HBM4EU

science and policy
for a healthy future

HBM4EU project

THE GENE-ENVIRONMENT INTERACTIONS AND ASBESTOSIS

Assoc Prof Alenka Franko, MD, PhD

1st HBM4EU Training School 2018

Diseases

environmental factors

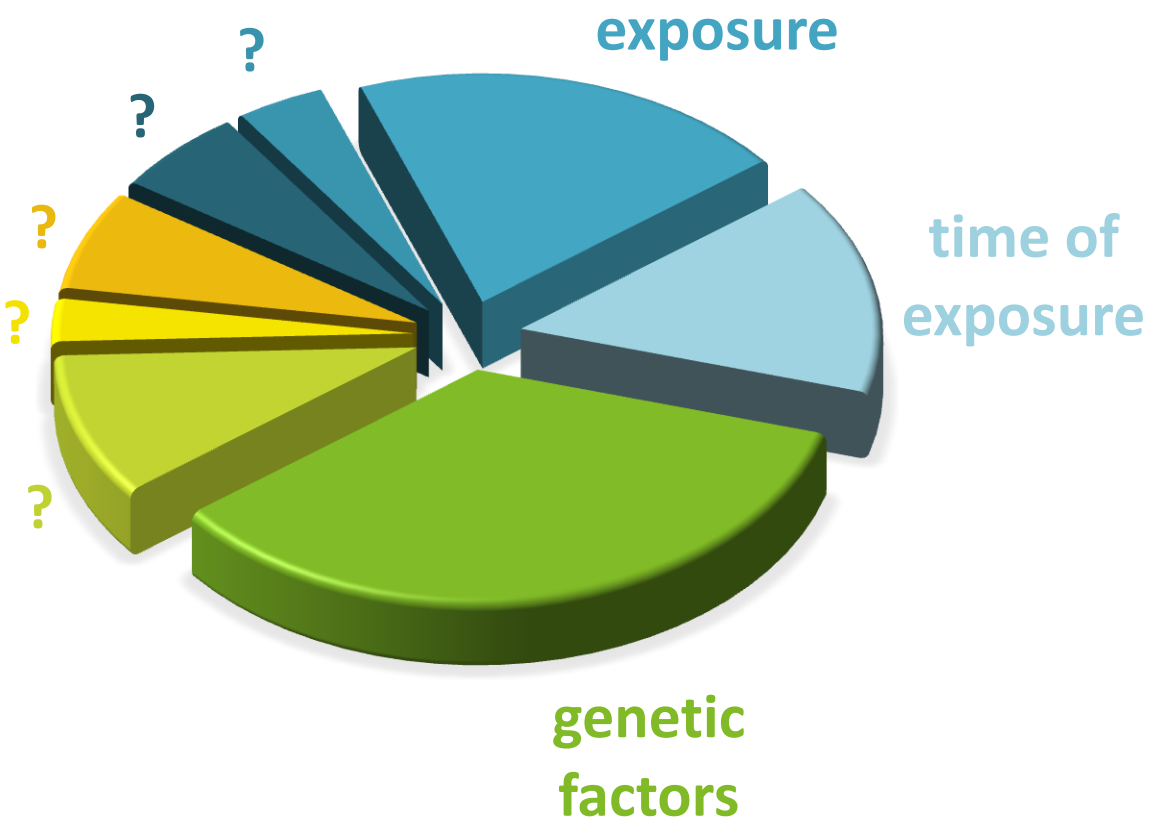
genetic factors

Gene environment interactions

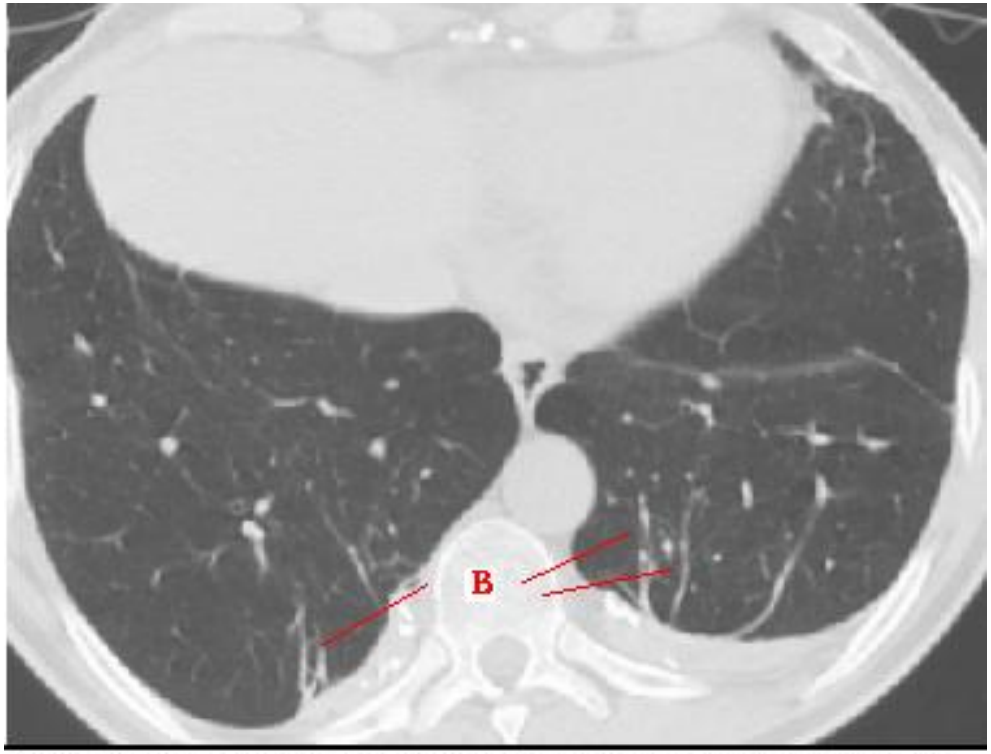
Primary candidates

- genes coding for enzymes that are involved in the metabolism of foreign chemical substances

Model of causation



Asbestosis

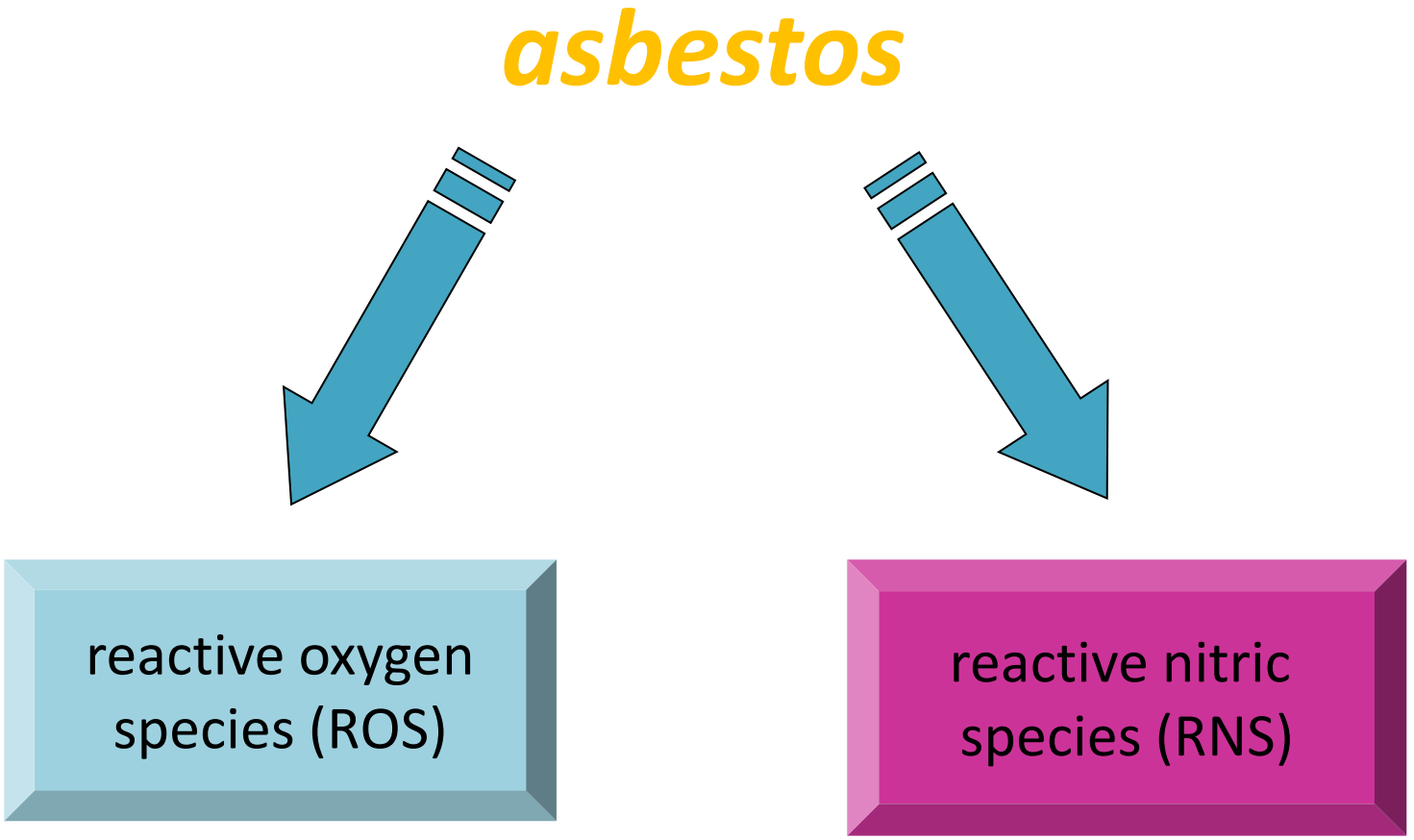


HRCT scan (obtained prone) shows multiple parenchymal bands (A) that are consistent with fibrosis.

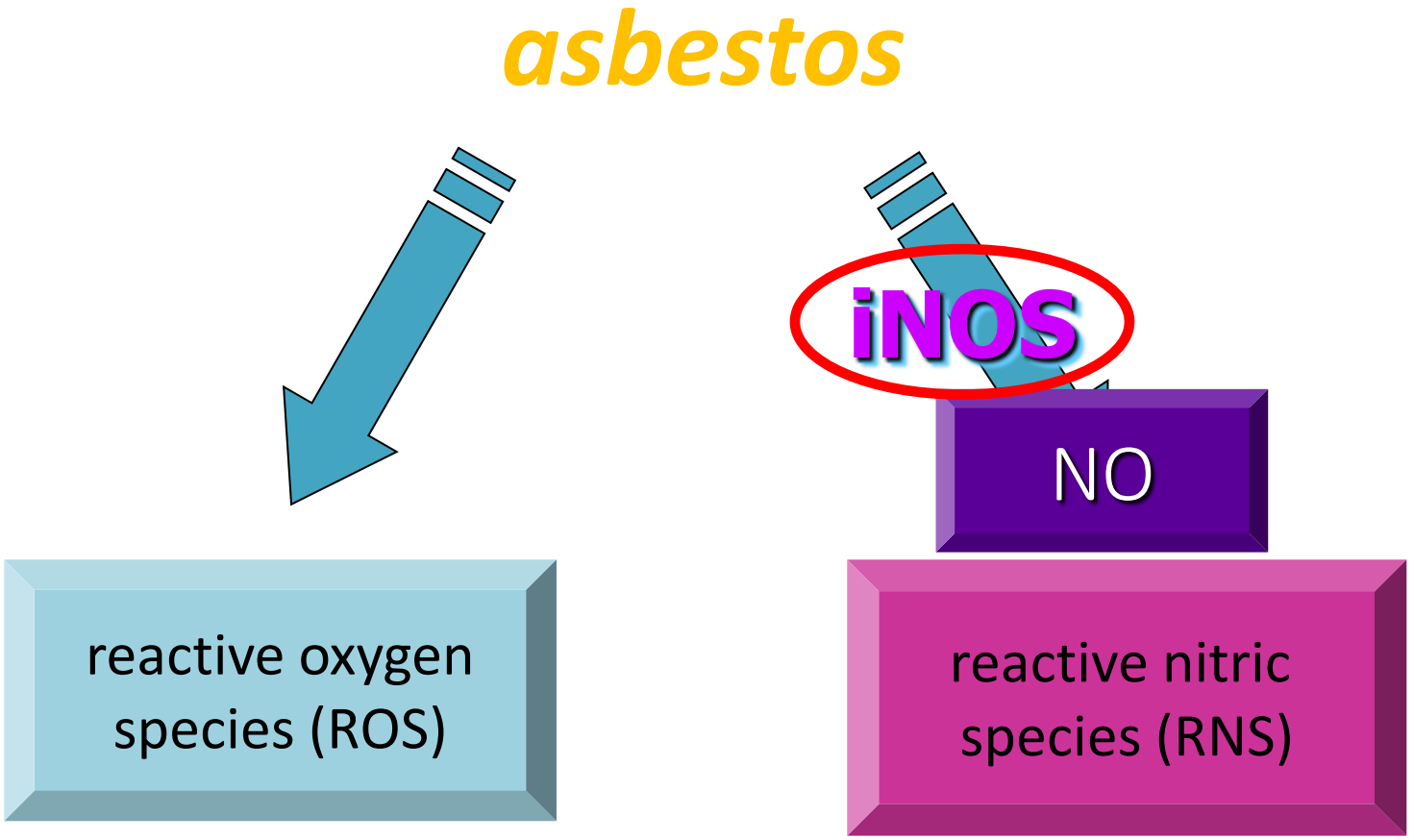
asbestos exposure

? genetic factors ?

Pathogenesis



Pathogenesis



Defense system

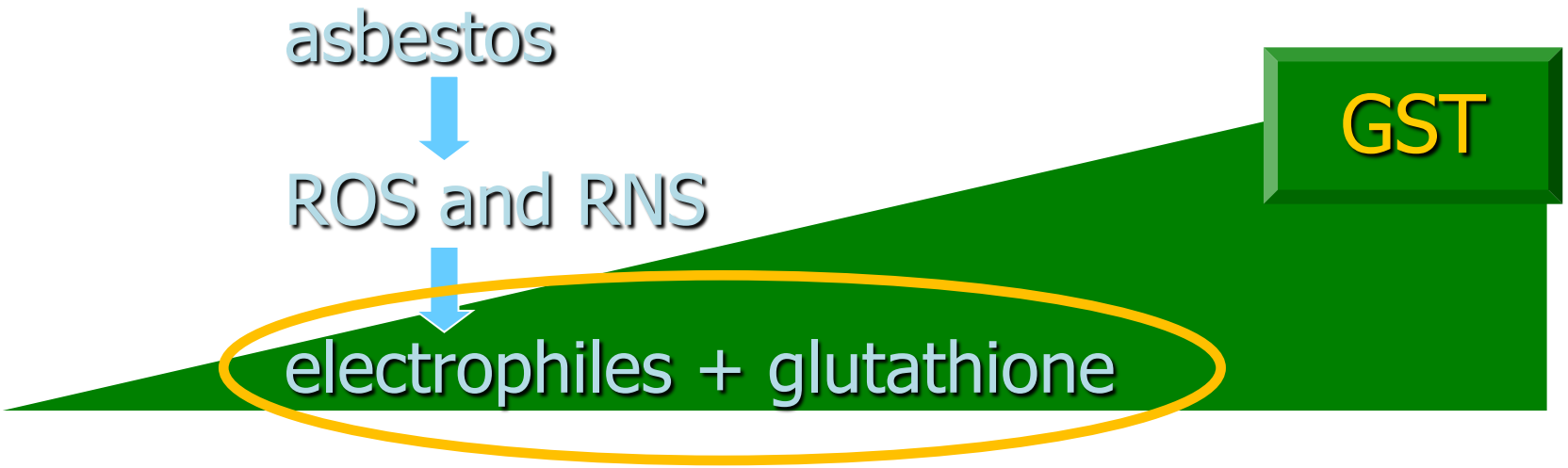
Superoxide dismutases	Catalase
MnSOD, ECSOD	CAT

$$O_2^{\bullet -} + O_2^{\bullet -} + 2H^+ \xrightarrow{SOD} H_2O_2 + O_2$$

$$2H_2O_2 \xrightarrow{CAT} 2H_2O + O_2$$

GLUTATHIONE S-TRANSFERASES: GSTM1,GSTT1, GSTP1

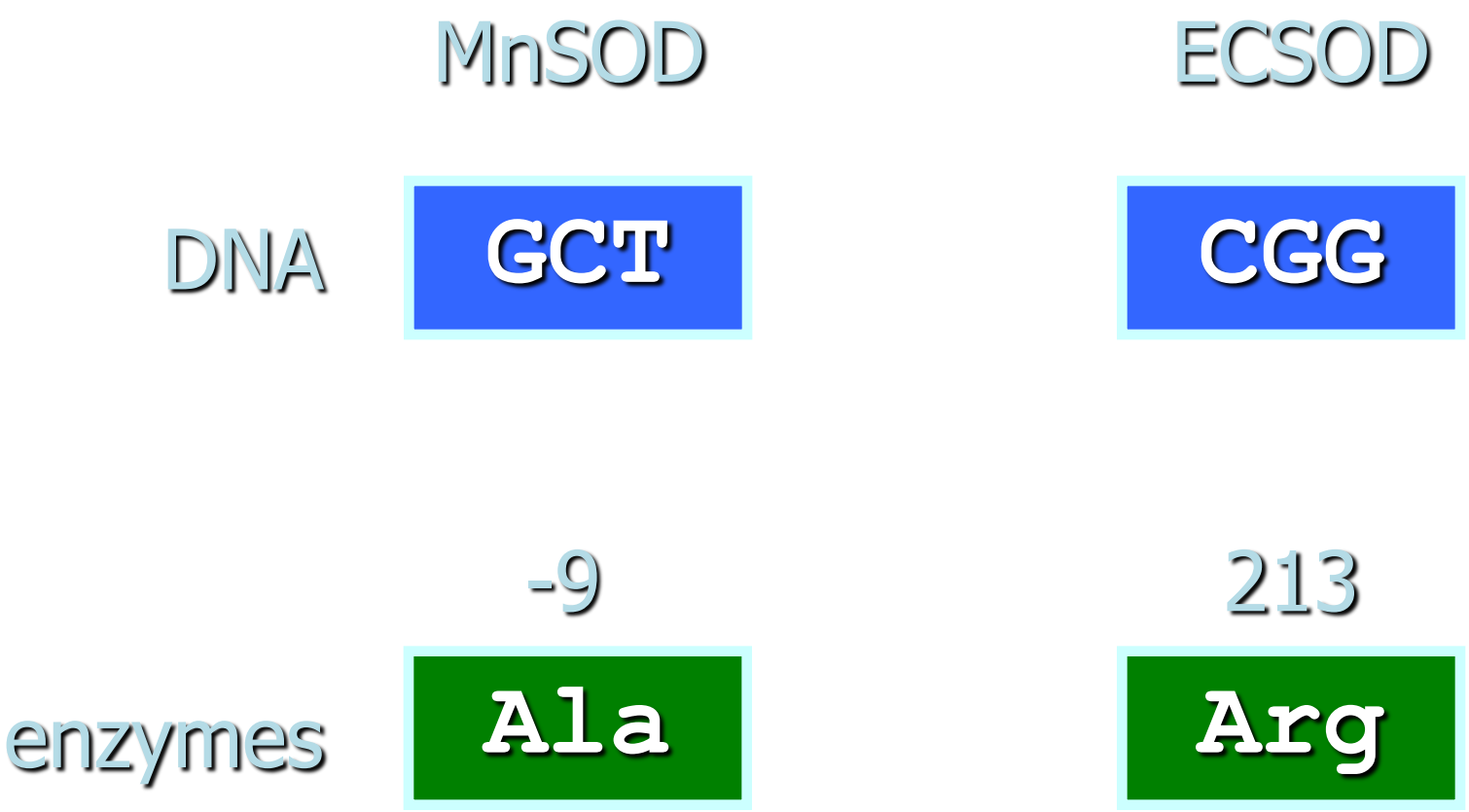
Inactivate the electrophiles produced by ROS and RNS



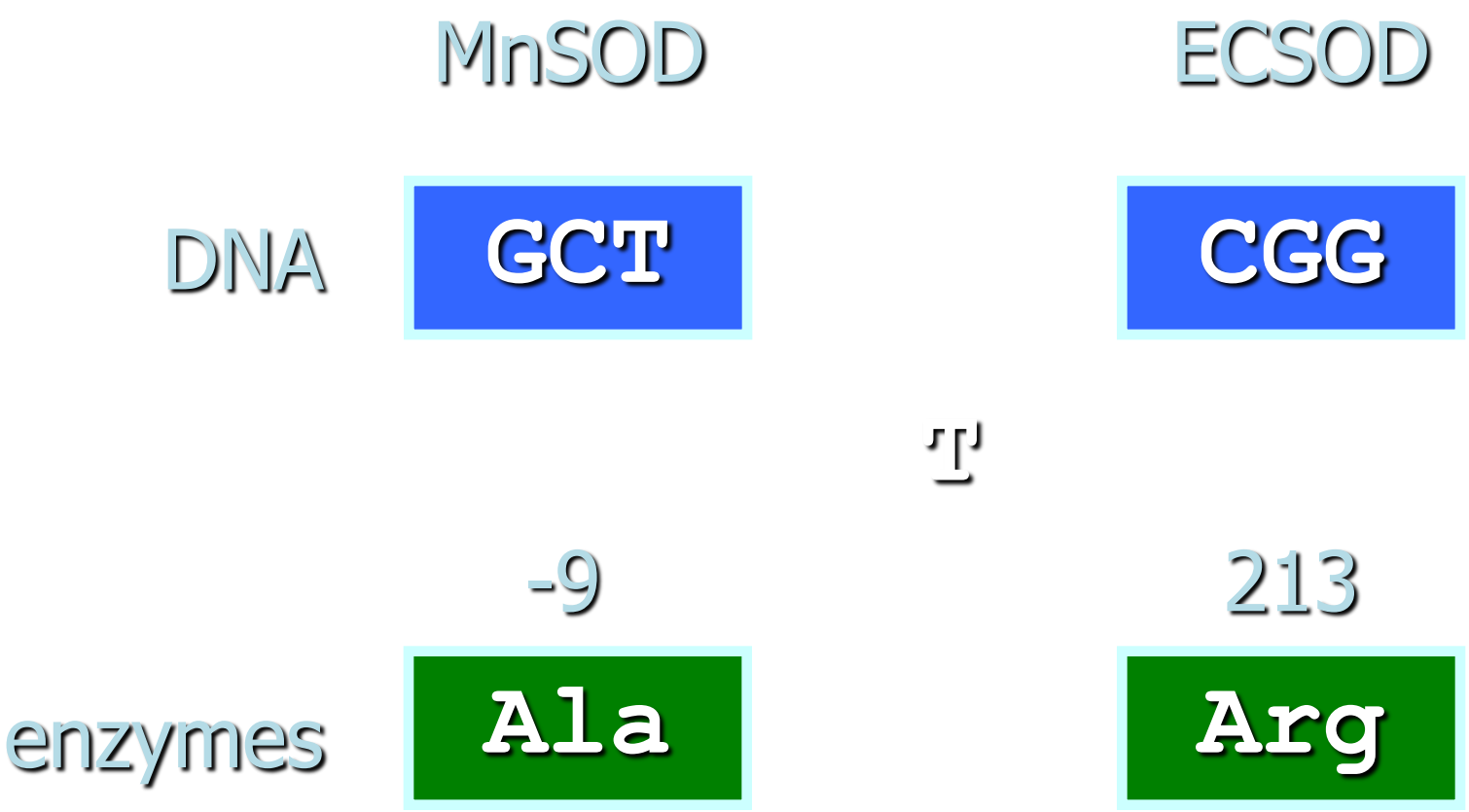
Genetic polymorphisms

The genes coding for MnSOD, ECSOD, CAT, GSTM1, GST T1, GSTP1 and iNOS are polymorphic

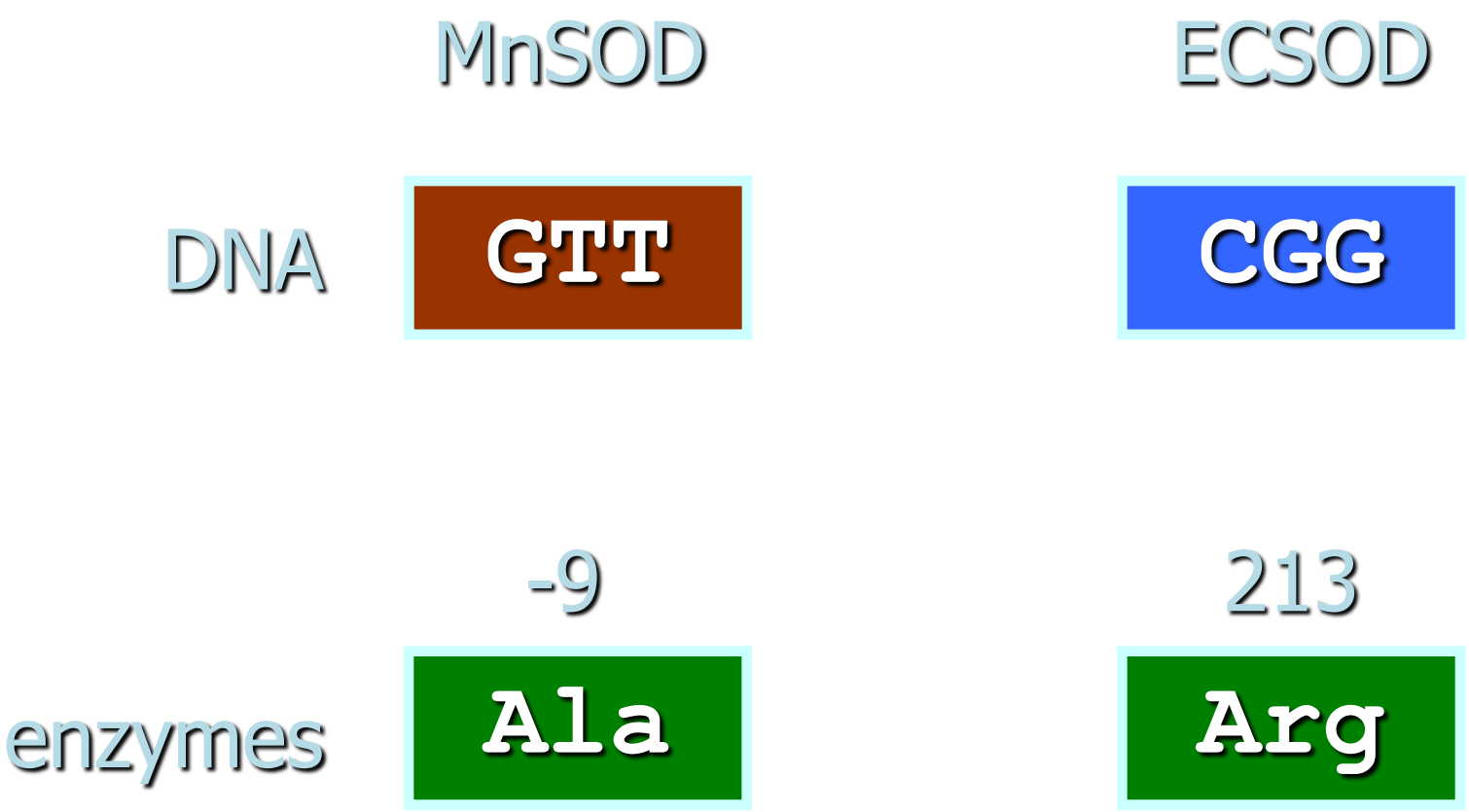
MnSOD and ECSOD polymorphisms



MnSOD and ECSOD polymorphisms



MnSOD and ECSOD polymorphisms



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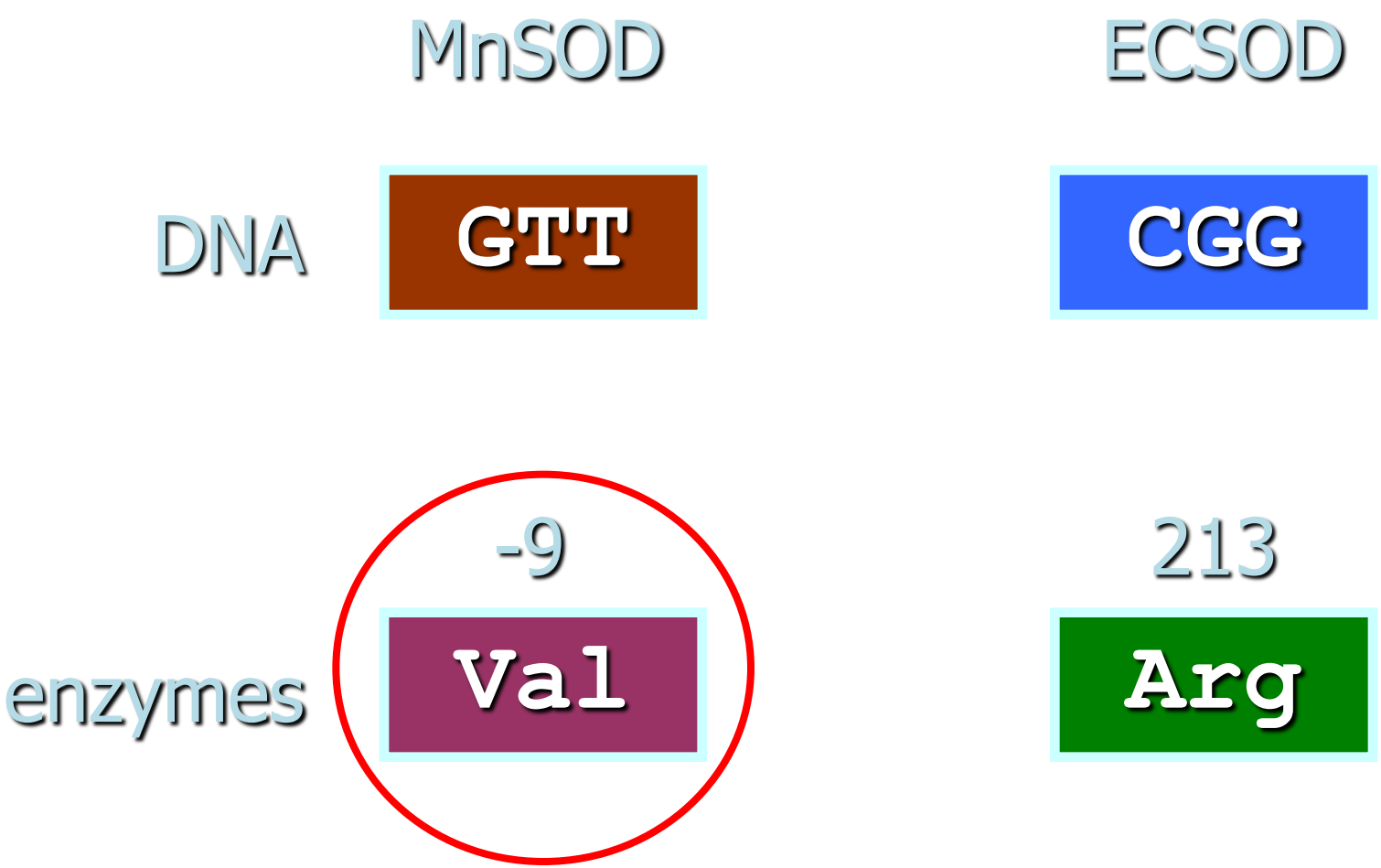
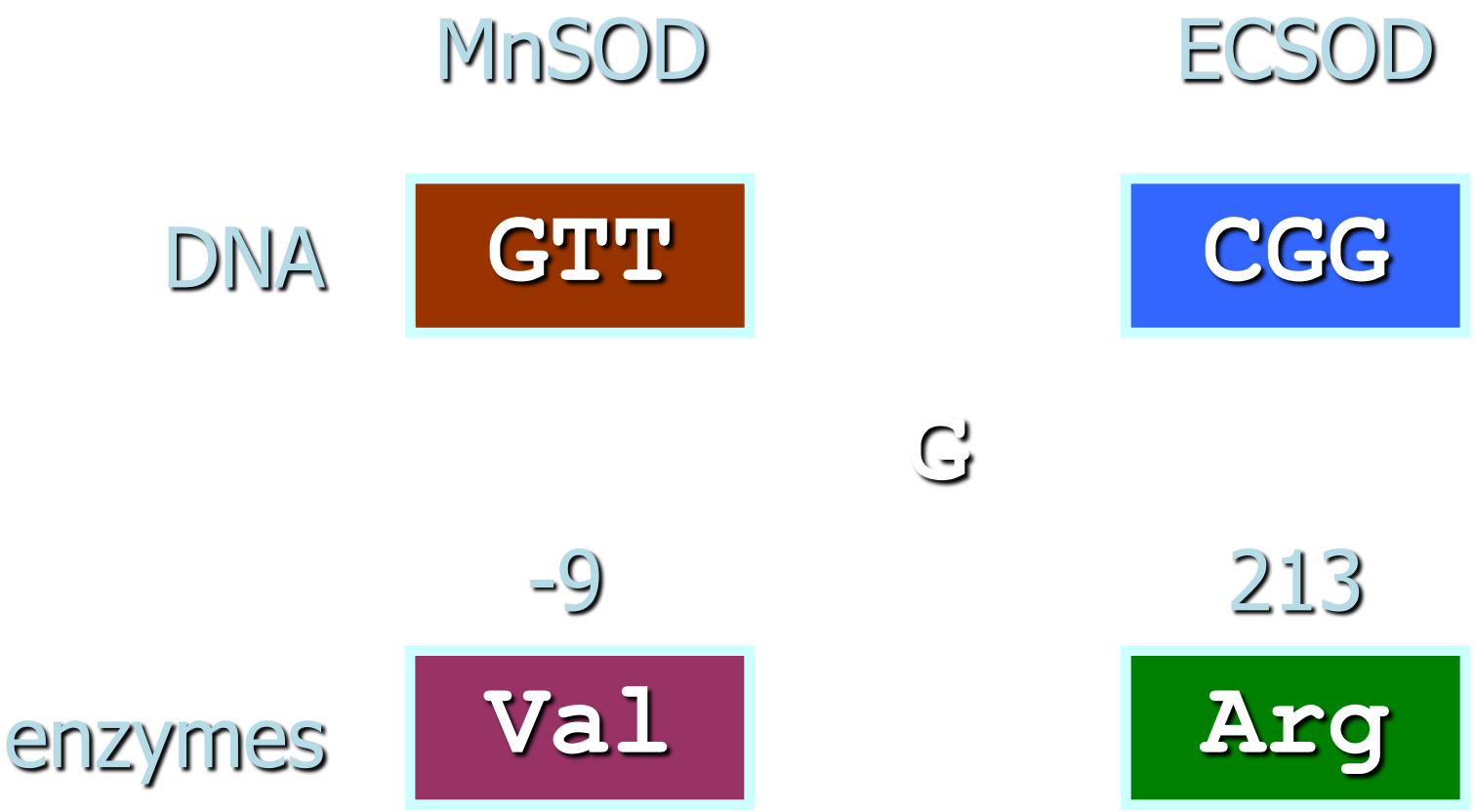
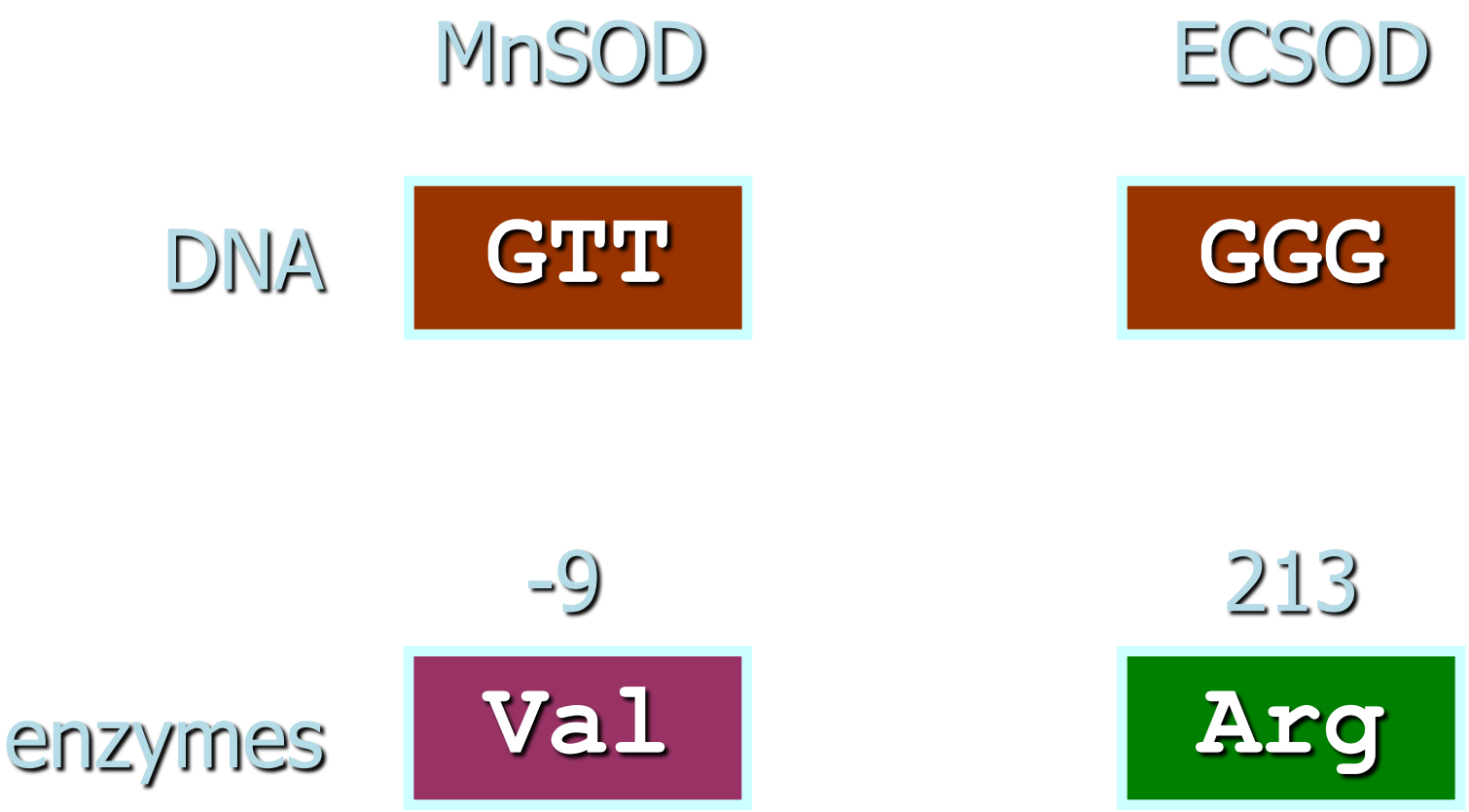


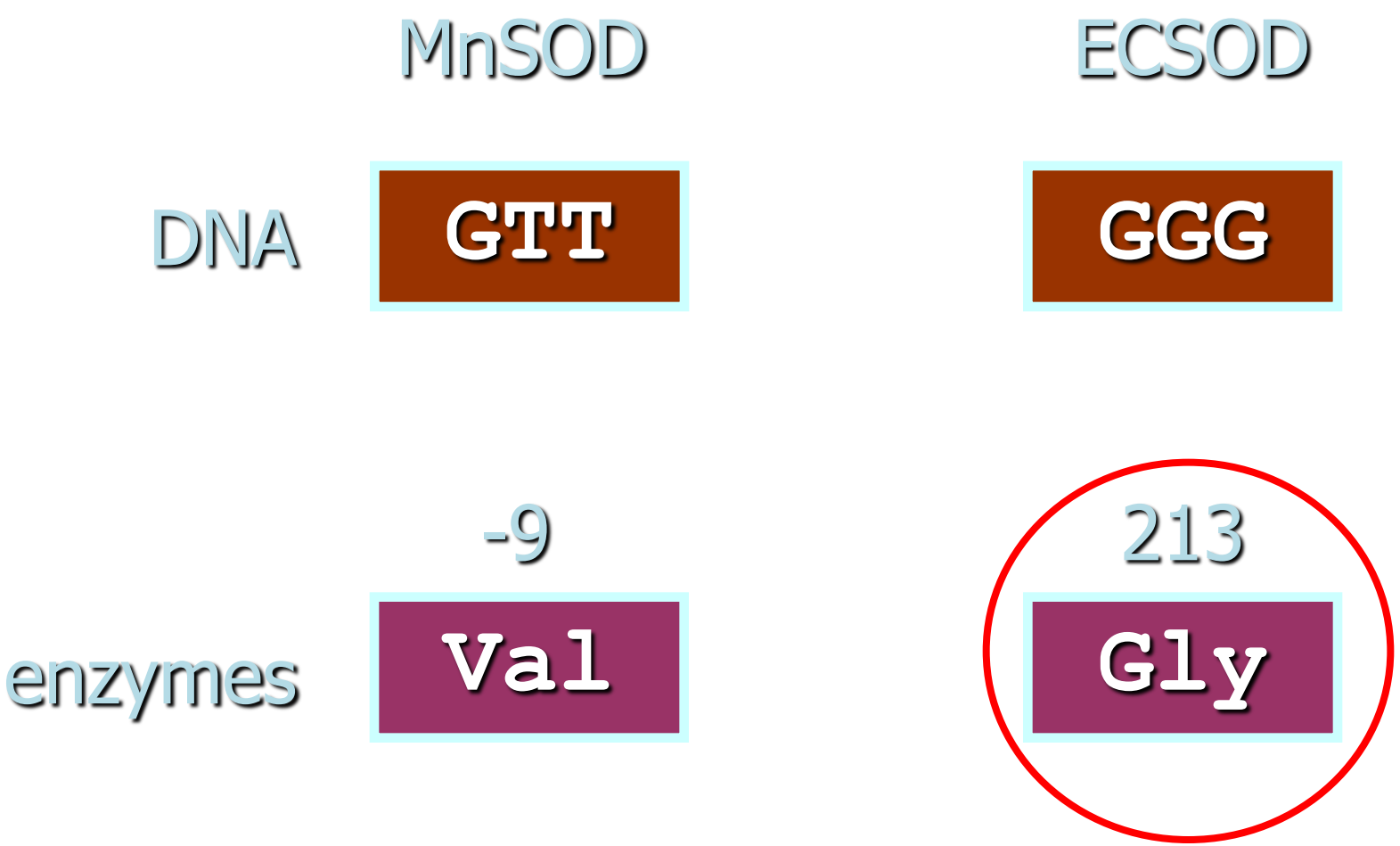
MnSOD and ECSOD polymorphisms



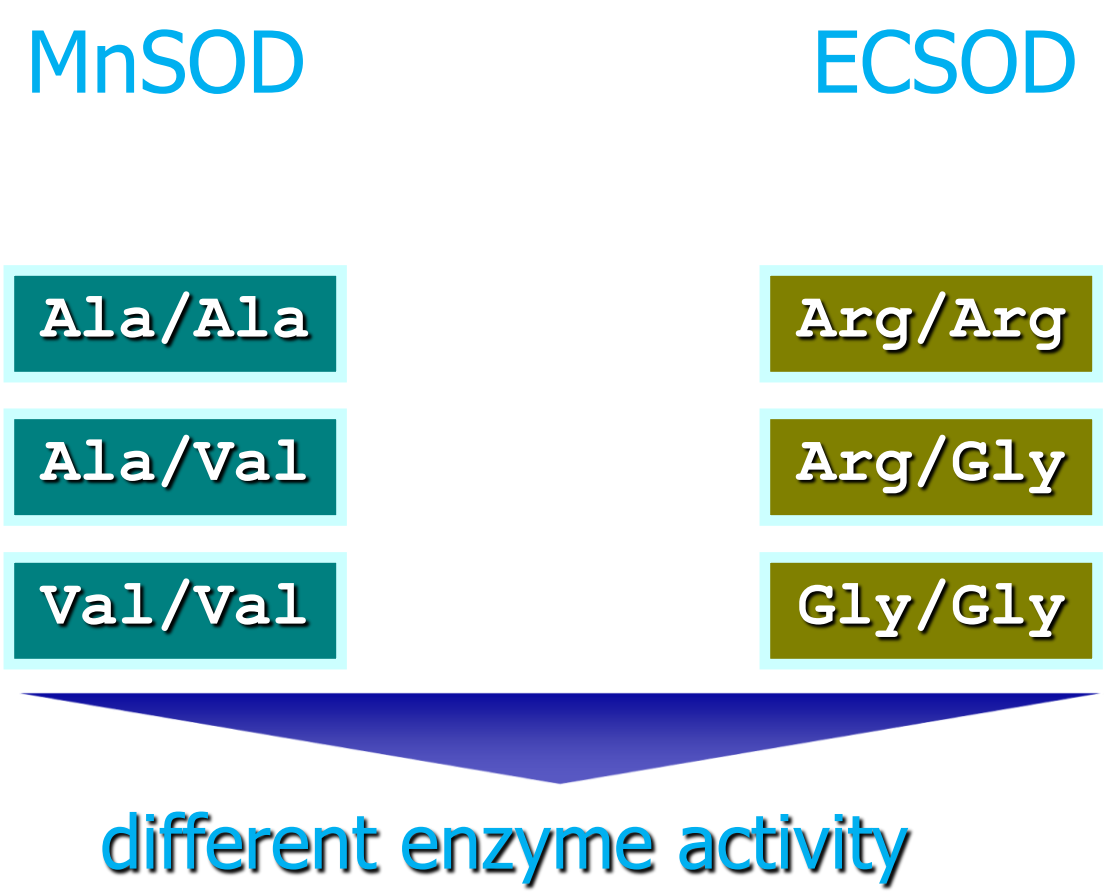
MnSOD and ECSOD polymorphisms



MnSOD and ECSOD polymorphisms



MnSOD and ECSOD polymorphisms

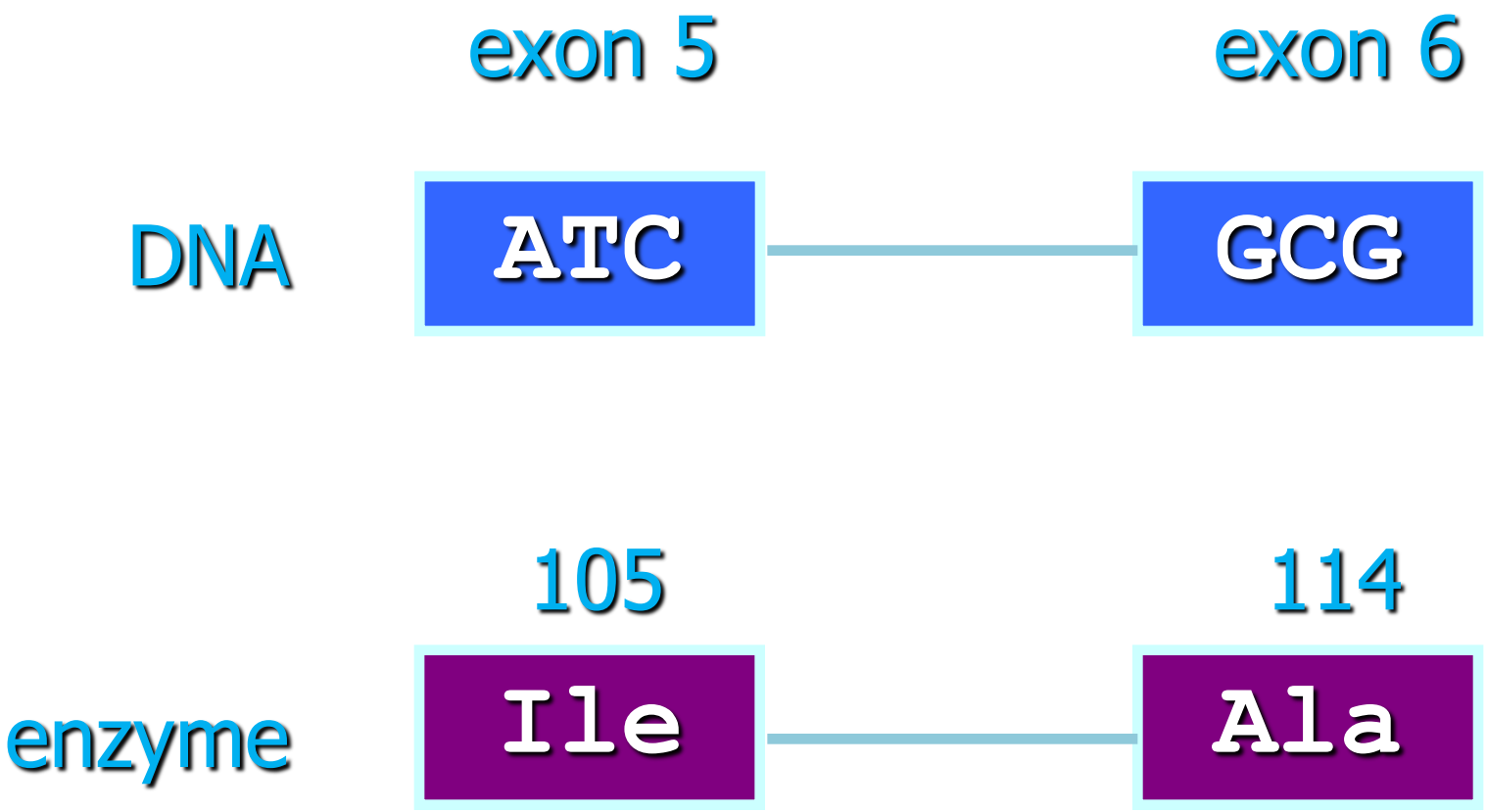


CAT polymorphism

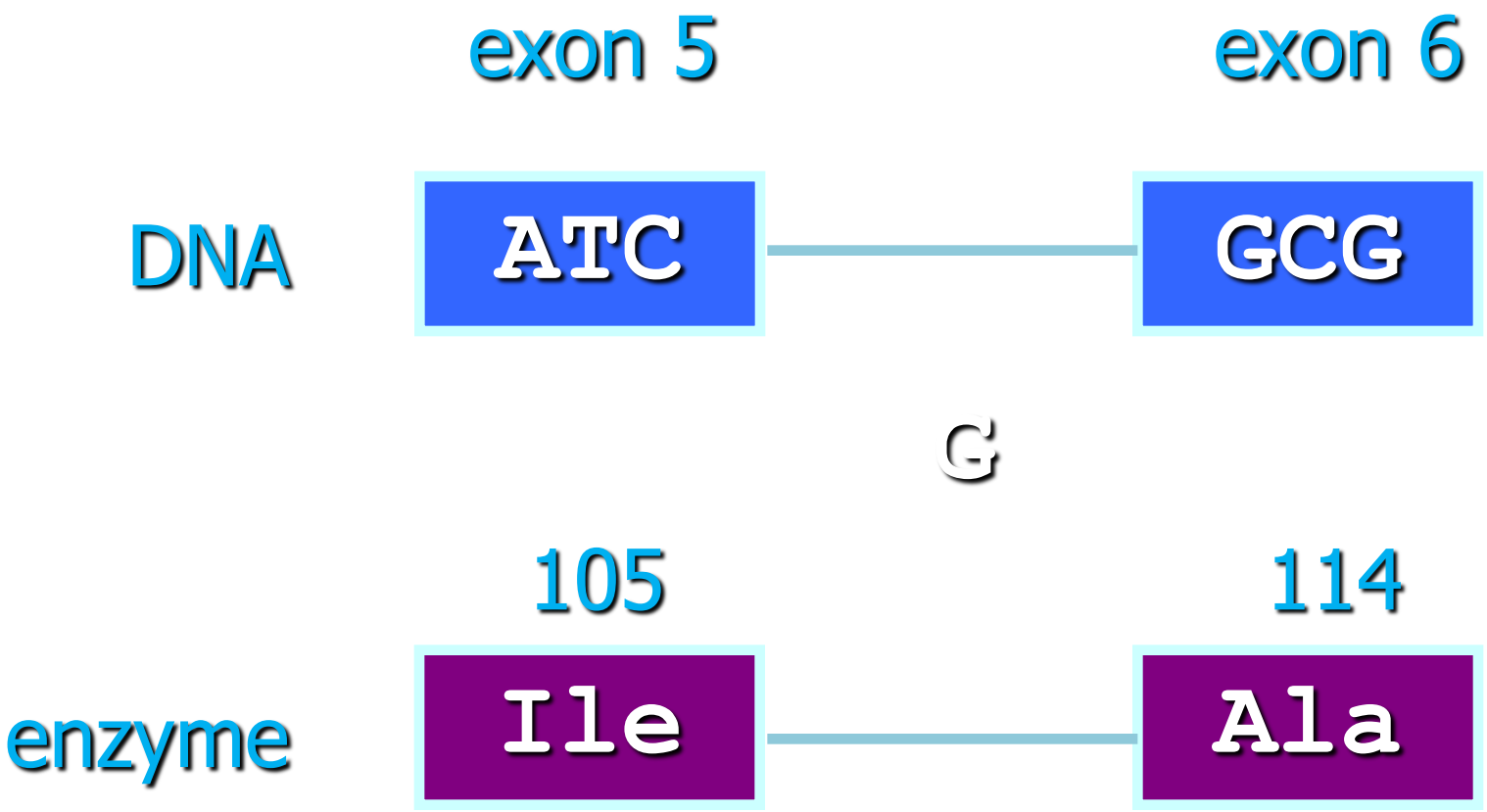
Position -262 in the promoter region:

cytosine (C) to thymine (T) substitution

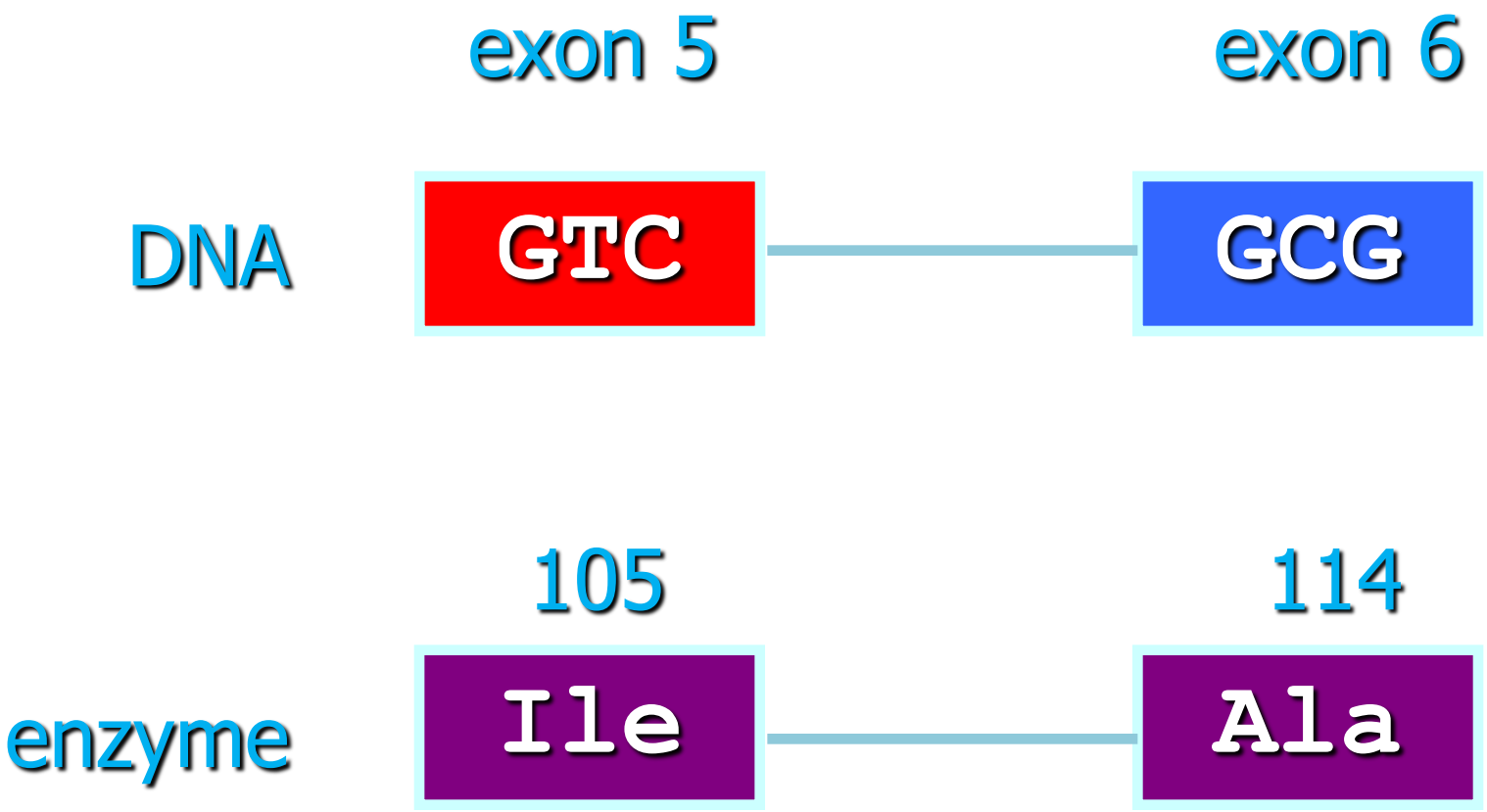
GSTP1 polymorphisms



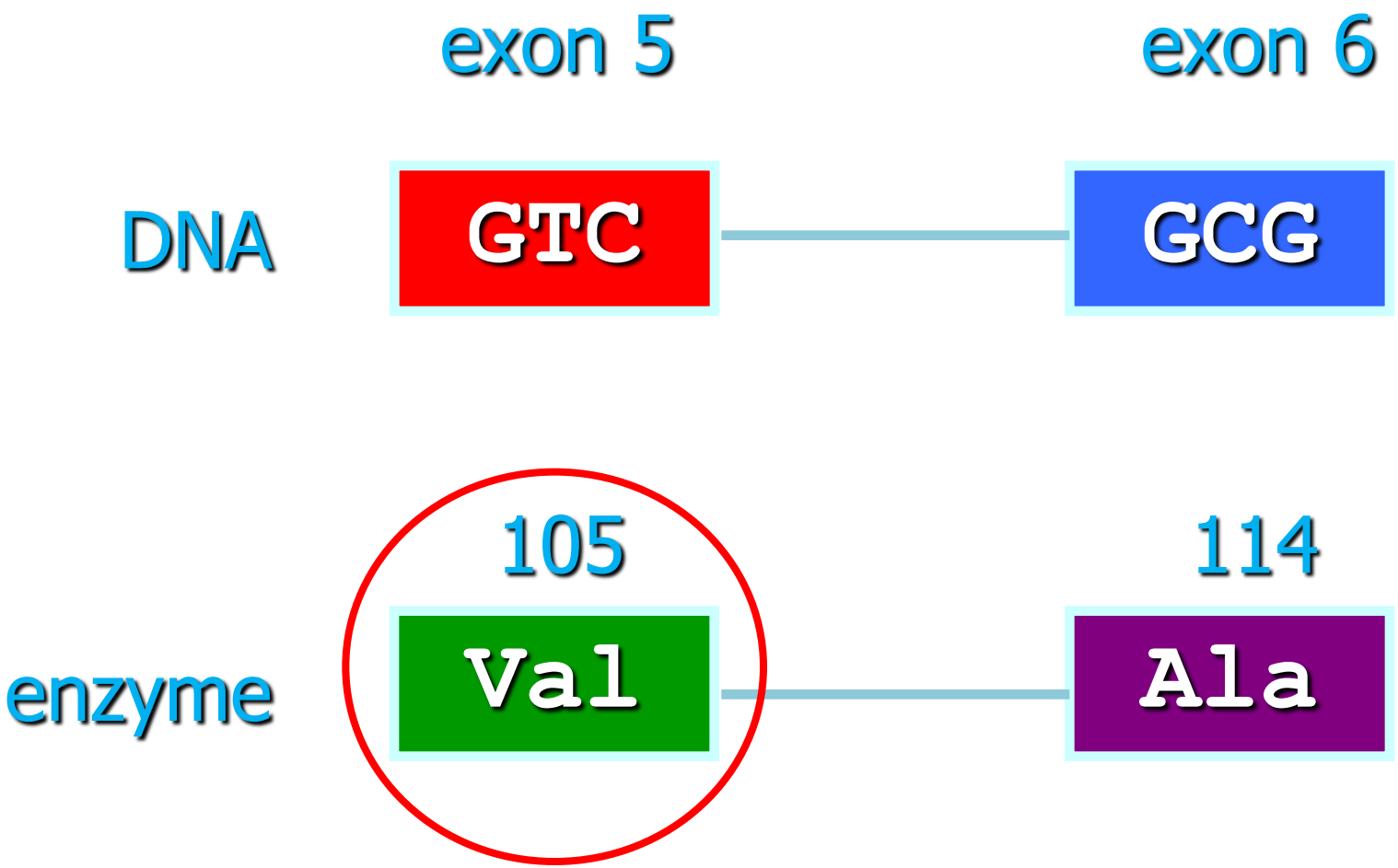
GSTP1 polymorphisms



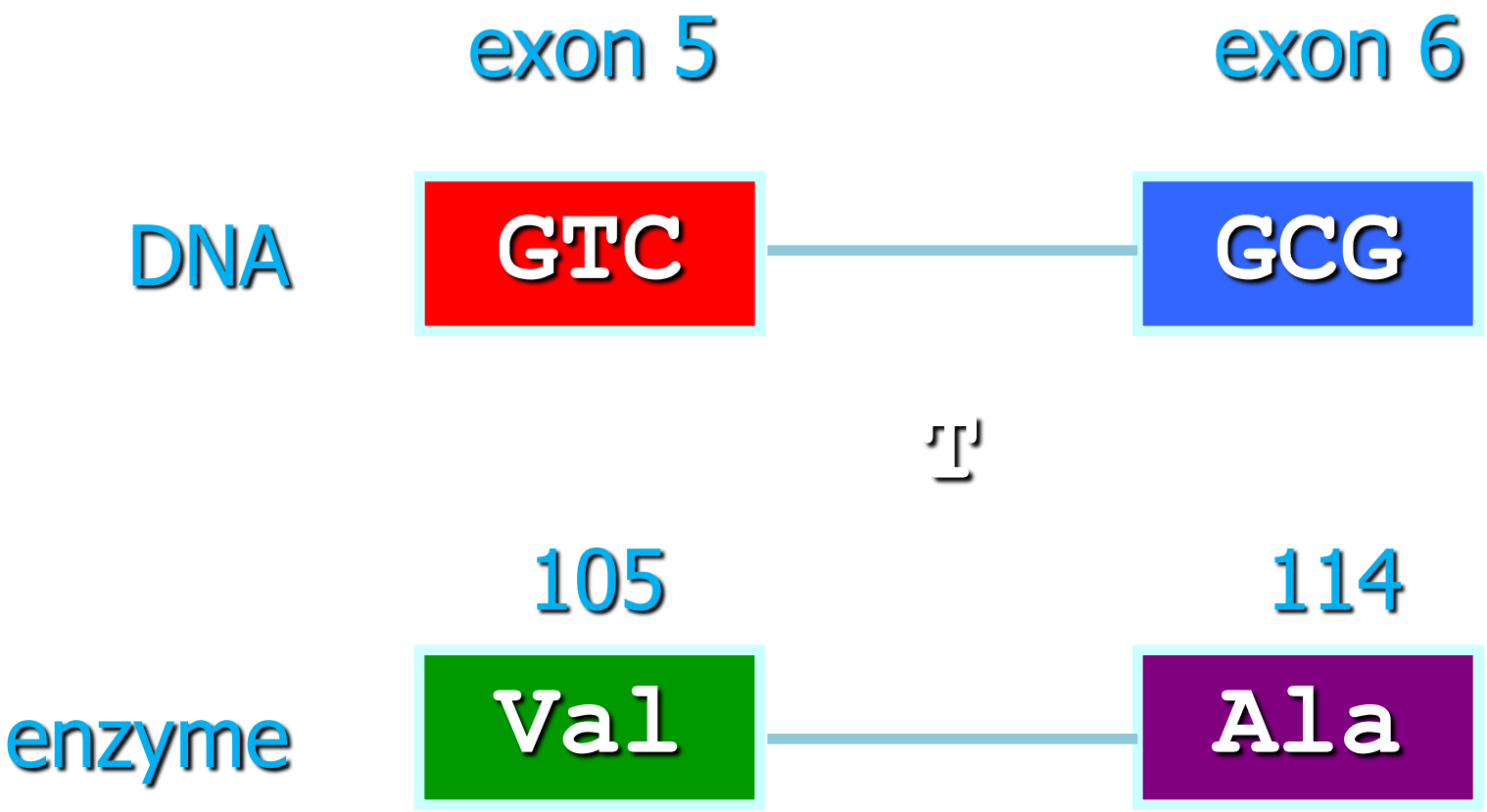
GSTP1 polymorphisms



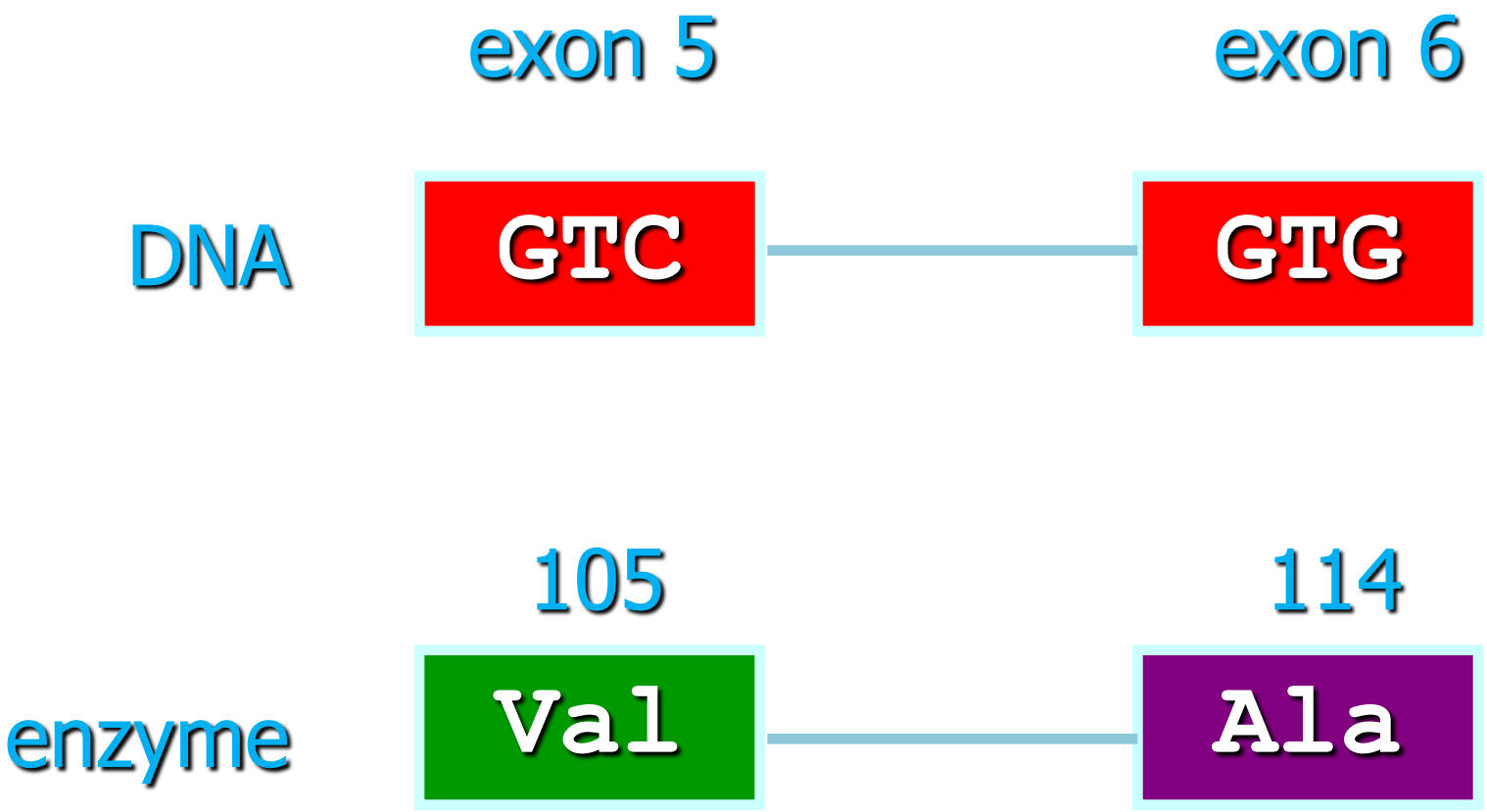
GSTP1 polymorphisms



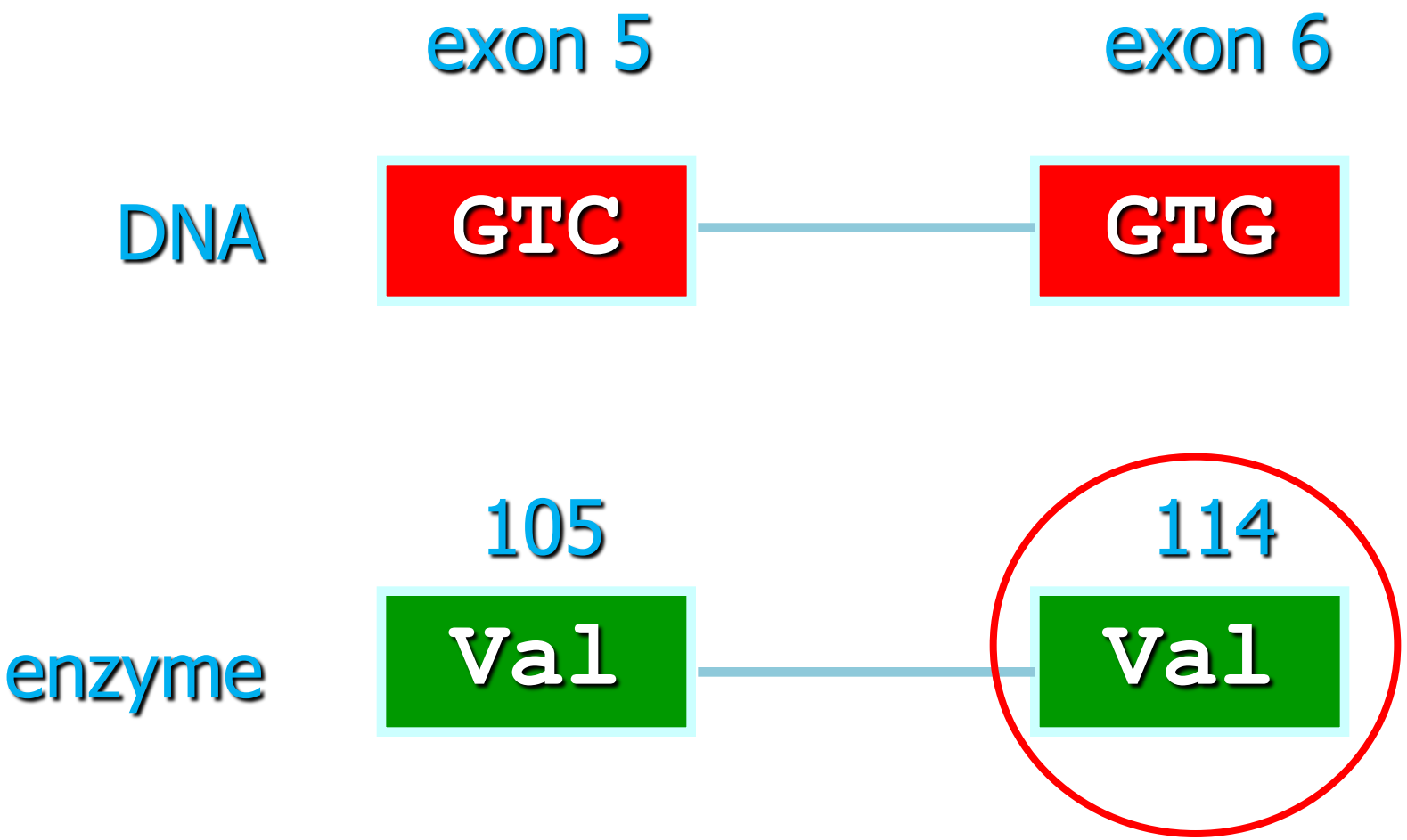
GSTP1 polymorphisms



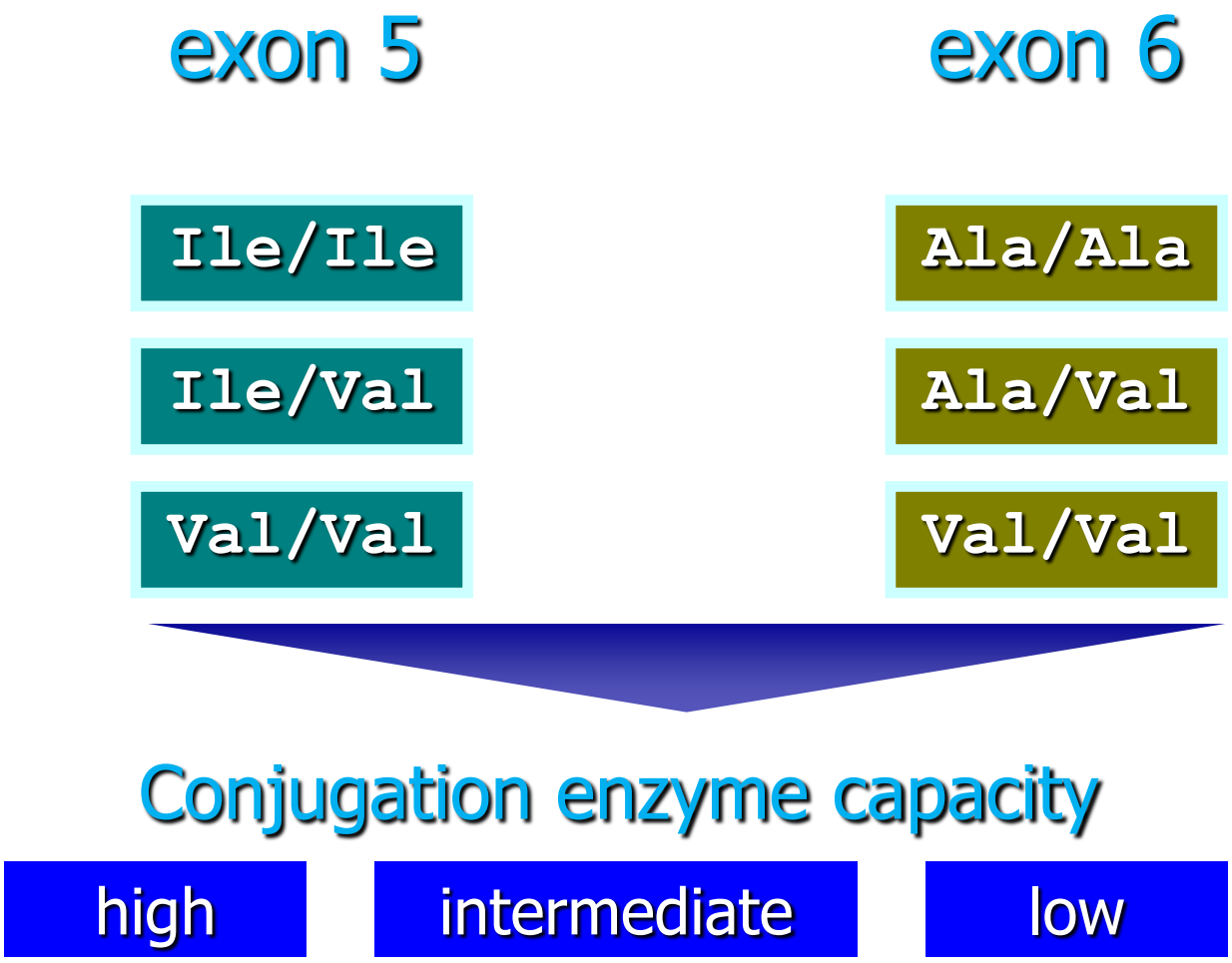
GSTP1 polymorphisms



GSTP1 polymorphisms



GSTP1 polymorphisms



GSTM1 and GSTT1 polymorphism

NULL (I.E. DELETION) POLYMORPHISM

iNOS polymorphism

PROMOTOR REGION:

CCTTT pentanucleotide repeat

≤ 11 repeats: short alleles (S)

≥ 12 repeats: long alleles (L)

- Genotypes: SS, SL, LL

The aim of the study

- to investigate influence of gene-gene and gene-environment interactions on the risk of developing asbestosis

Cohort of 2,080 workers

356 cases with asbestosis

186 male

76 female

40 died, 2 cancer, 52 refused to participate → **262**

356 controls

183 male

82 female

29 died, 9 cancer, 63 refused to participate → **265**

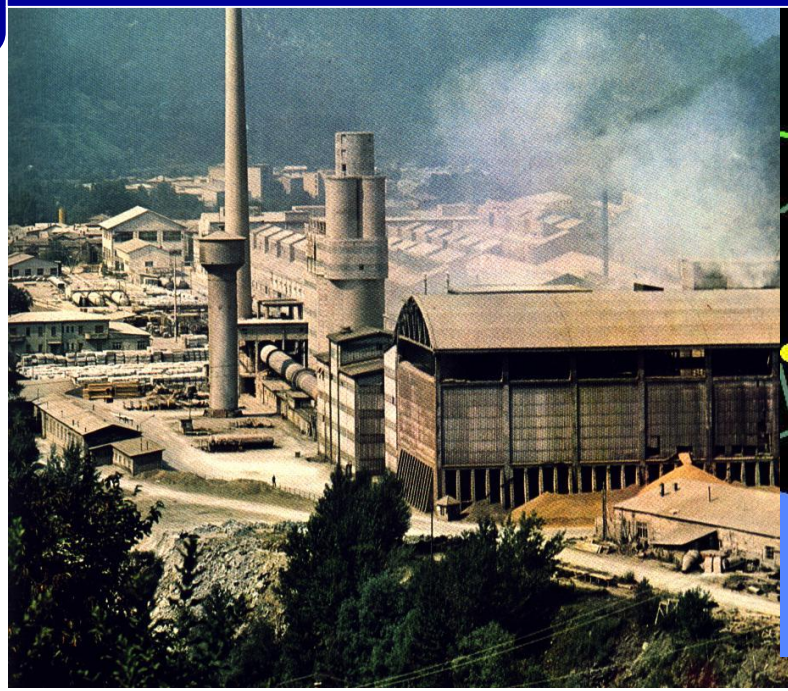
Data on smoking

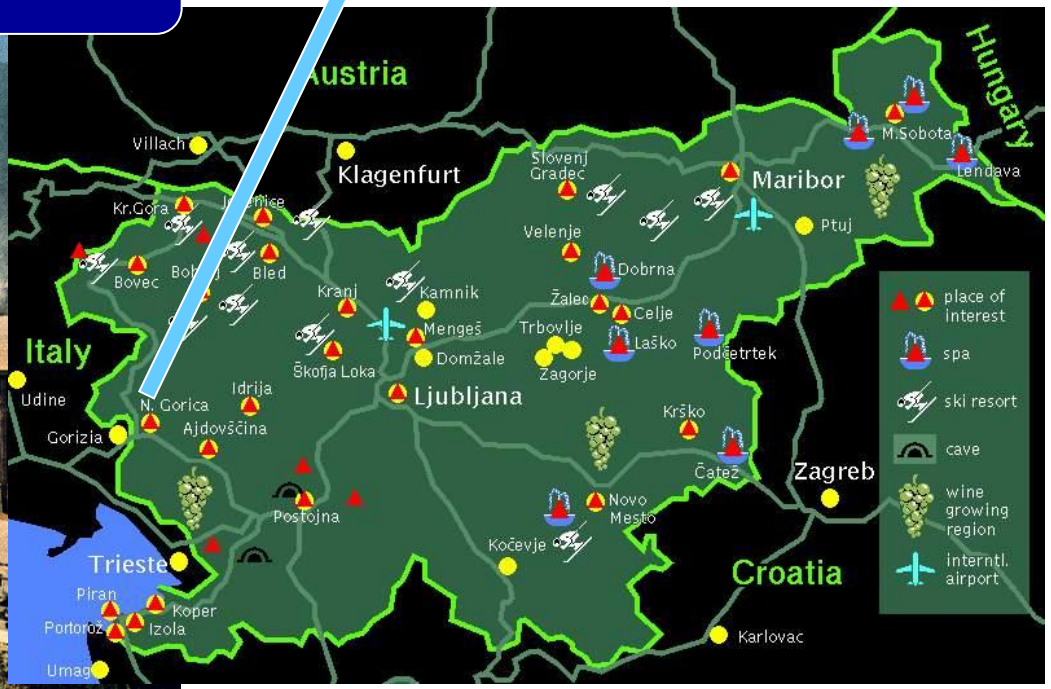
interview

standardized questionnaire

Salonit Anhovo

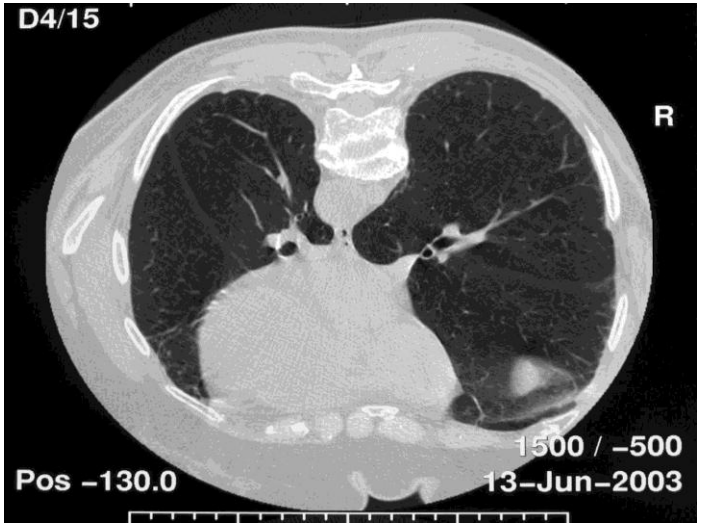
Cumulative exposure

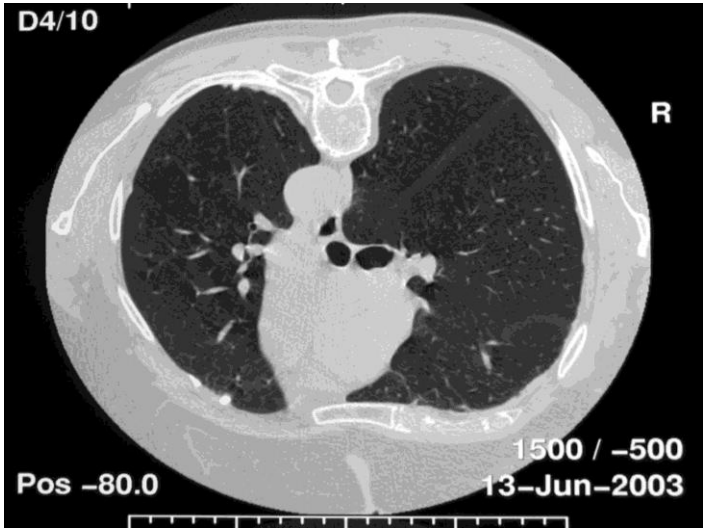




Diagnosis

- State Board for Recognition of Occupational Asbestos Diseases
- The Helsinki Criteria
- American Thoracic Society recommendations





Analyses of polymorphisms

Real-time PCR:

- *MnSOD* Ala-9Val
- *ECSOD* Arg213Gly
- *CAT* -262C>T
- *GSTP1* Ile105Val and Ala114Val

Multiplex PCR:

- *GSTT1*-null
- *GSTM1*-null

Short tandem repeat

- (CCTTT)n in the *iNOS* gene

Statistical methods

logistic regression analysis

Results

ASBESTOSIS

	OR	95%CI
Cumulative exposure	3.21	2.4 - 4.23
Smoking	0.98	0.69 - 1.39

Results

ASBESTOSIS

GENOTYPE	*MnSOD Ala/Ala*		*ECSOD Arg/Gly*		*CAT−262 TT*	
	OR	**95 % CI**	**OR**	**95 % CI**	**OR**	**95 % CI**
Unadjusted	**1.50**	**1.01–2.24**	1.63	0.62–4.27	1.36	0.70–2.62
Adjusted by						
Gender	1.49	1.00–2.23	1.61	0.61–4.22	1.34	0.70–2.60
Age	1.46	0.97–2.19	1.49	0.56–3.96	1.31	0.67–2.57
Smoking (ever/never)	1.49	1.00–2.23	1.65	0.63–4.32	1.37	0.71–2.66
Cumulative exposure	1.48	0.96–2.28	2.07	0.72–5.94	1.91	0.93–3.91

Results

ASBESTOSIS

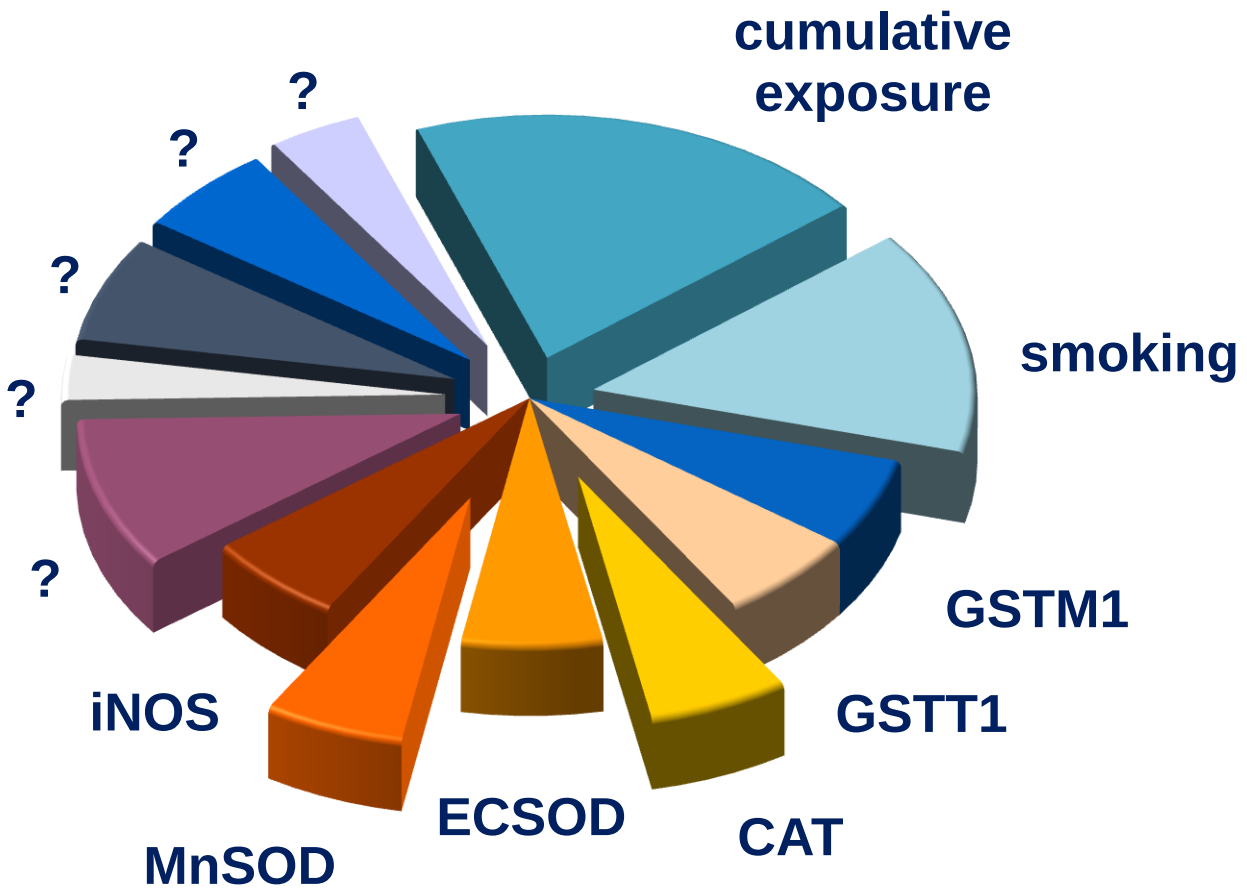
GENOTYPE	*GSTM1-null*		*GSTT1-null*		*GSTP1 105Ile/Ile*		*GSTP1 114Ala/Ala*	
	OR	95 % CI	OR	95 % CI	OR	95 % CI	OR	95 % CI
Unadjusted	1.01	0.71–1.43	**0.61**	**0.40–0.94**	**1.52**	**1.08–2.15**	0.97	0.64–1.48
Adjusted by								
Gender	1.00	0.70–1.42	0.62	0.40–0.94	1.53	0.60–1.28	0.97	0.64–1.48
Age	0.94	0.66–1.35	0.63	0.40–0.97	1.49	1.04–2.11	0.99	0.65–1.53
Smoking (ever/never)	0.99	0.70–1.41	0.63	0.41–0.97	1.54	1.08–2.18	0.94	0.62–1.44
Cumulative exposure	0.99	0.70–1.41	0.63	0.41–0.97	1.41	0.97–2.05	0.86	0.55–1.36

Results

ASBESTOSIS

GENOTYPE	*iNOS* LL	
	RO	95 % IZ
Unadjusted	1.20	0.85-1.69
Adjusted by		
Gender	1.20	0.85–1.70
Age	1.19	0.84–1.69
Smoking (yes/no)	1.17	0.83–1.66
Cumulative exposure	1.19	0.82–1.73

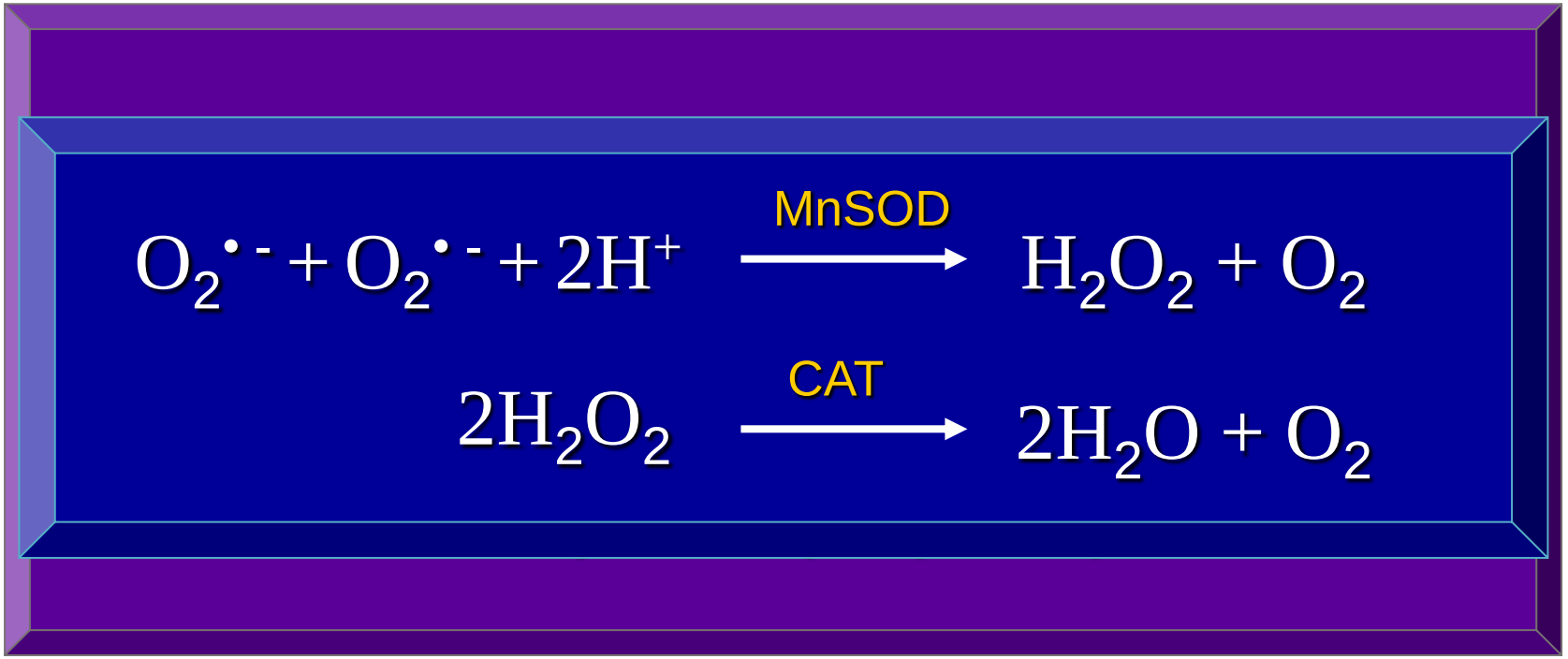
Model of causation



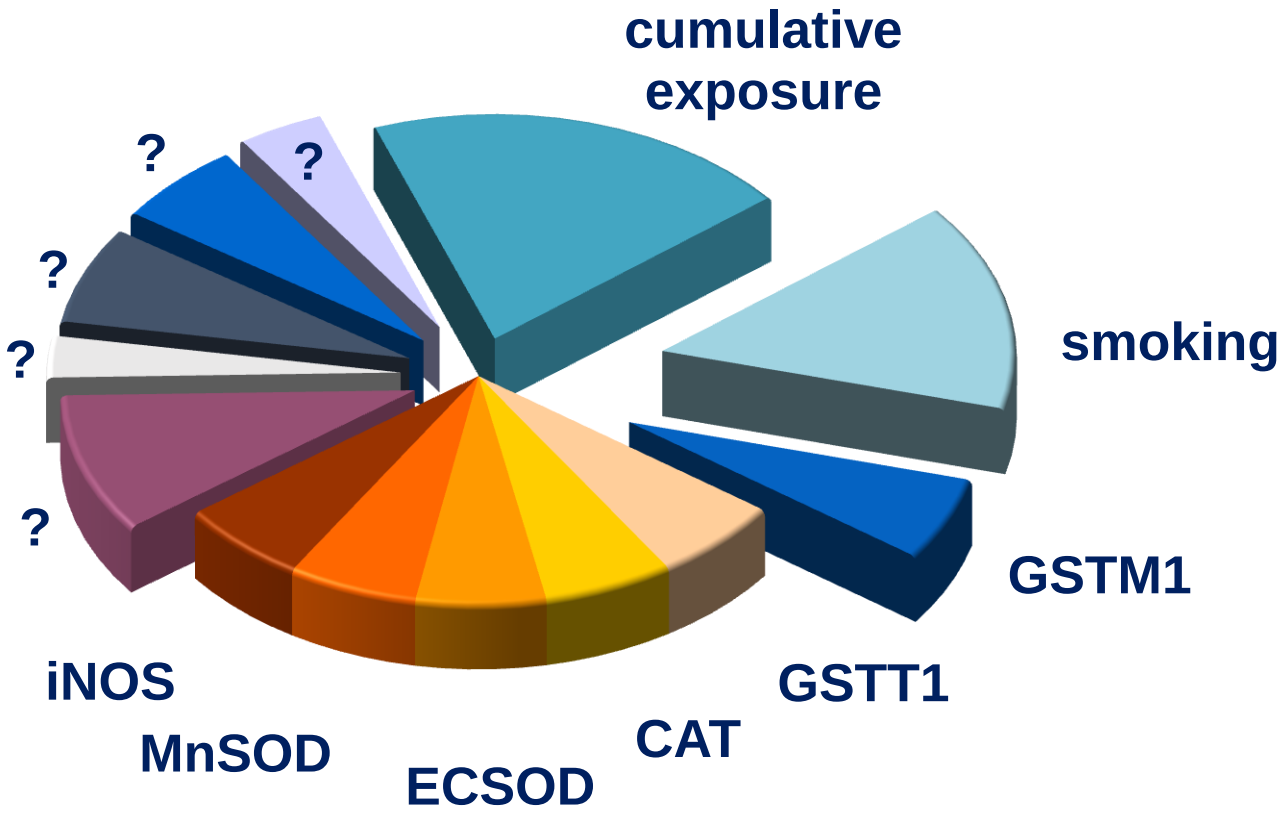
MnSOD and CAT

Interaction:
OR = 4.49 (95% CI = 1.08–18.61);
p = 0.038

MnSOD and CAT



Model of causation



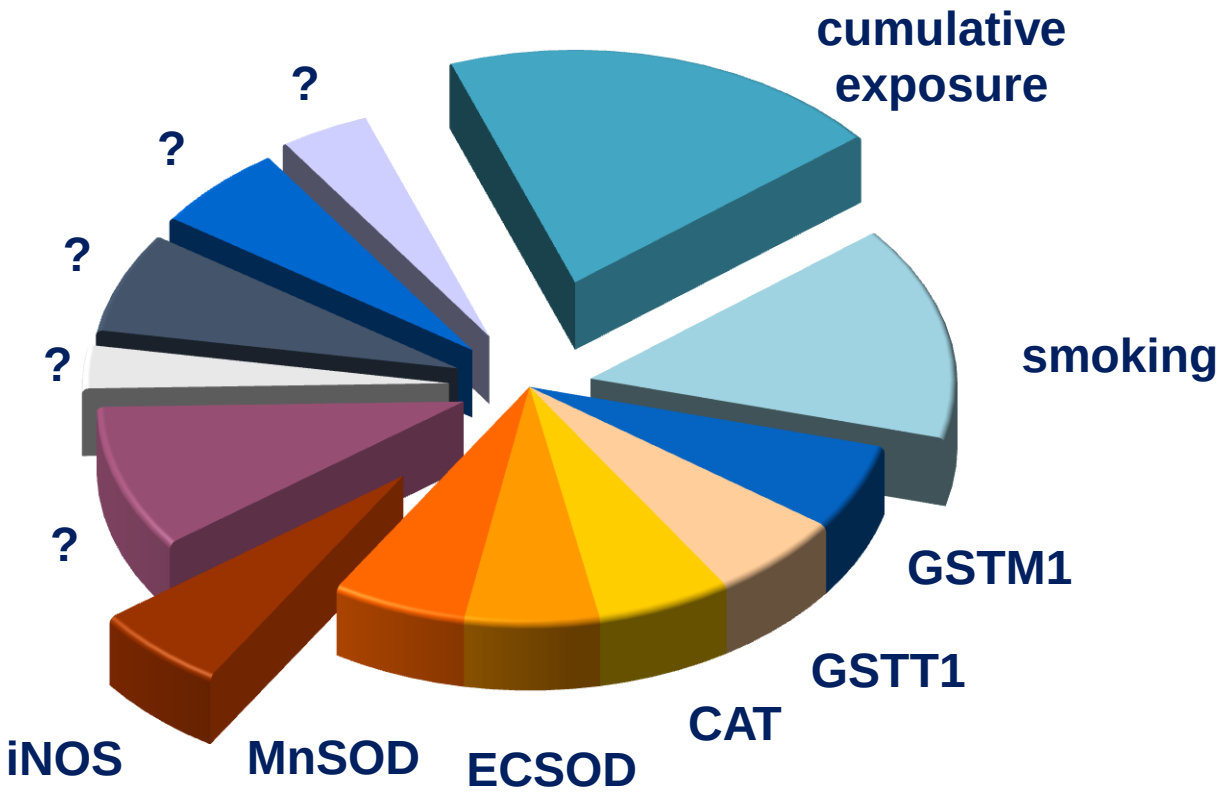
GSTM1 and smoking

Interaction:
OR = 2.67 (95% CI = 1.31–5.46); p = 0.007

GSTM1 and smoking

- both asbestos and smoking increase the production of ROS
- role of *GSTM1*

Model of causation



iNOS and cumulative exposure

Interaction:
OR = 0.55 (95% CI = 0.31–0.97); p = 0.037

Diseases

GENETIC FACTORS
GENE-GENE
GENE-ENVIRONMENT
INTERACTIONS

Conclusions

- basis for the development of new methods for an earlier diagnosis of diseases
- to identify new targets for a more effective treatment

Conclusions

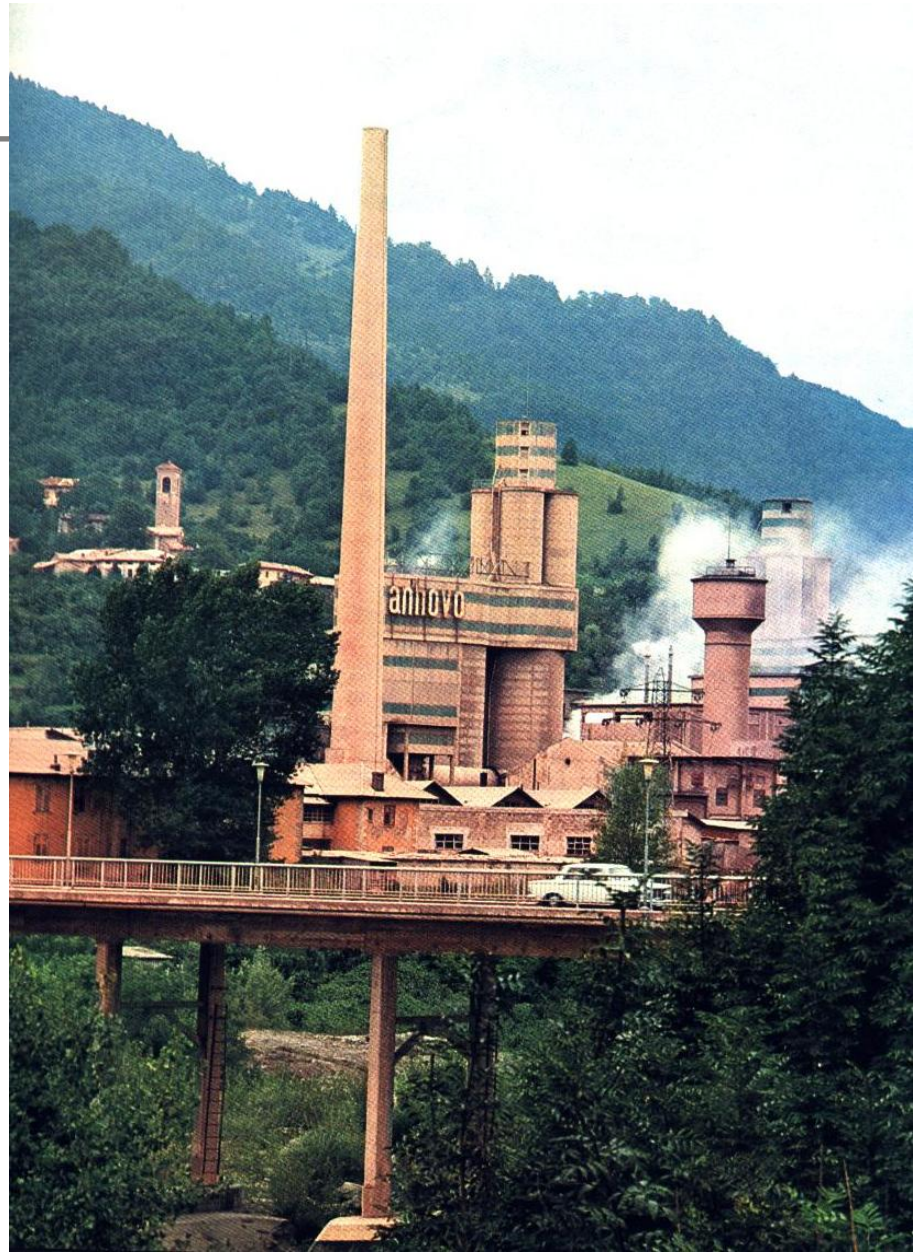
- understanding of pathogenesis of diseases and enable their prevention
- improvement of the quality of life as well as to **prolonging lifespan and aging**

Genetic factors

Researchers

Prof Vita Dolzan, MD, PhD
Assoc Prof Viljem Kovac, MD, PhD
Assistant Katja Goricar, PhD
Assoc Prof Metoda Dodic Fikfak, MD, PhD
Assoc Prof Alenka Franko, MD, PhD

Thank you for your attention



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Alenka Franko, PhD, MD, works as an associate professor at the Clinical Institute of Occupational Medicine, University Medical Centre Ljubljana, Slovenia. Dr Franko's research and teaching follow up several themes: Occupational and environmental toxicology, molecular epidemiology, genetics and gene-environment interactions, occupational medicine. She conducts this work nationally and internationally. In HBM4EU, she is involved in WP2.

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