The George Pantziarka TP53 Trust

Helping families with Li Fraumeni Syndrome and related conditions

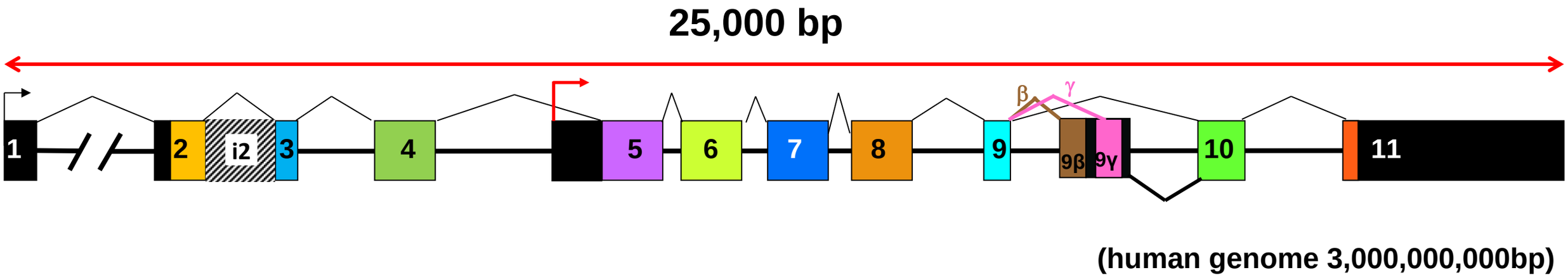
Is Li-Fraumeni Syndrome a rare disease ?

Jean-Christophe Bourdon,

Cancer Research Division
Dundee Cancer Centre
University of Dundee

Human TP53 gene structure

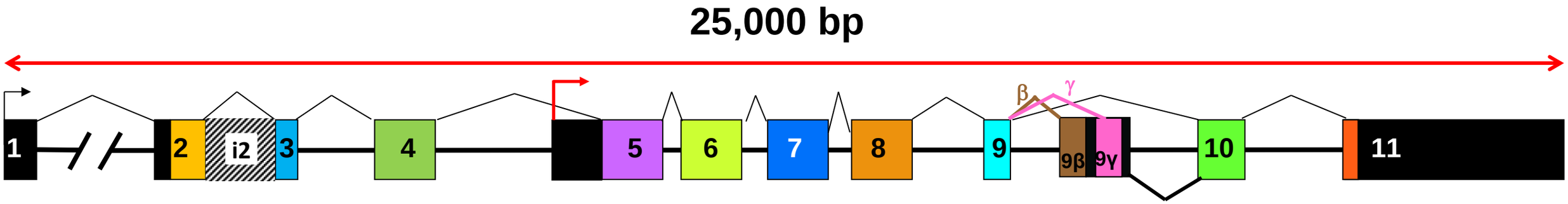
(Chromosome 17)



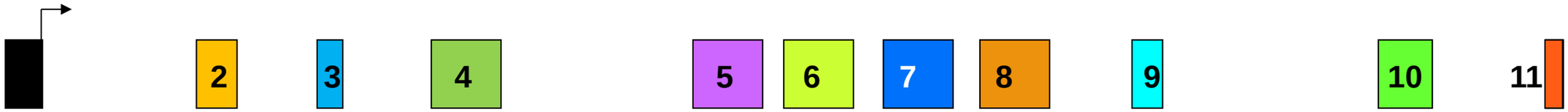
(human genome 3,000,000,000bp)

Human TP53 gene structure

(Chromosome 17)

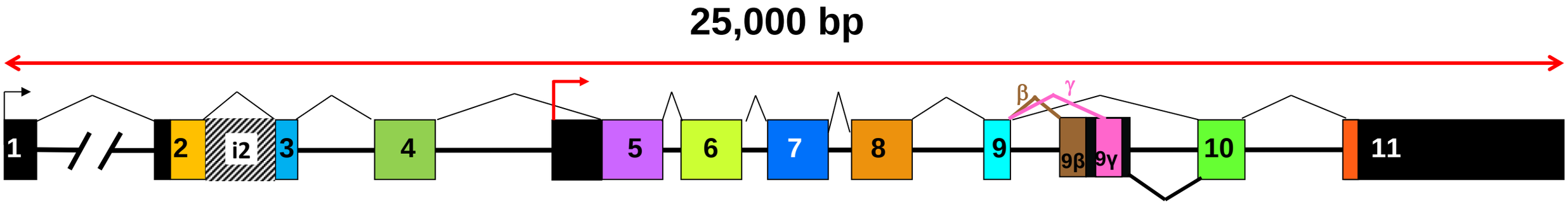


In the clinic, only mutations in the coding region are taken into consideration

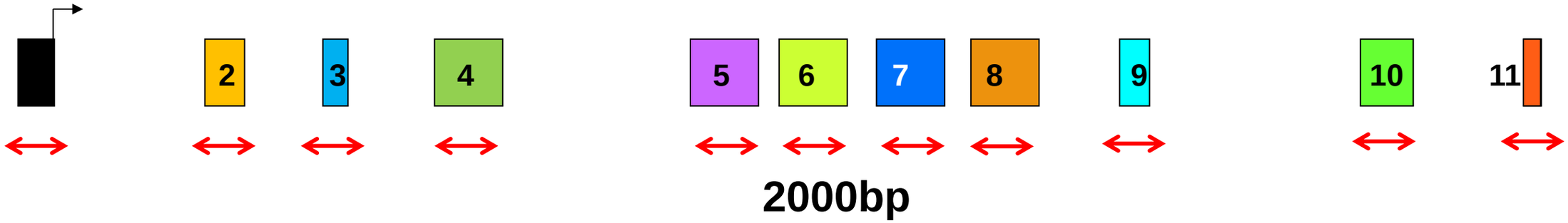


Human TP53 gene structure

(Chromosome 17)

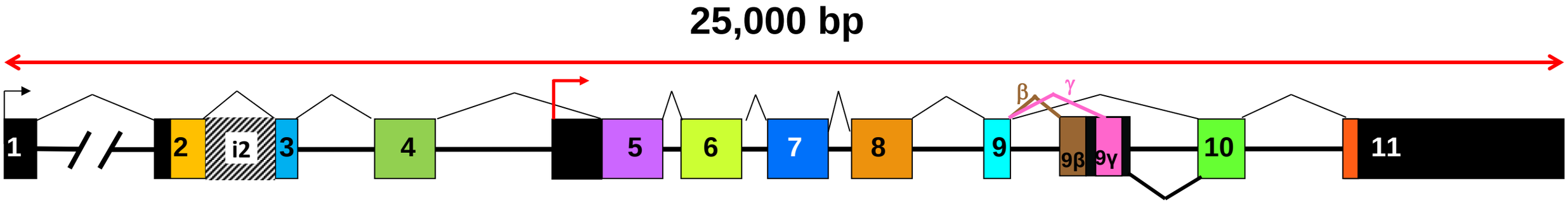


In the clinic, only mutations in the coding region are taken into consideration

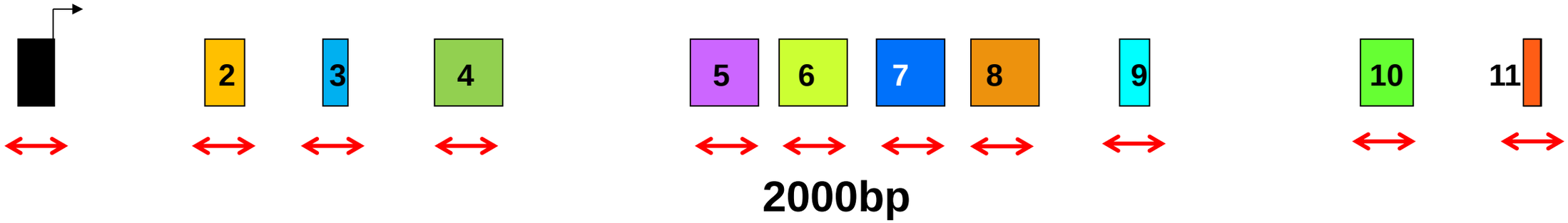


Human TP53 gene structure

(Chromosome 17)



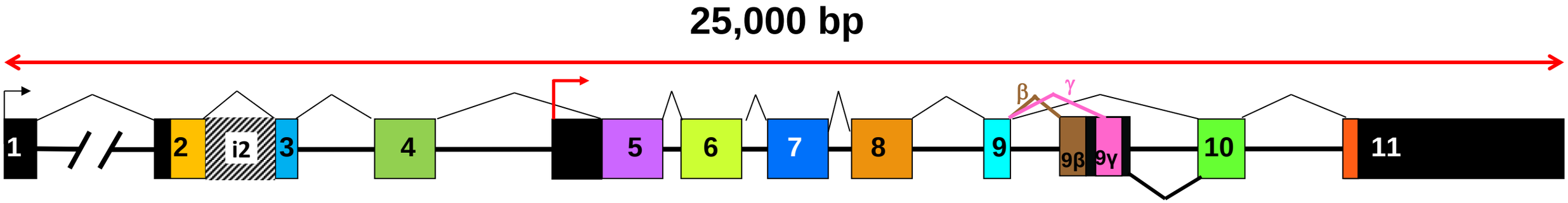
In the clinic, only mutations in the coding region are taken into consideration



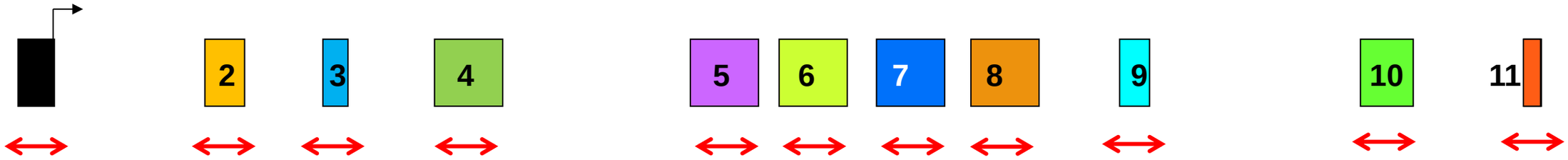
Is it because there are no mutation in the non-coding region?

Human TP53 gene structure

(Chromosome 17)



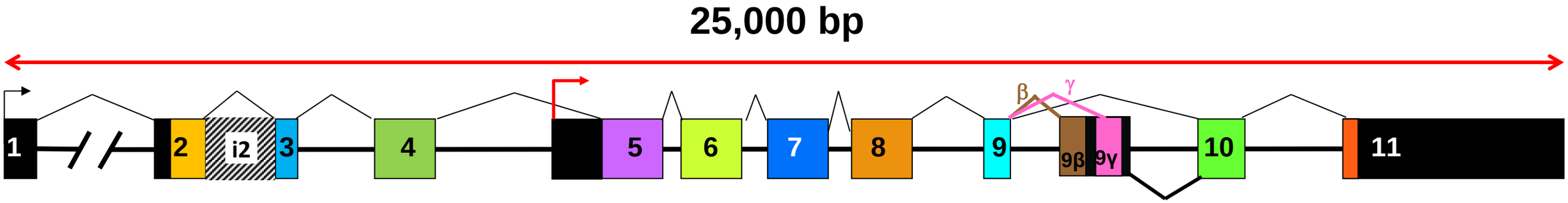
In the clinic, only mutations in the coding region are taken into consideration



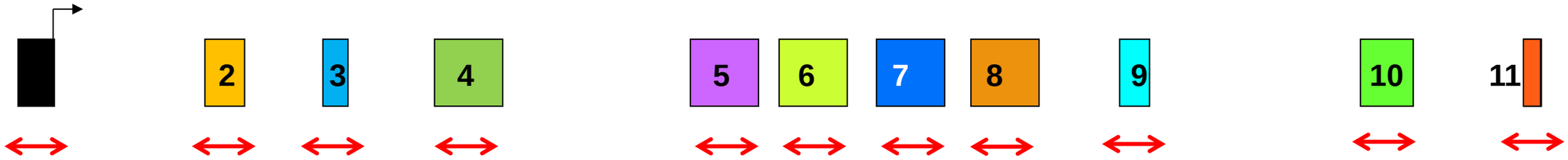
Is it because there are no mutation in the non-coding region?

Is it because mutation in the non-coding region do not induce LFS?

Human TP53 gene structure
(Chromosome 17)



In the clinic, only mutations in the coding region are taken into consideration



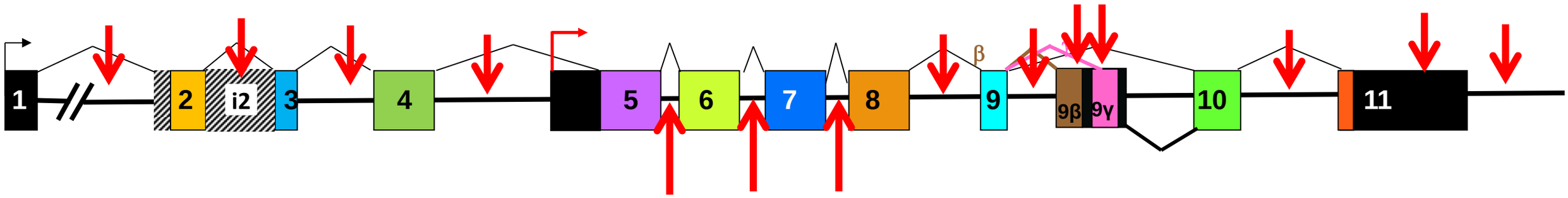
Is it because there are no mutation in the non-coding region?

Is it because mutation in the non-coding region do not induce LFS?

Are we thus neglecting a large number of cancer-prone families and not providing them the care they deserve?

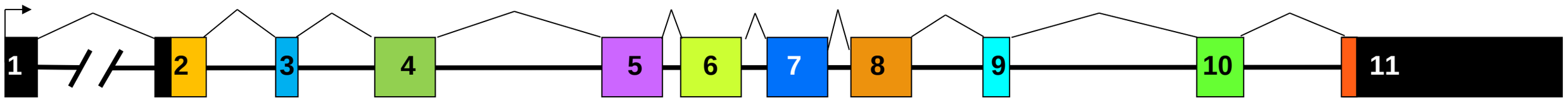
TP53 gene structure

Are there mutations in the non-coding regions?
What do the non-coding regions?

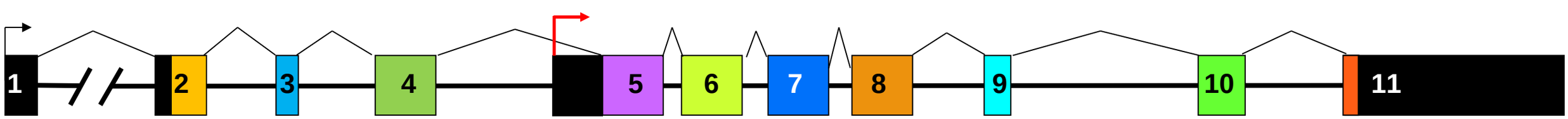


Human TP53 gene structure

(Chromosome 17)

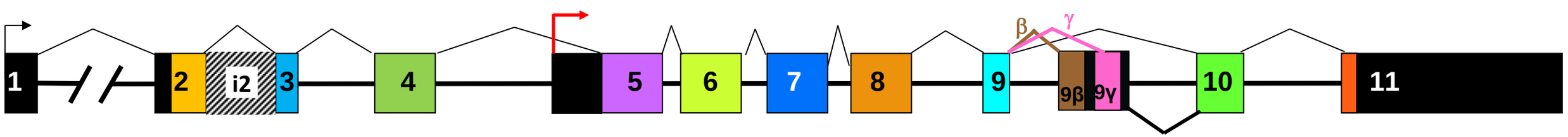


Human TP53 gene structure



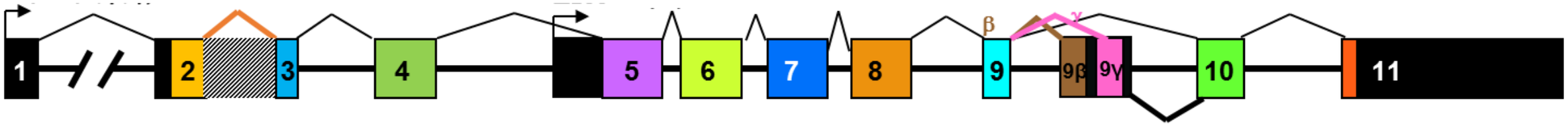
Internal promoter

Human TP53 gene structure

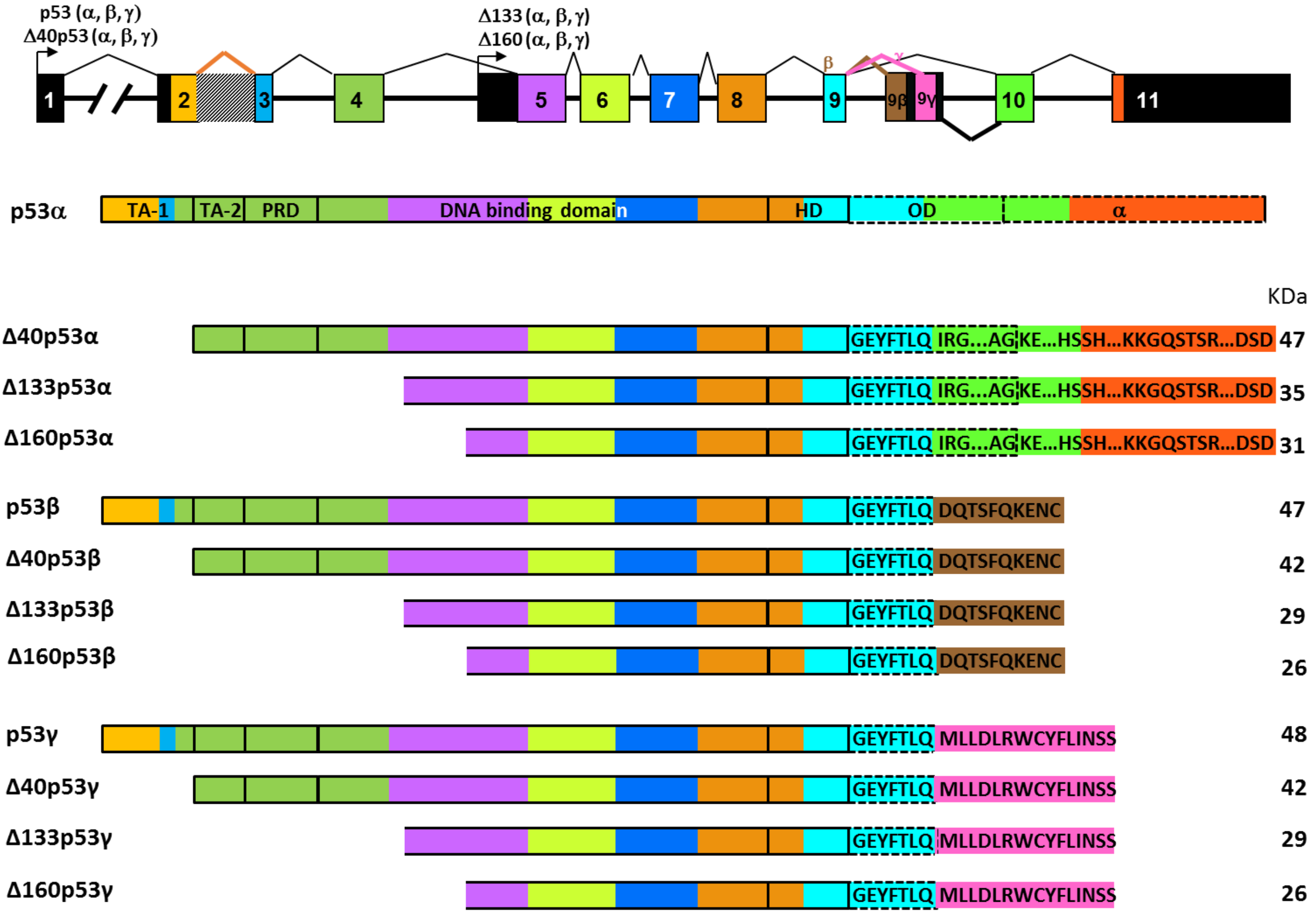


Internal promoter

Alternative splicing


1
2
3
4
5
6
7
8
β
9
9β
γ
9γ
10
11

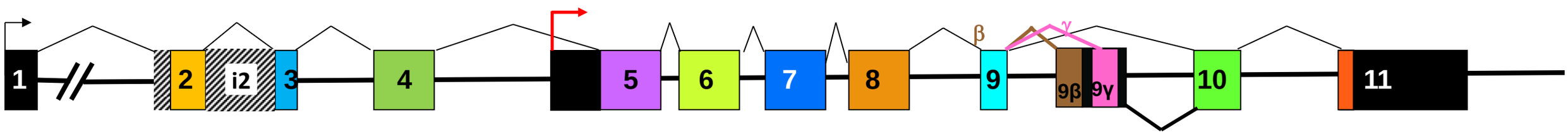

p53α
TA-1
TA-2
PRD
DNA binding domain
HD
OD
α



Bourdon et al., 2005, Genes &Dev

TP53 gene structure

Are there mutations in the non-coding regions?



Define the "wild-type" sequence of the TP53 gene

The Genome Aggregation Database (gnomAD):
Worldwide effort to sequence genome of millions of unrelated individuals from different continents.

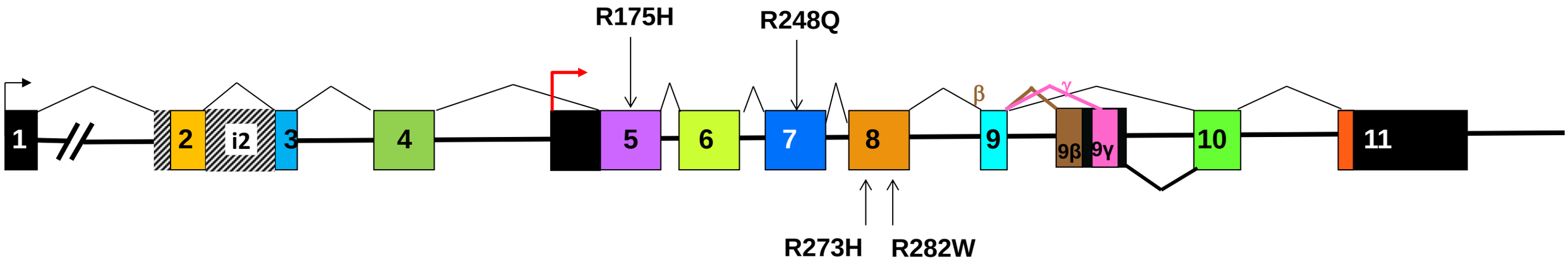
The data set provided on this website spans 123,136 exomes and 15,496 genomes from unrelated individuals sequenced as part of various disease-specific and population genetic studies. (i.e people genomes were sequenced because of a particularity)

Individuals known to be affected by severe pediatric disease, as well as their first-degree relatives were removed, so this data set should serve as a useful reference set of allele frequencies for severe disease studies –

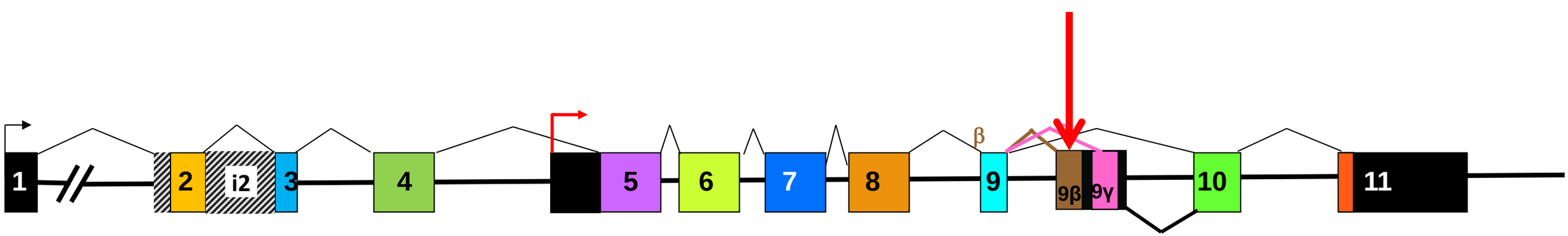
however, note that some individuals with severe disease may still be included in the data set,

17:7577061 C / A (rs587780076)	E	G	p.Gly293Trp	missense	3	277226	0	1.082e-5
17:7577061 C / T (rs587780076)	E		p.Gly293Arg	missense	2	246264	0	8.121e-6
17:7577063 T / C (rs121912663)		G	p.Lys292Arg	missense	1	30960	0	3.23e-5
17:7577066 T / C (rs781490101)	E		p.Lys291Arg	missense	2	246266	0	8.121e-6
17:7577068 G / GCGGTTTCCGC (rs764803020)	E		p.Lys291ArgfsTer18	frameshift	1	246264	0	4.061e-6
17:7577069 C / T (rs55819519)	E	G	p.Arg290His	missense	42	277220	0	0.0001515
17:7577070 G / A (rs770374782)	E	G	p.Arg290Cys	missense	4	277216	0	1.443e-5
17:7577071 G / A (rs778138282)	E		p.Leu289Leu	synonymous	1	246266	0	4.061e-6
17:7577077 C / G (rs748891343)	E		p.Glu287Asp	missense	1	246262	0	4.061e-6
17:7577079 C / T (rs587782006)	E		p.Glu287Lys	missense	1	246258	0	4.061e-6
17:7577083 C / T	E	G	p.Glu285Glu	synonymous	2	277216	0	7.215e-6
17:7577086 T / G (rs786203004)	E		p.Thr284Thr	synonymous	1	246258	0	4.061e-6
17:7577090 C / T (rs371409680)	E		p.Arg283His	missense	10	246244	0	4.061e-5
17:7577091 G / A (rs149633775)	E	G	p.Arg283Cys	missense	24	277184	0	8.659e-5
17:7577091 G / T (rs149633775)	E		p.Arg283Ser	missense	1	246228	0	4.061e-6
17:7577093 C / T (rs730882008)	E	G	p.Arg282Gln	missense	2	277176	0	7.216e-6
17:7577094 G / A (rs28934574)	E		p.Arg282Trp	missense	1	246198	0	4.062e-6
17:7577097 C / T (rs764146326)	E		p.Asp281Asn	missense	1	246230	0	4.061e-6
17:7577100 T / G (rs753660142)	E		p.Arg280Arg	synonymous	4	246202	0	1.625e-5
17:7577108 C / A (rs763098116)	E		p.Cys277Phe	missense	1	246102	0	4.063e-6
17:7577120 C / A (rs28934576)	E		p.Arg273Leu	missense	1	245868	0	4.067e-6
17:7577121 G / A (rs121913343)	E		p.Arg273Cys	missense	3	245670	0	1.221e-5
17:7577122 C / T (rs756421198)	E		p.Val272Val	synonymous	1	245774	0	4.069e-6
17:7577138 C / T (rs587780075)	E		p.Arg267Gln	missense	3	244182	0	1.229e-5
17:7577149 A / G (rs770598448)	E		p.Asn263Asn	synonymous	1	241890	0	4.134e-6
17:7577151 T / C (rs72661119)	E		p.Asn263Asp	missense	28	241248	0	0.0001161
17:7577154 C / T (rs200579969)	E	G	p.Gly262Ser	missense	3	270602	0	1.109e-5
17:7577166 T / C (rs771914358)	E			intron	2	231696	0	8.632e-6

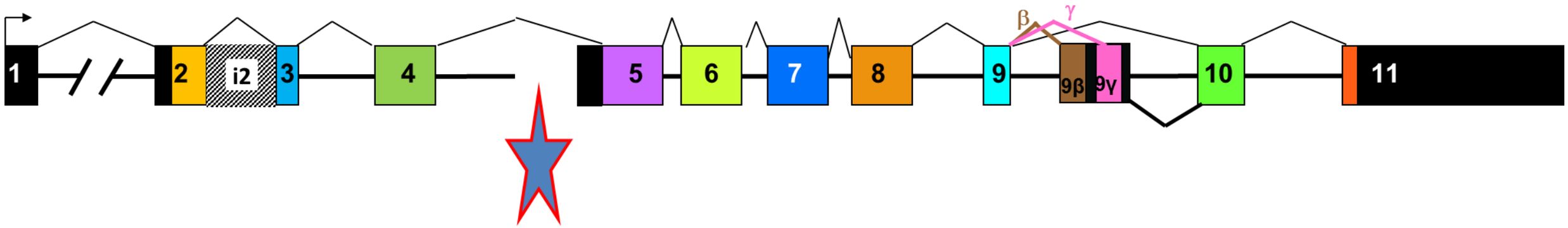
Patients carrier of the TP53 mutation found in LFS



Are there mutations in the alternatively spliced exons?



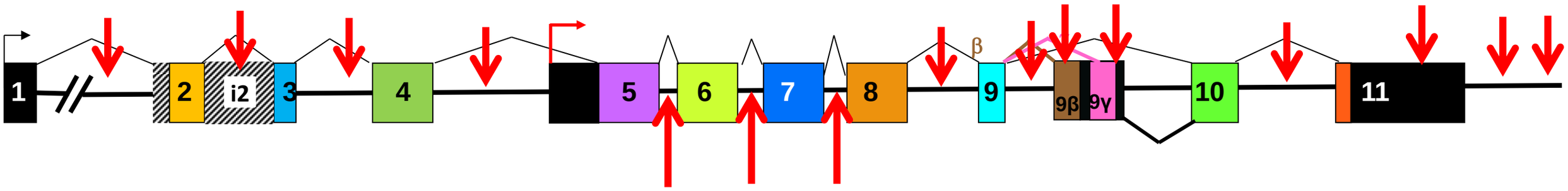
Are there mutations in the p53 internal promoter?



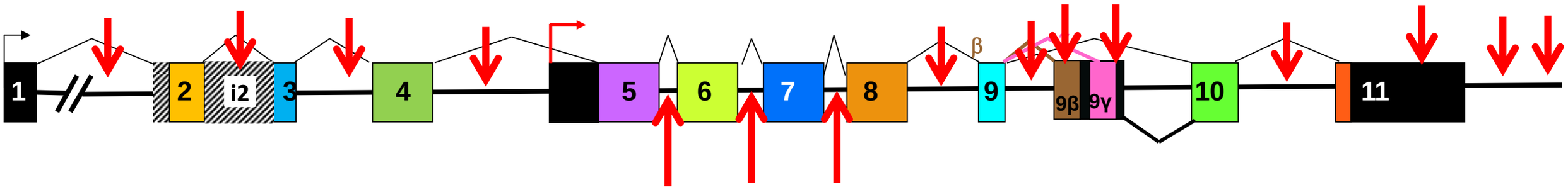
2500< patients have mutations in internal promoter (<0.001)

17:7578533 T / C	E		p.Met1?†	start lost	1	245768	0	4.069e-6
17:7578536 T / C (rs747342068)	E		p.Lys132Glu	missense	1	245678	0	4.07e-6
17:7578537 G / T (rs769270327)	E	G	p.Asn131Lys	missense	4	276552	0	1.446e-5
17:7578540 G / A (rs781537596)	E		c.376-7C>T†	splice region	6	245376	0	2.445e-5
17:7578552 GTAC / G	E		c.376-1_377delGTA	splice acceptor	1	244932	0	4.083e-6
17:7578555 C / CT (rs751253294)	E		c.376-2dupA	splice acceptor	2	244736	0	8.172e-6
17:7578556 T / G (rs786202799)	E		c.376-2A>C	splice acceptor	1	244718	0	4.086e-6
17:7578558 T / A	E		c.376-4A>T	splice region	1	244544	0	4.089e-6
17:7578564 G / A	E			non coding transcript exon	1	243668	0	4.104e-6
17:7578565 A / C (rs747705704)	E			non coding transcript exon	1	243734	0	4.103e-6
17:7578570 G / A	E			non coding transcript exon	1	242542	0	4.123e-6
17:7578571 G / A (rs376713749)	E			non coding transcript exon	5	242232	0	2.064e-5
17:7578571 G / GA (rs376713749)	E			non coding transcript exon	1	242232	0	4.128e-6
17:7578573 G / A	E			non coding transcript exon	1	241414	0	4.142e-6
17:7578574 A / G	E			non coding transcript exon	1	241202	0	4.146e-6
17:7578575 CAG / C	E			non coding transcript exon	3	240834	0	1.246e-5
17:7578577 G / A (rs773029752)	E			non coding transcript exon	3	240336	0	1.248e-5
17:7578578 A / T	E			non coding transcript exon	1	239936	0	4.168e-6
17:7578598 G / A	E			non coding transcript exon	1	222130	0	4.502e-6
17:7578601 A / C (rs774330271)	E			non coding transcript exon	2	218542	0	9.152e-6
17:7578617 G / A		G		non coding transcript exon	2	30942	0	6.464e-5
17:7578624 G / A		G		non coding transcript exon	1	30940	0	3.232e-5
17:7578640 A / G (rs113530090)		G		non coding transcript exon	234	30898	1	0.007573
17:7578645 C / T (rs2909430)		G		non coding transcript exon	25863	30762	10948	0.8407
17:7578655 T / A (rs145153611)		G		non coding transcript exon	51	30812	0	0.001655
17:7578666 A / G		G		non coding transcript exon	5	30588	0	0.0001635
17:7578671 C / T (rs35850753)		G		non coding transcript exon	562	30678	7	0.01832
17:7578672 G / A		G		non coding transcript exon	2	30668	0	6.521e-5
17:7578676 TAGAG / T		G		non coding transcript exon	1	30498	0	3.279e-5
17:7578679 A / G (rs9895829)		G		non coding transcript exon	2488	30596	118	0.08132

Hundred of Thousand people carry mutation in TP53 non-coding regions



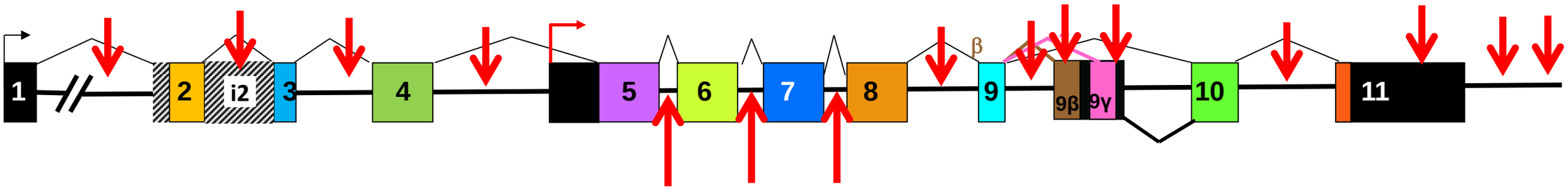
Hundred of Thousand people carry mutation in TP53 non-coding regions



Not all mutations cause cancer but it is likely that some mutations will cause cancer as they affect TP53 gene expression

therefore what should we say to the patients?

Hundred of Thousand people carry mutation in TP53 non-coding regions

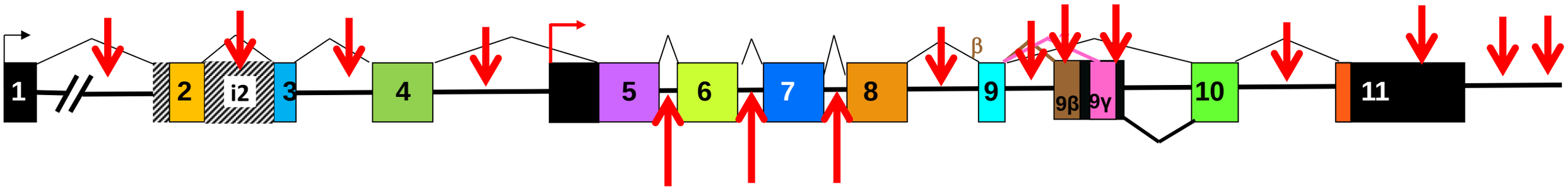


Not all mutations cause cancer but it is likely that some mutations will cause cancer as they affect TP53 gene expression

therefore what should we say to the patients?

- We might make the patient worry all his/her life for nothing and stop him/her enjoying life ?

Hundred of Thousand people carry mutation in TP53 non-coding regions



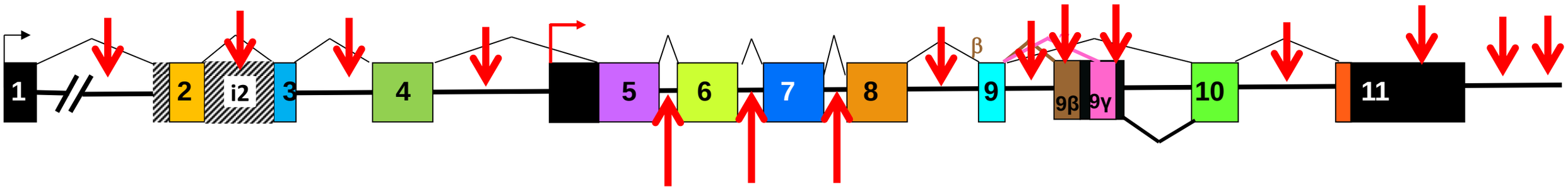
Not all mutations cause cancer but it is likely that some mutations will cause cancer as they affect TP53 gene expression

therefore what should we say to the patients?

- **We might make the patient worry all his/her life for nothing and stop him/her enjoying life ?**

- **We may help family members and enable LFS patients to be monitored and treated adequately?**

Hundred of Thousand people carry mutation in TP53 non-coding regions



Not all mutations cause cancer but it is likely that some mutations will cause cancer as they affect TP53 gene expression

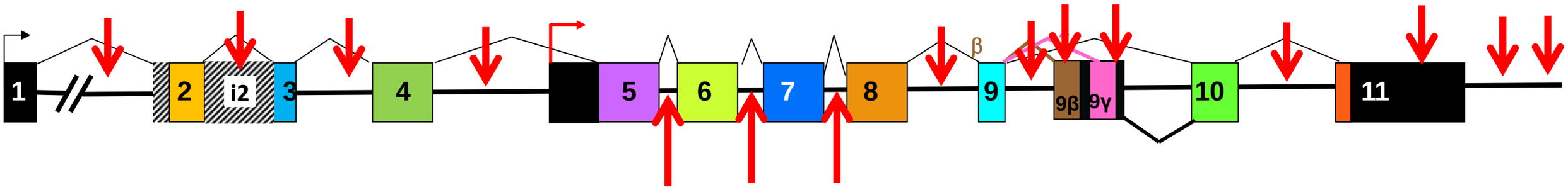
therefore what should we say to the patients?

- **We might make the patient worry all his/her life for nothing and stop him/her enjoying life ?**

- **We may help family members and enable LFS patients to be monitored and treated adequately?**

- **If we do not tell them, then patients will not be monitored and will be treated with conventional treatments (radiotherapy, DNA-damaging agent) which are known to promote tumour formation in Li-Fraumeni patients**

Hundred of Thousand people carry mutation in TP53 non-coding regions



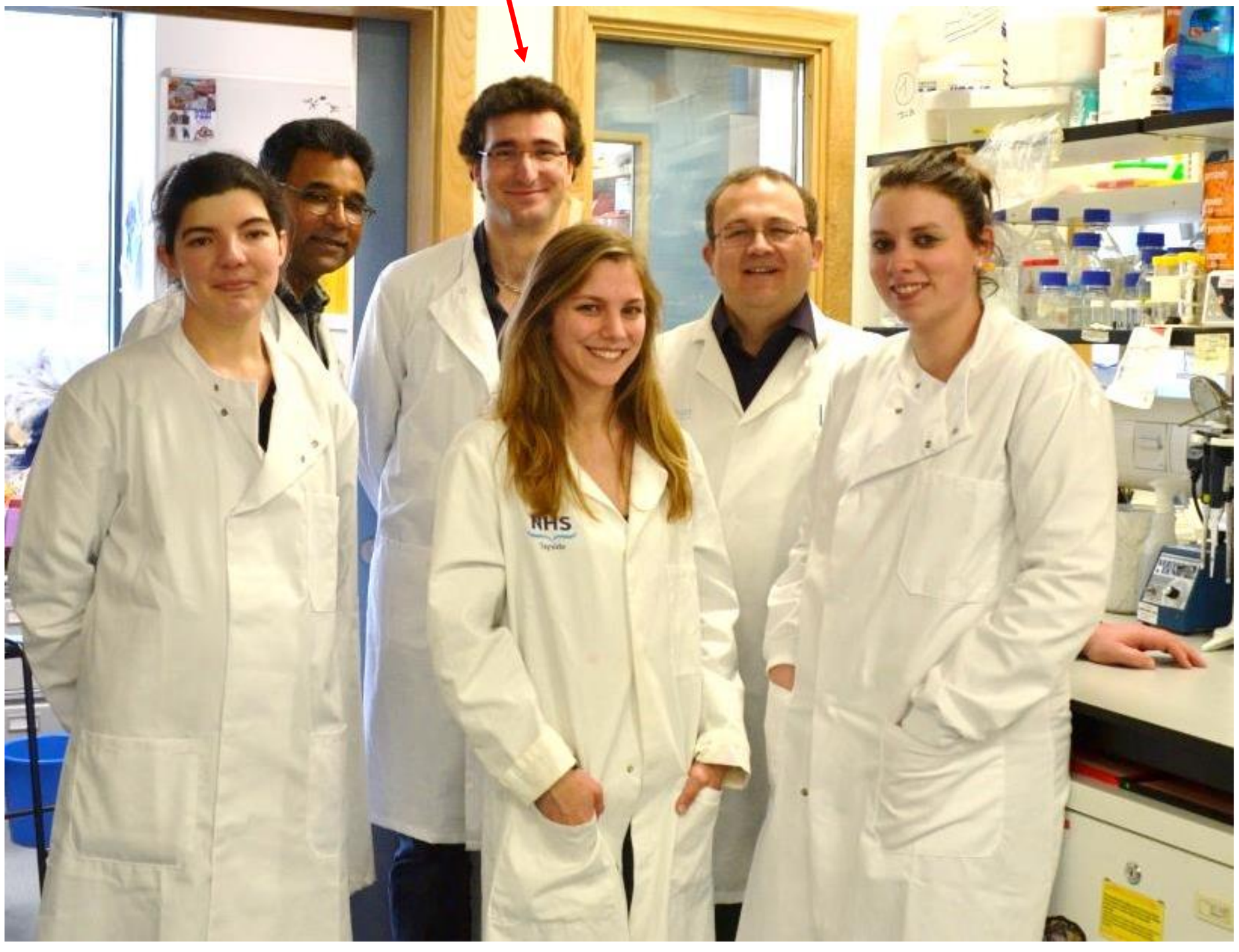
Not all mutations cause cancer but it is likely that some mutations will cause cancer as they affect TP53 gene expression

therefore what should we say to the patients?

If mutation is in non-coding region, then the patient is NOT DECLARED as a LFS patients even if she/he has cancer-family history

- because there is no experimental evidence demonstrating that such mutations affect p53 activity.

Sebastien Joruiz



Study the biochemical and biological activities of intronic/splicing mutant p53 gene

Generate scientific tools:

- **Generate antibodies against the mutant proteins**
- **Establish cell lines from patients**
- **Clone and produce gene expression vectors for the mutant proteins**
- **Investigate their biological and biochemical activities**

Conclusions

⇒ ***Large population of patients are not diagnosed as Li-Fraumeni because functional assays have not been designed to assess biological effect of intronic mutation on TP53 gene expression and activity.***

The number of Li-Fraumeni patients is largely underestimated

⇒ ***Li-Fraumeni may NOT be such a rare disease!***