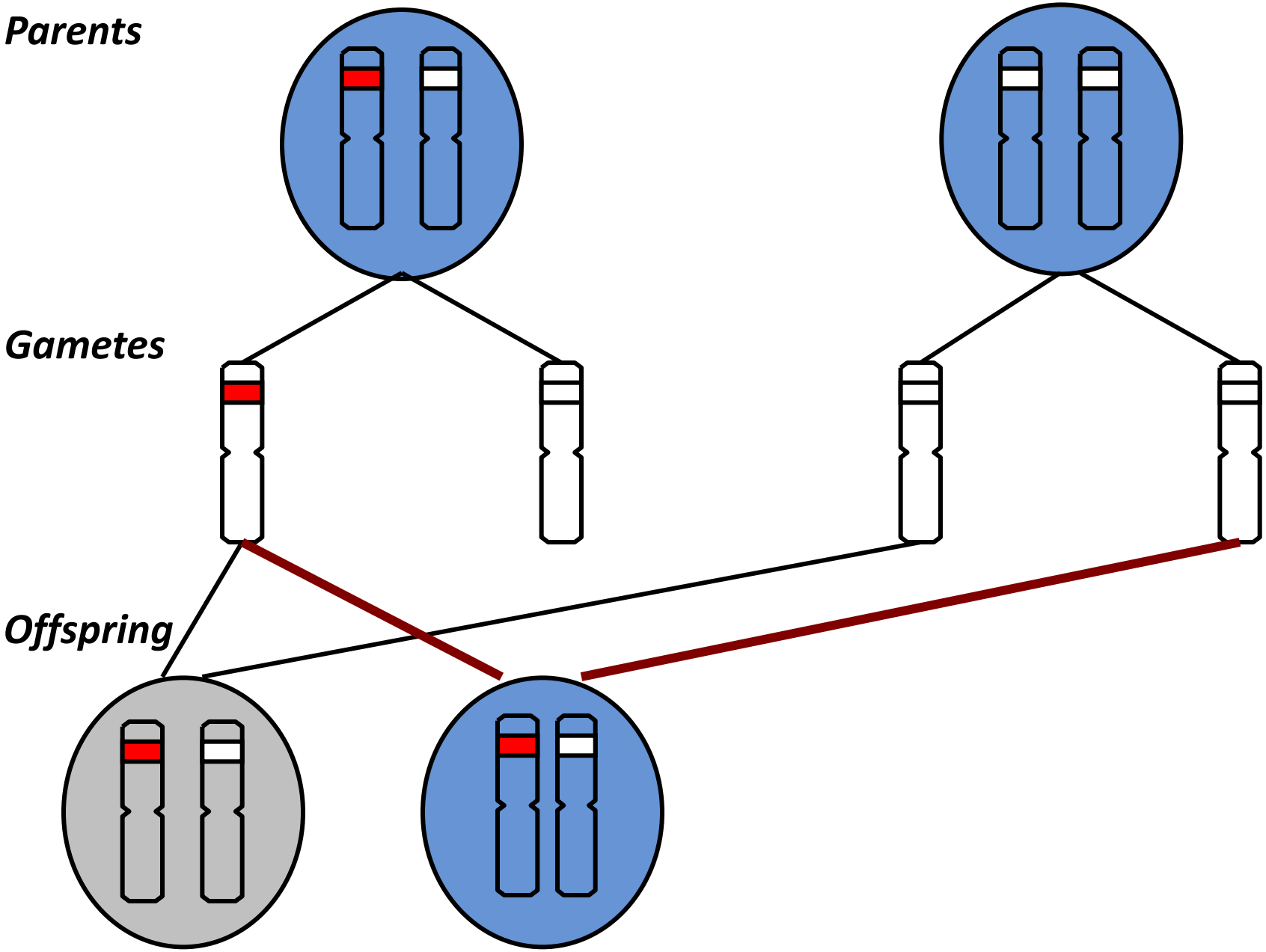

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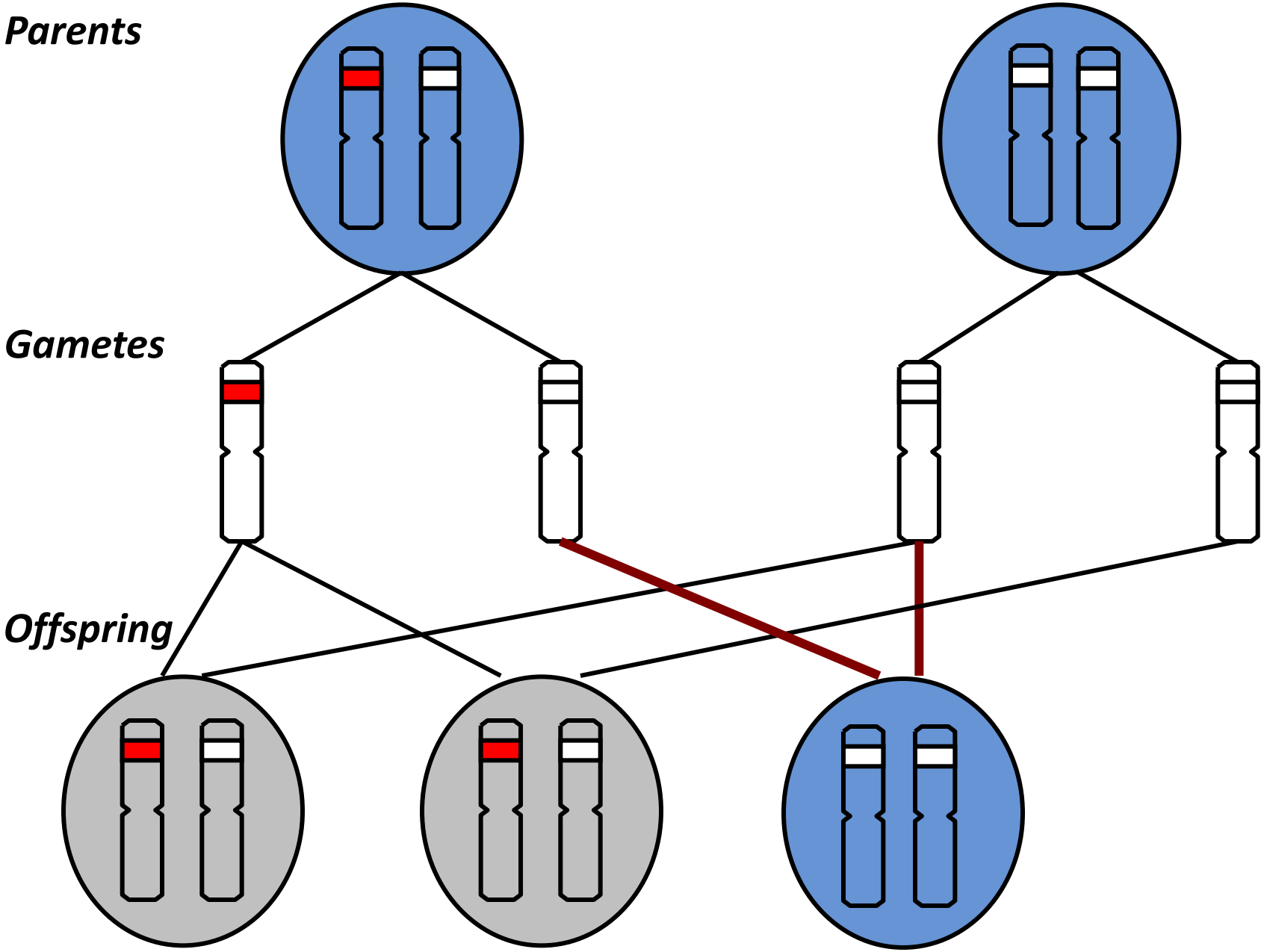

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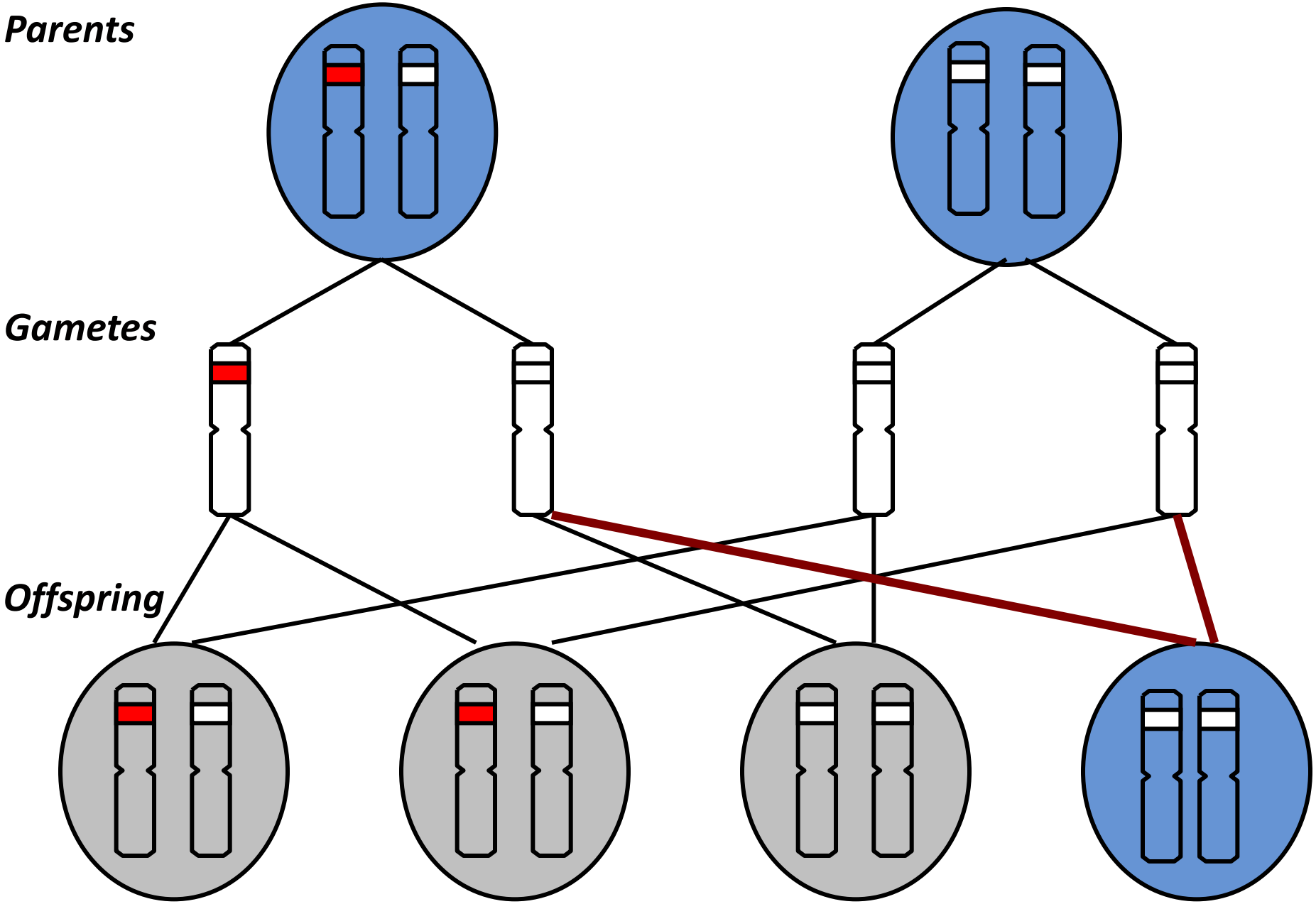

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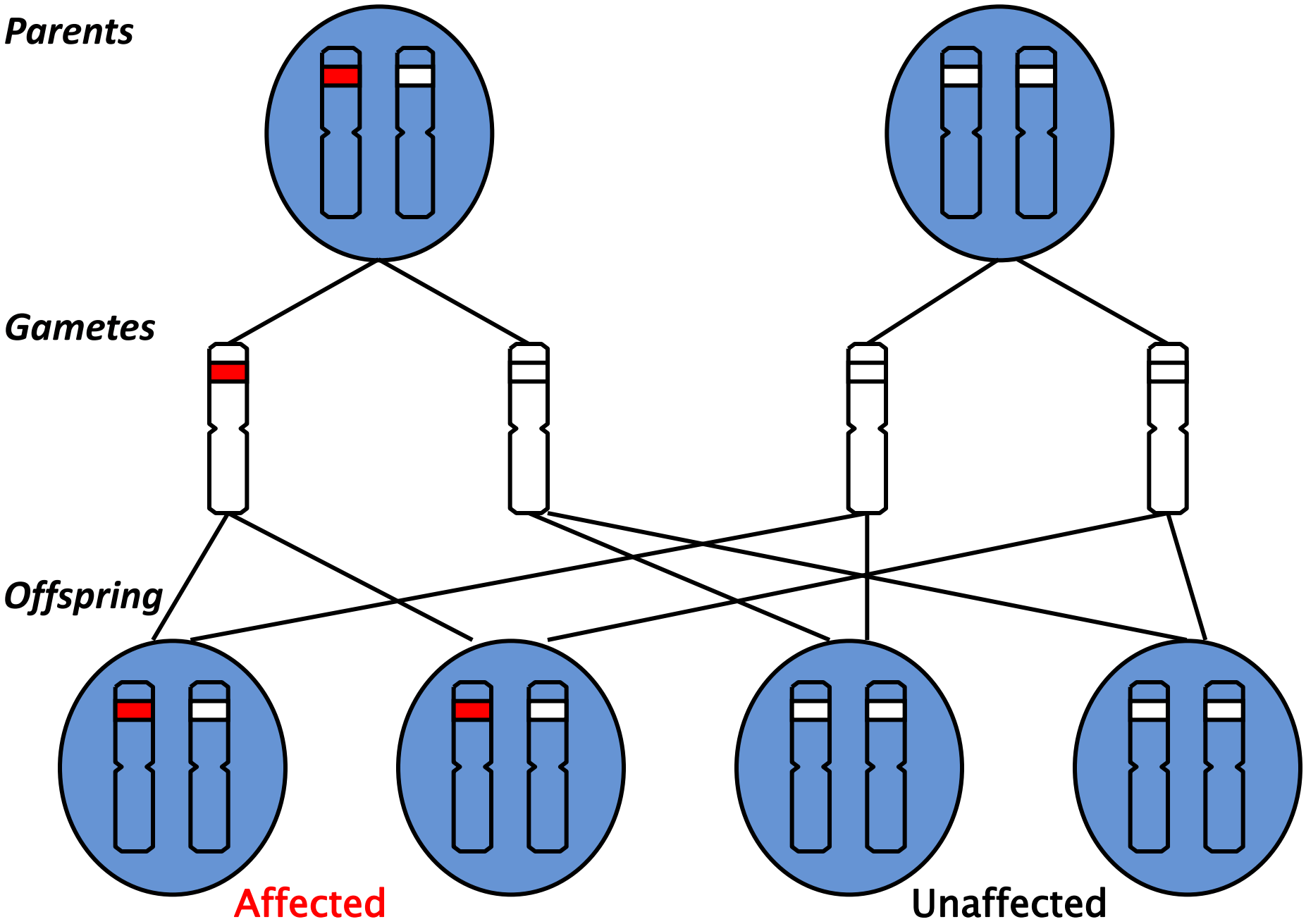

Reproductive options

- Pre-implantation genetic diagnosis
- Prenatal diagnosis

De novo mutations

- About 7% TP53 germline mutations have arisen de novo –i.e not inherited from parent
- Mutation arises in egg or sperm
- May mean individuals are not tested as no family history

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Next generation sequencing technologies

Genetic technologies have advanced meaning we now have the ability to test more cancer genes in more patients

Thank you
Any questions?