The role of patients genetic variations in drugs cancer therapy

By

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The effectiveness of any drug must associate with:

--its good absorption,

--correct metabolism,

--specific target and

--un accumulated metabolites

-This make any drug as very effective weapon against specific disease.

-But the reality is some think quite different from that.

-This due to the differences of patients response to drug.

-Some patients have good response to drug therapy, others are either with mild to poor response or resist the drug.

- On the other hand, some patients are reflect a kind of toxicity when they use a kind of drug.

-- Statistically, 30 to 50 % of patients have poor response or resist the drug in addition to 5% reflect high drug toxicity.

-- This will coast the community a lot of money.

If we look to in deep we will find that the drug effectiveness leads by enzymes which are the mirror copies of genes.

This mean that response/resist and toxicity to drug depend not just on drug but on genes(enzymes) that metabolite the drugs.

This mean that response / resistance and toxicity to drug depends on individual genetic variations.

So what are the sources of genetic variations??

-Sources of variations in individuals

A. Crossing Over

B. Dominance & Recessive

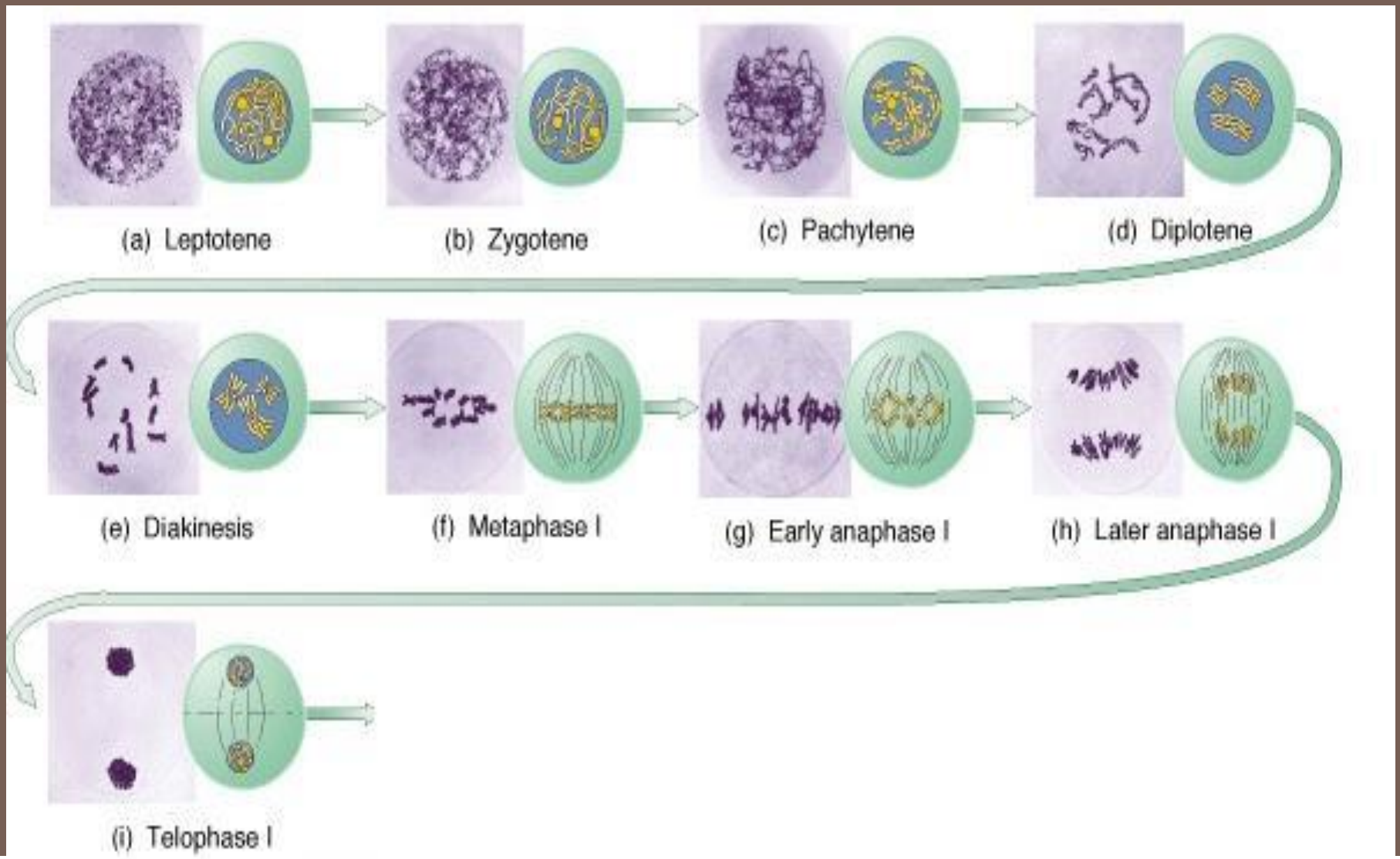
C. Allelic Polymorphism

D. Hormonal Influence

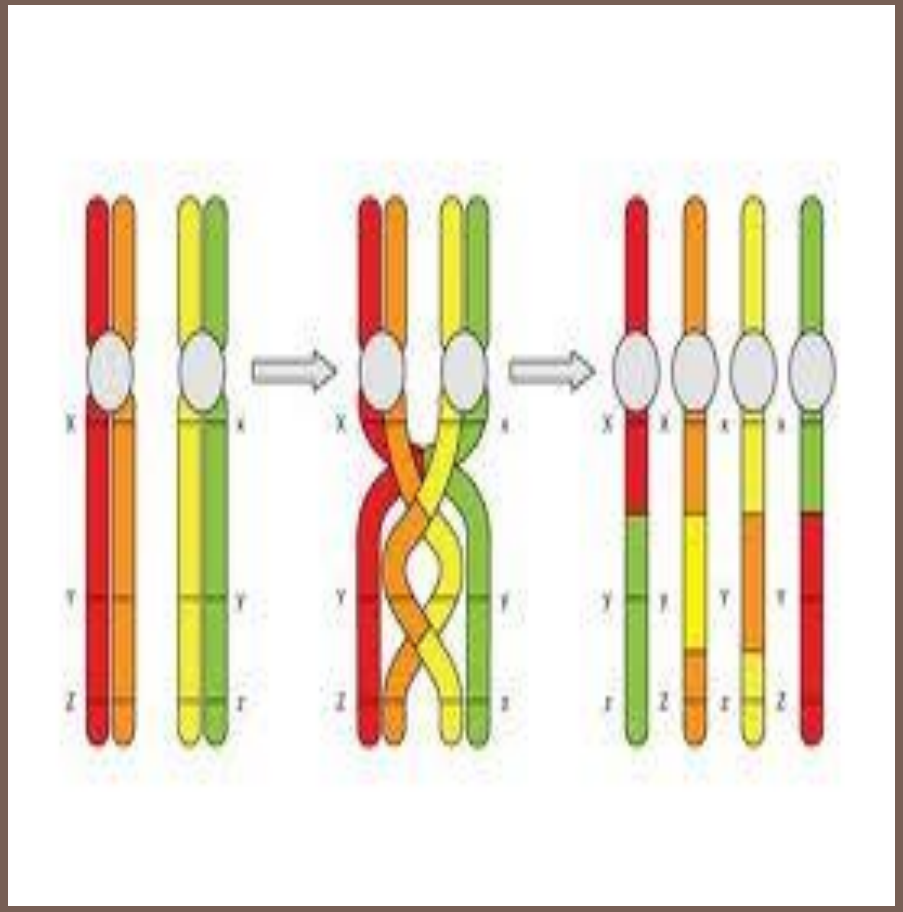
E. Chromosome X inactivation

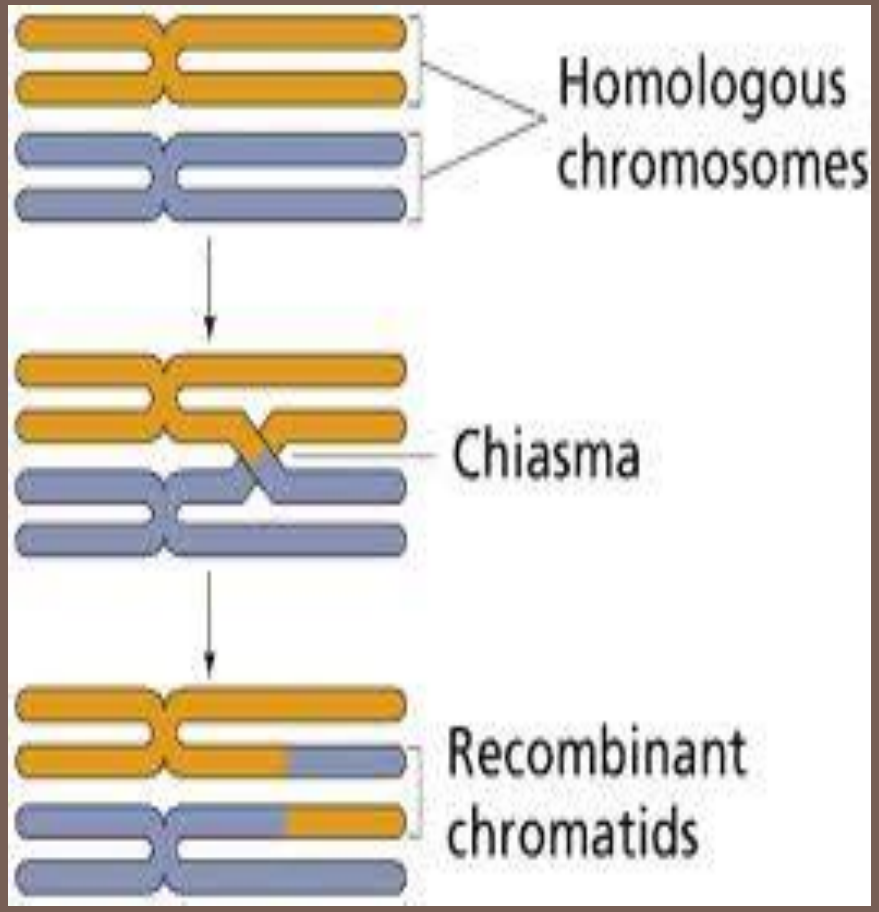
F. Race

Meiosis I division in Sex or Germ Cells



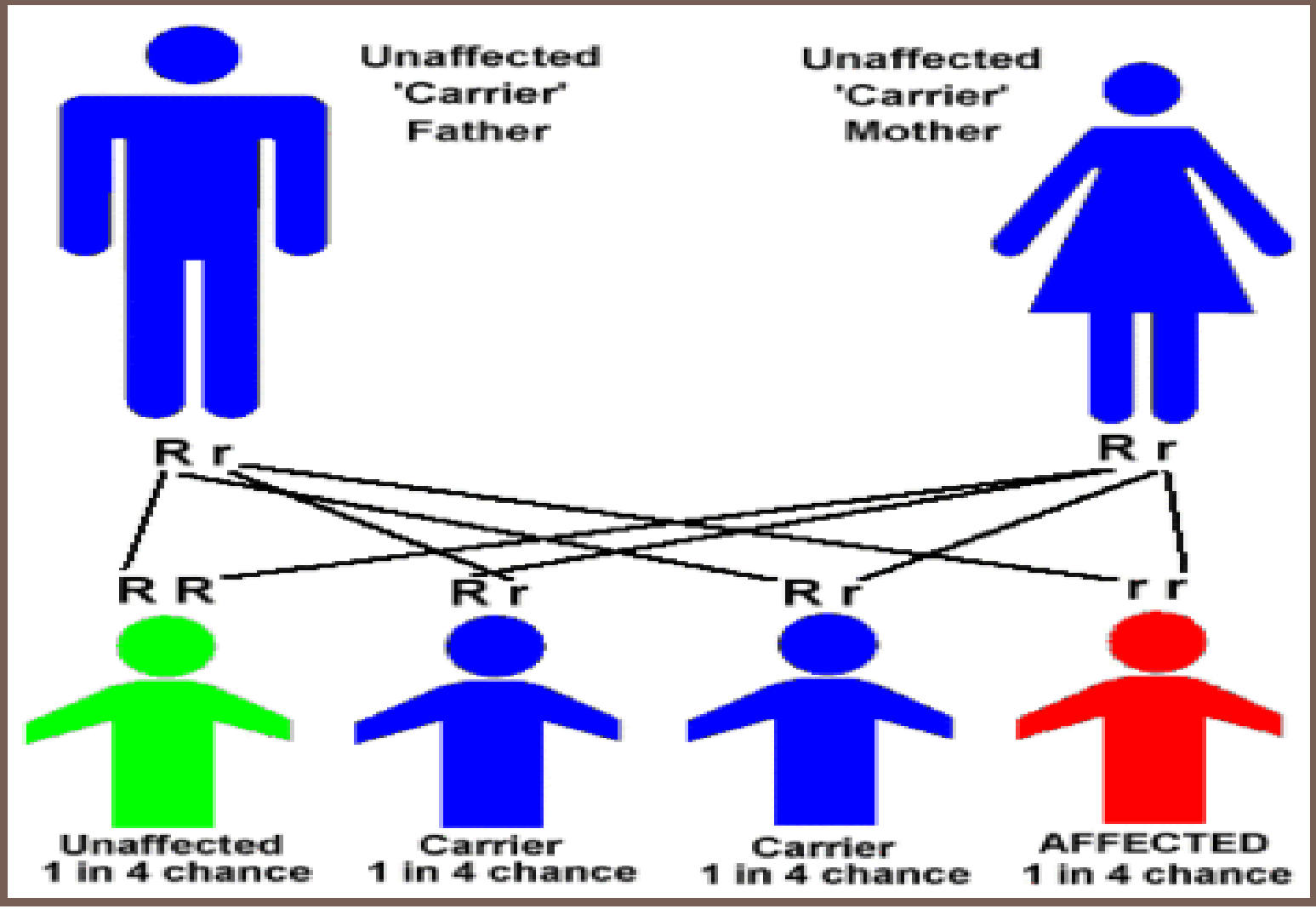
Crossing Over





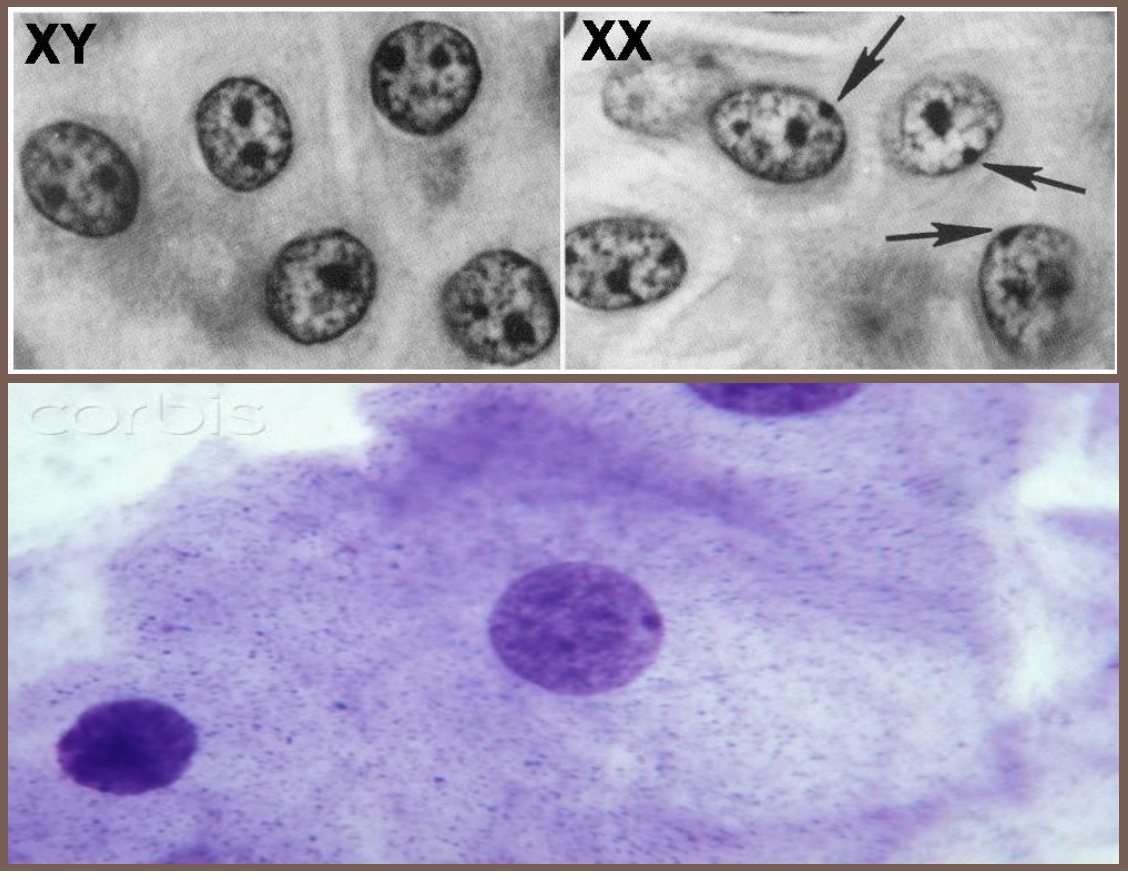
B. Dominance & Recessive

T



D. Hormonal Influence

E. Chromosome X inactivation



The most important genetic source for drug response-resistance and toxicity is the

Allelic Polymorphism

Single Nucleotide Polymorphisms-SNPs

--Enzymes: CYP450, CYP2D6, thiopurine S-methyltransferase (TPMT)

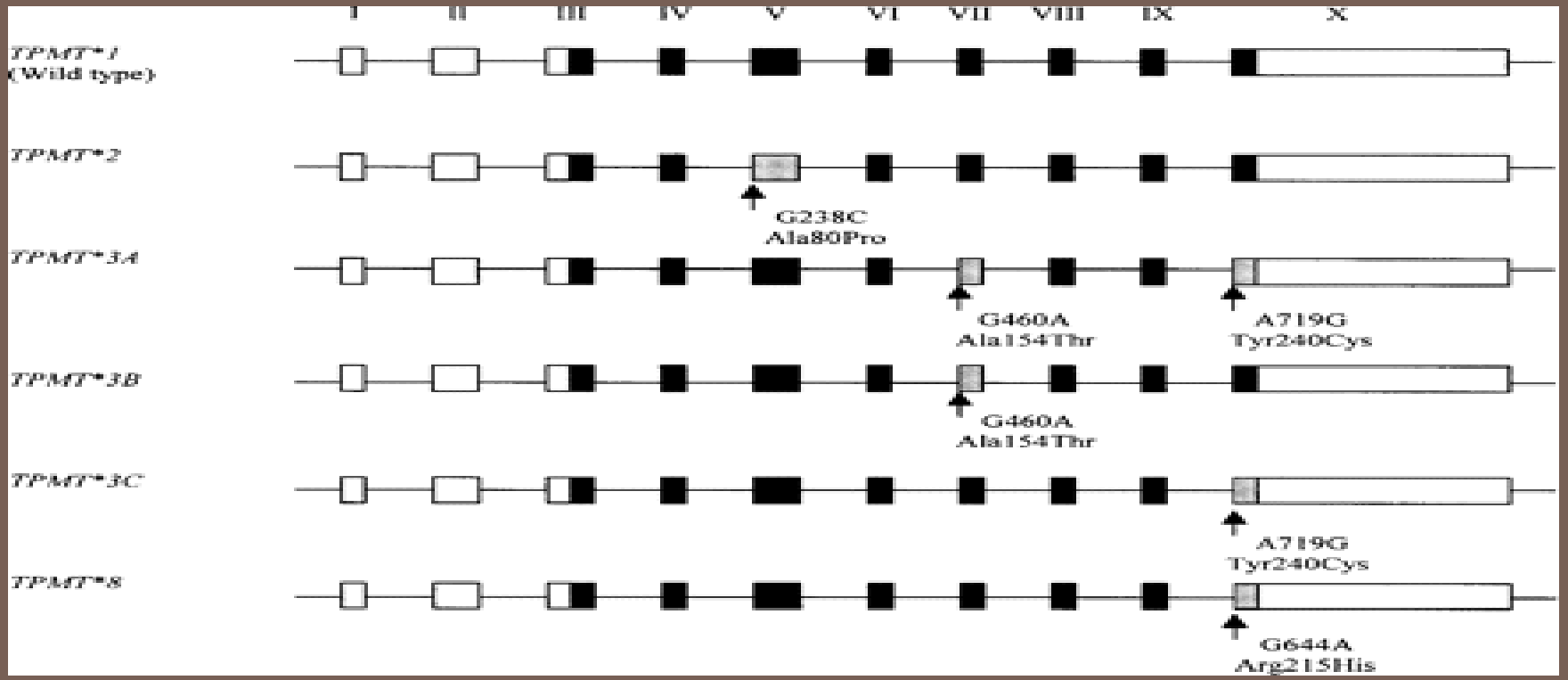
--Drugs: 6-mercaptopurine,

6-thioguanine,azathioprine,Thiopurine

autoimmune disease, inflammatory bowel disease, anticancer

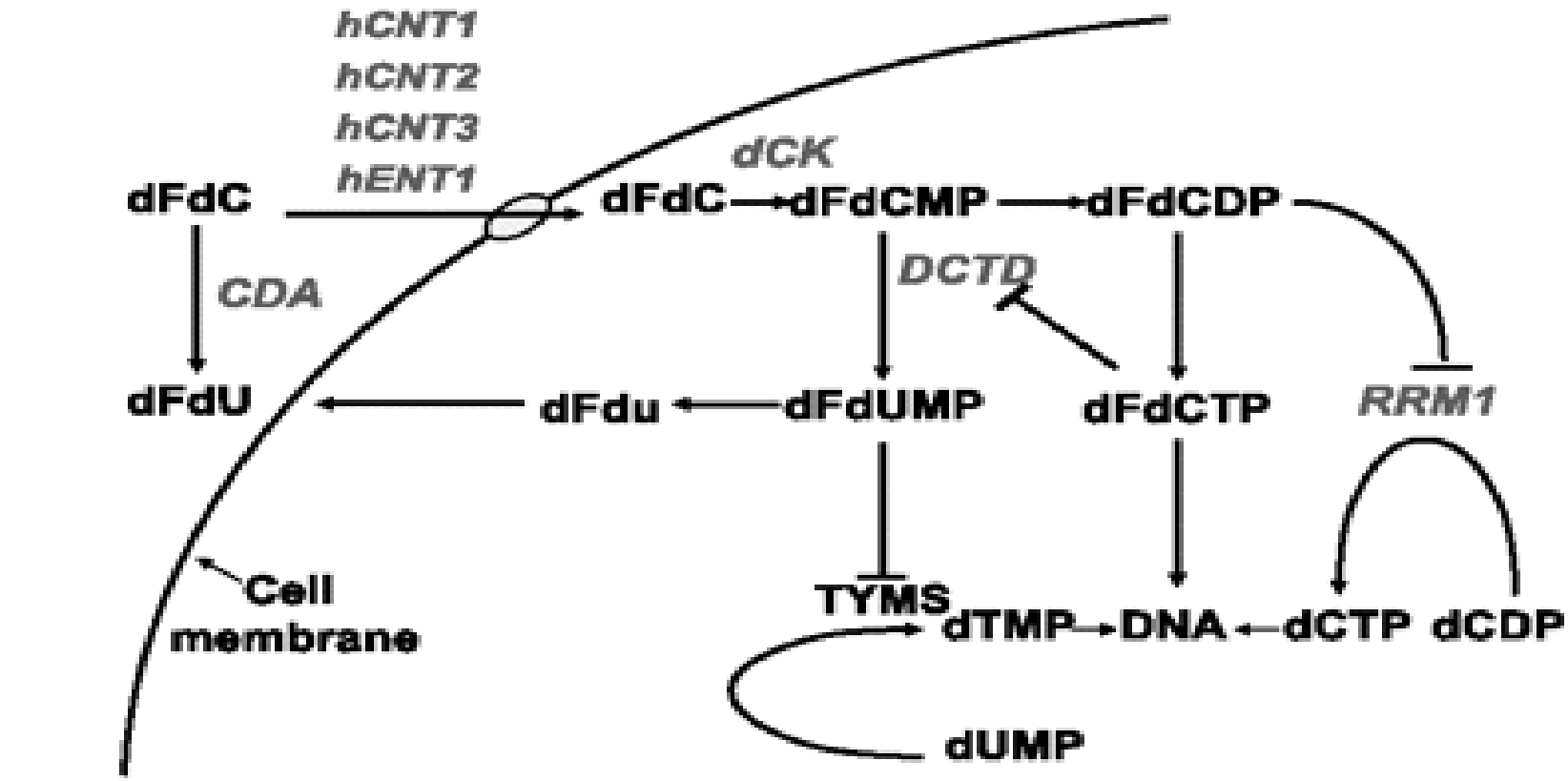
Vit B12…no absorption cause malignant anemia

Iressa, Herceptin ….Lung cancer



Allelic variants at the human *TPMT* locus. Boxes depict exons in the human *TPMT* gene. White boxes are untranslated exonic regions and black boxes represent exons in the ORF. Grey boxes represent exons that contain mutations that result in changes to amino acids.

Schematic description of gemci tabine (*dFdC*) transportation and metabolism. this study.



Single Nucleotide Polymorphisms of Gemcitabine Metabolic Genes and Pancreatic Cancer Survival and Drug Toxicity

Table : Genotype and tumor response to preoperative treatment

Genotype	≤50%*	>50%	*OR (95% CI)†	*Pn* (%)*n* (%)
***dCK* C-1205T**				
TT	31 (73.8)	11 (26.2)	1.0	
CT/CC	37 (53.6)	32 (46.4)	2.73 (1.15-6.45)	0.022
***dCK* A9846G**				
GG	31 (75.6)	10 (24.4)	1.0	
AG/AA	37 (53.6)	32 (46.4)	2.96 (1.23-7.13)	0.015*h*
***CNT3* A25G**				
AA	42 (70.0)	18 (30.0)	1.0	
AG/GG	24 (49.0)	25 (51.0)	2.733 (1.21-6.17)	0.016*h*
***CNT3* C-69T**				
CC	55 (68.8)	25 (31.2)	1.0	
CT/TT	14 (43.8)	18 (56.3)	3.08 (1.30-7.31)	0.011
No. of at-risk genotypes				
0-2	52 (72.2)	20 (27.8)	1.0	
3-4	14 (38.9)	22 (61.1)	5.77 (2.23-14.9)	<0.001

SNPs in cancer risk evaluation

Analysis of MDR1C1236T Genotype Risk Factors of AML and Control

Genotype	AML Cases	Controls	Odd Ratios	ORs (95%CI)
CC	6(19.35)	4(40)	CC vs CT	0.26 (0.002-28.26)
CT	17(54.83)	3(30)	CT vs TT	2.15 (0.15-29.93)
TT	8(25.8)	3(30)	CC vs TT	0.56 (0.074-4.245)

++ CC & TT are protective genotypes against AML

--- CT genotype with high risk to have AML

Relationship between MDR1 Gene Expression and MDR1 C1236T Genotype with AML Clinical Outcomes

Genotype	MDR1 Fold Change of NR AML	MDR1 Fold Change of CR AML
	n=17	n=14
CC n=6	0.45 ± 0.02 (3)	0.37 ± 0.02 (3)
CT n=17	3.32 ± 0.11 (10)	0.30 ± 0.02 (7)
TT n=8	3.01 ± 0.08 (4)	0.41 ± 0.01 (4)
p-value	0.013 ** 0.317	NS

Increasing of MDR1 Gene expression cause NR to drug

Thank you