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A09

Polymorphisms at genes involved in the purine metabolic pathway influence the risk of non-cirrhotic portal hypertension (NCPH) in HIV-infected patients

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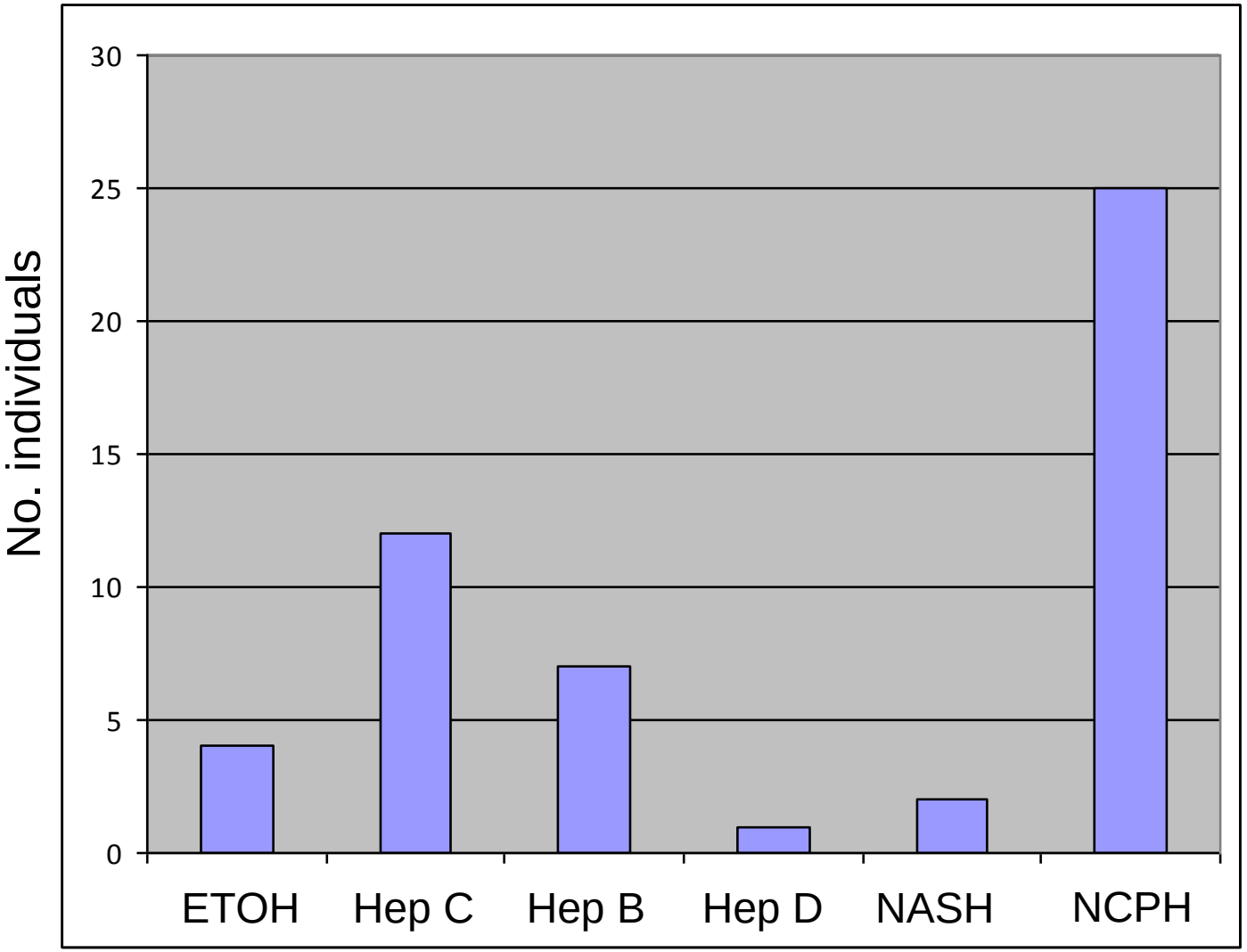
Background 1

- Liver disease in HAART era is one of the leading cause of mortality and morbidity
- Cause of liver abnormalities remain unknown for some groups of HIV positive patients
- NCPH is one of the rare but potentially life threatening complication of HAART

Soriano et al, 2008; Maida et al, 2006; Weber et al, 2006

Aetiology of variceal bleeding in 48 HIV patients over 10 years



Scourfield et al. BHIVA 2011 Abstract O6

Background 2

- NCPH described as the features of portal hypertension in the absence of cirrhosis on liver biopsy
- Prior exposure to ddI (+cumulative use) recognized as the most important predisposing factor
- The prevalence of NCPH is very low despite the large number of patients exposed to ddI

Vispo et al 2011; Maida et al, 2005; Mallet et al, 2007; Schiano et al, 2007

ddI exposure and NCPH

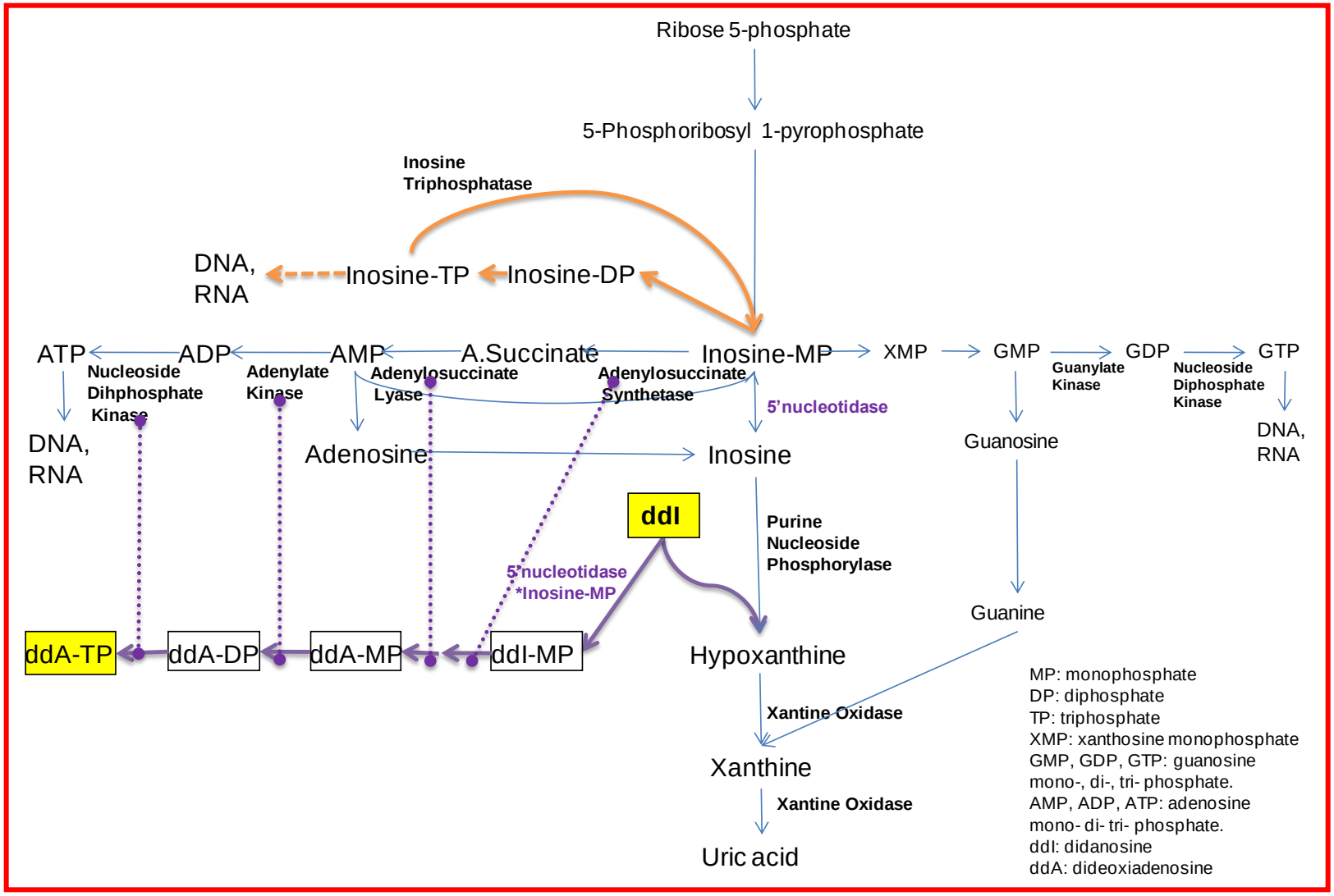
	Median months exposure (IQR)		P-value
	NCPH (n=16)	**Cohort (n=6,360)**	
AZT	41(10 to 60.5)	20.5(6.3 to 54.8)	0.629
D4T	14.5 (0.0 to 30.5)	28.6(10.8 to 56.6)	0.016
DDI	**59.5 (44.5 to 82.0)**	**21.1(7.18 to 54.33)**	**<0.001**
TDF	35.5 (4.5 to 50.5)	27.4(8.3 to 51.7)	0.583
ABC	13.5 (0 to 59.0)	28.5(12.1 to 67.0)	0.090
3TC or FTC	22.5 (9.0 to 57)	36.5(12.4 to 76.4)	0.237
Any PI	22 (7.5 to 47.5)	30.7(11.2 to 62.7)	0.153
Any NNRTI	65.5 (33.5 to 87.5)	27.5(9.0 to 66.8)	0.053

Scourfield et al, 2011

Proposed mechanisms

- Coagulation and thrombophilia
- Bacterial translocation
- Mitochondrial toxicity
- Chronic HIV related inflammation
- Genetic polymorphism in metabolism
- Endothelial dysfunction

Metabolism of purines and ddI



Objectives

- To investigate the impact of polymorphisms at genes coding enzymes involved in purine metabolic pathway

- To understand the role of genetic background in the development of NCPH

Hypothesis: We hypothesized that some metabolites emerging during ddI metabolism might cause damage in the endothelium of portal vessels.

Methods

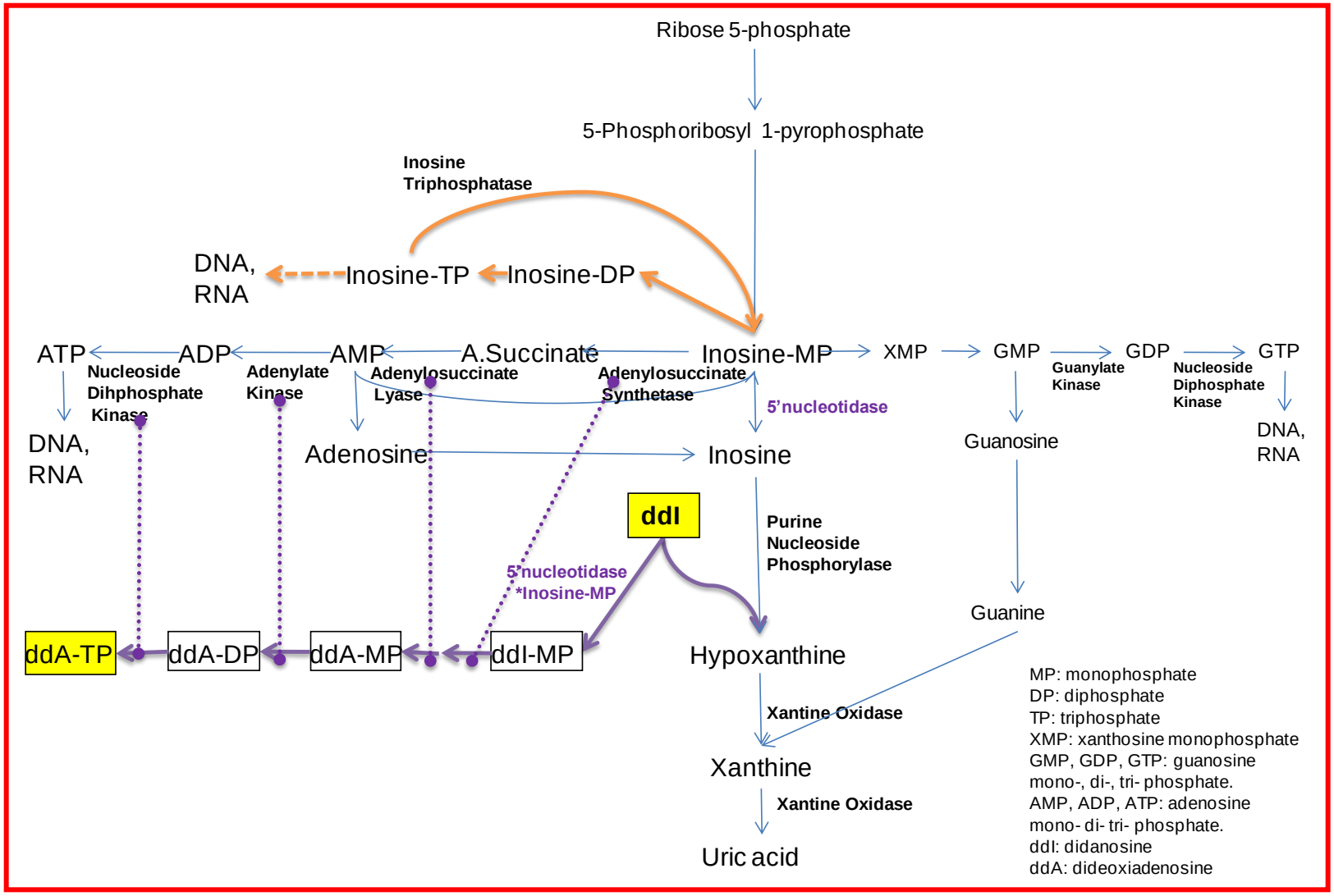
- Descriptive case-control study

- The two groups were matched by:
  - Length of ddI exposure,
  - Age
  - Gender

- Exclusion criteria:
  - Coinfection with hepatitis C/B
  - Alcohol abuse
  - Evidence of liver cirrhosis

- Tagging SNPs at 4 enzymes (was performed using SNPlex microarray)
  - inosine triphosphatase
  - 5’-nucleotidase cytosolic II
  - purine nucleoside phosphorylase
  - xanthine oxidase

Metabolism of purines and ddI



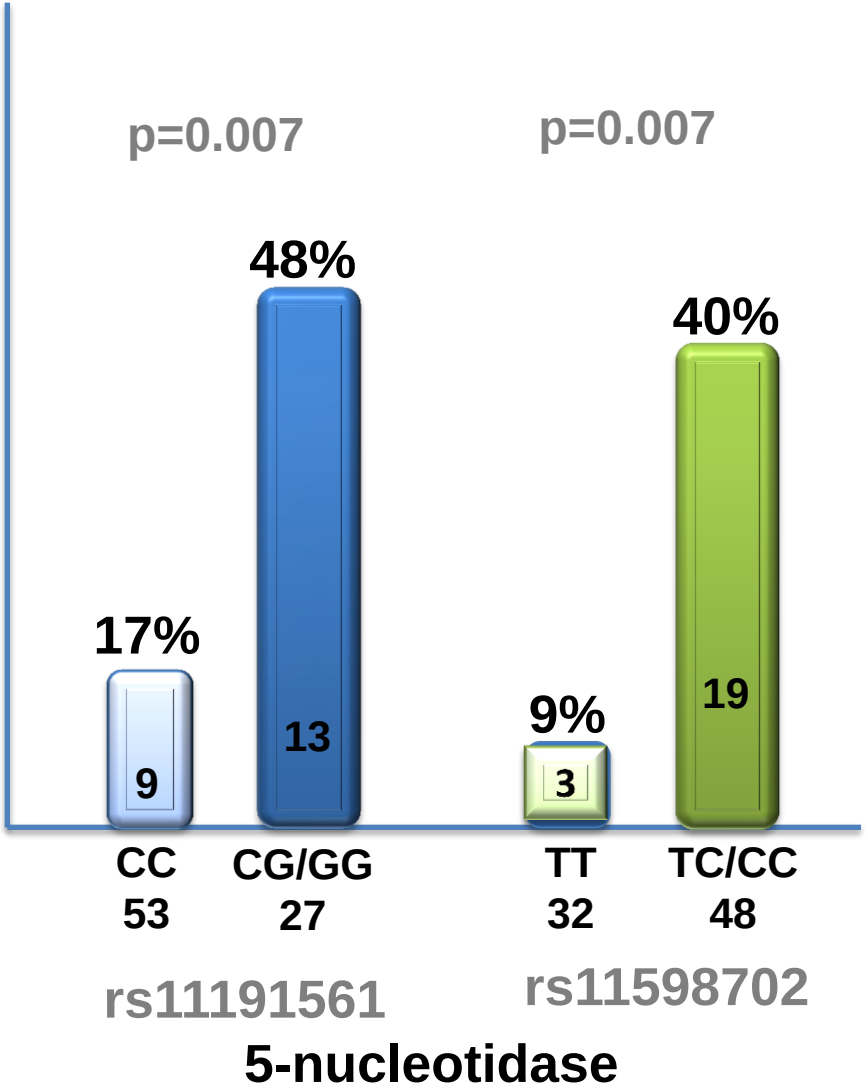
Results 1

Demographic and clinical characteristics

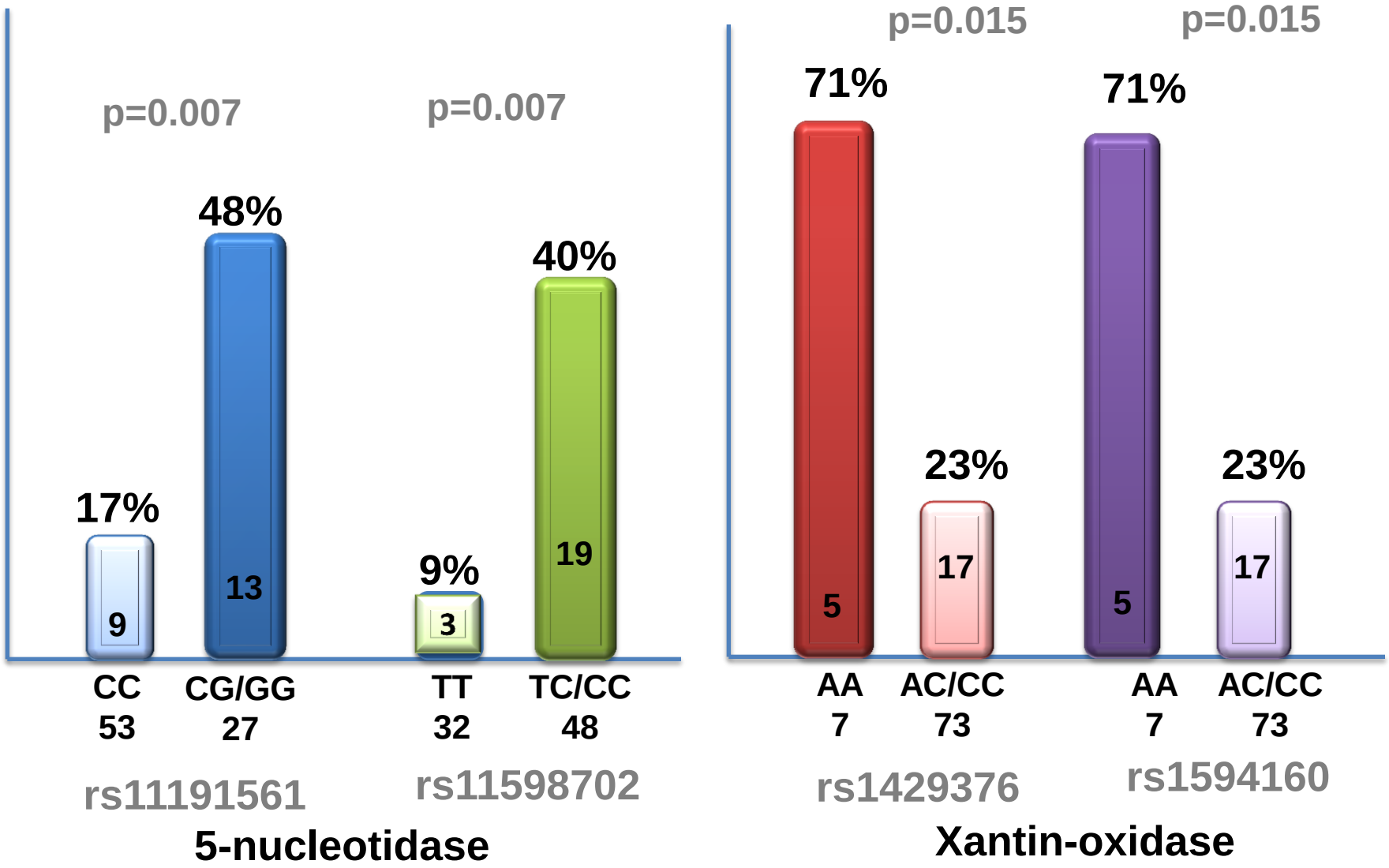
Parameter	Median (range)*
Number of patients [n (M/F)]	80 (53/27)
Case/Control	22/58
Age (yr)	47 (44-53)
ddI exposure (months)	66 (48-86)
Total SNPs analysed	36

*unless differently specified

Genetic polymorphisms influencing the risk of NCPH in HIV



Genetic polymorphisms influencing the risk of NCPH in HIV



Conclusions

- SNPs at the 5’-nucleotidase and xanthine oxidase genes influence the risk of developing NCPH
- Endothelial damage at portal vessels caused by increased levels of harmful purine metabolites of ddI
- Descriptive study, might not influence the clinical management at this stage

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