

**IMPACT OF GENETIC POLYMORPHISMS ON RESPIRATORY MORBIDITY OF CHILDREN**

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**BACKGROUND**

- ➔ Recent studies suggest adverse effects of PM2.5 and carcinogenic PAHs on respiratory morbidity (I.Hertz-Picciotto et al., ISEE Conference, Johannesburg 2005).
- ➔ These adverse effects can be modified by individual susceptibility (genetic polymorphisms).
- ➔ Our aim: to study the effects of metabolic and DNA repair genotypes on children respiratory morbidity.

**GENOTYPING**

Polymerase chain reaction and restriction fragment length polymorphisms techniques

were used for

genotype analysis in samples of fetal parts of placentas

**CHILDREN**

- ➔ 800 children born in 1994-1998 in two districts of the Czech Republic (Teplice and Prachatice).
- ➔ At delivery - maternal and medical questionnaires
- ➔ At the age of 3 or 4.5 years medical records of illnesses abstracted by pediatricians (ICD10)

**ILLNESSES**

- ➔ Multiple diagnoses on the same visit or hospitalization were considered one illness.
- ➔ Any diagnosis reported sooner than 3 weeks after the preceding diagnosis was discarded.
- ➔ Associations of polymorphic alleles with frequency of lower respiratory illnesses were analyzed using multiple logistic regression

**Description of the polymorphisms and their distribution in the studied cohort of children (N=800)**

	Allele (frequency)			
Biotransformation phase I enzymes	CYP 1A1-Msp	TT (666)	TC (132)	CC (2)
	CYP 1A1-Ile/Val	AA (749)	AG (50)	GG (1)
Biotransformation phase II enzymes	GSTM1	+ (377)	- (423)	
	GSTT1	+ (693)	- (108)	
	GSTP1	AA (368)	AG (356)	GG (76)
	EPHX exon 3	TT (373)	TC (302)	CC (125)
	EPHX exon 4	AA (544)	AG (222)	GG (34)
DNA repair enzymes	XPD exon 6	CC (235)	CA (399)	AA (164)
	XPD exon 23	AA (322)	AC (357)	CC (121)
	XRCC1	GG (304)	GA (397)	AA (99)
	hOGG1	CC (514)	CG (245)	GG (41)

# CHILD HEALTH AND THE ENVIRONMENT: RESULTS FROM EU FRAMEWORK 5

## Lower respiratory illnesses (LRI)

- J04 Acute laryngitis and tracheitis
- J05 Acute obstructive laryngitis and epiglottitis
- J12 Viral pneumonia
- J14 Pneumonia due to Hemophilus influenzae
- J15 Bacterial pneumonia
- J16 Pneumonia due to other infect. organisms
- J18 Pneumonia, organism unspecified
- J20 Acute bronchitis
- J21 Acute bronchiolitis
- J40 Bronchitis, not specified as acute or chronic
- J44 Other chronic obstructive pulmonary dis.
- J45 Asthma

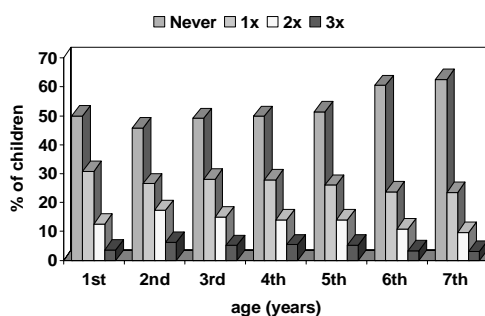
## Variables used in logistic regression

- Genetic polymorphisms
- Low birth weight, premature delivery (LBW/PMD)
- District - Teplice, Prachatice
- Gender
- Ethnicity – Gypsies
- Other children in household
- Ever breastfed
- Length of breastfeeding in months
- Coal for heating or cooking
- Mother smokes

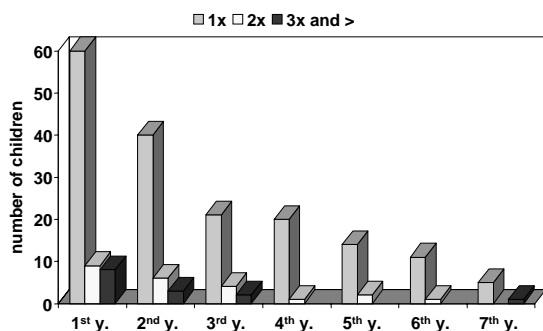
## Frequency of LRI diagnoses

Age (years)	1 <sup>st</sup> - 2 <sup>nd</sup>	3 <sup>rd</sup> - 5 <sup>th</sup>	6 <sup>th</sup> - 7 <sup>th</sup>
Number of children	799	799	577
At pediatric offices	1418	1851	1011
Hospitalizations	126	64	18
<b>Total</b>	<b>1544</b>	<b>1915</b>	<b>1029</b>

## LRI at pediatric offices



## LRI - hospitalizations



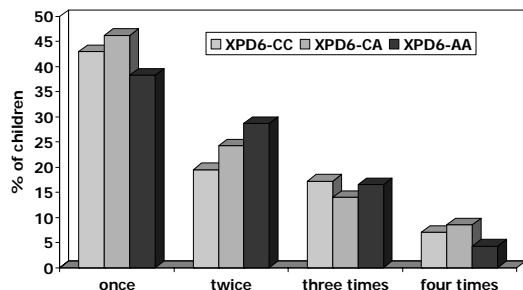
## LRI – all diagnoses

Multiple logistic regression, OR adjusted

	OR	Prob	95% CI
Ped. - 1th + 2nd year XPD exon 6 allele AA	1.6	0.018	1.1 – 2.5
Hosp. - 1th + 2nd year XPD exon 6 allele AA GSTP1 allele AG	1.9 1.7	0.018 0.018	1.1 – 2.5 1.1 – 2.7
Ped. + Hosp. - 3rd-5th year XRCC1 allele CC	1.9	0.035	1.1 – 3.6

# CHILD HEALTH AND THE ENVIRONMENT: RESULTS FROM EU FRAMEWORK 5

**Frequency of bronchitis in the first two years**  
ever diagnosed bronchitis in each genotype group = 100%

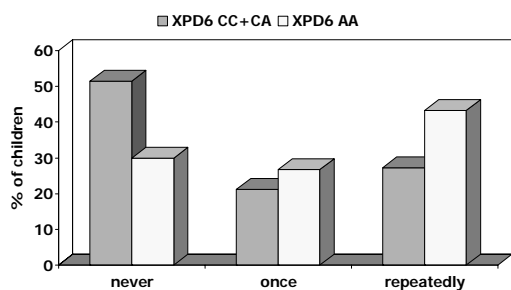


**Acute bronchitis (J20) in the 1<sup>st</sup> and 2<sup>nd</sup> year**  
(including hospitalizations)

Logistic regression N = 782, Prob. >  $\chi^2$  < 0.00001

	OR	Prob.	CI 95%
Mother smokes	1.6	0.002	1.19 - 2.27
XPD exon 6 AA	1.8	0.003	1.22 - 2.61
Other children	1.5	0.004	1.14 - 2.07
Girls	0.7	0.017	0.52 - 0.94
LBW/PMD	0.6	0.020	0.38 - 0.92
Gypsies	2.0	0.028	1.08 - 3.62

**Bronchitis – repeatedly in the first two years**



## CONCLUSIONS

- ➔ The present study suggests impact of genetic polymorphisms on the frequency of LRI in early childhood:
  - ➔ Mutations in gene XPD 6 and GSTP1 increased the risk of LRI up to the age of 2 years
  - ➔ Mutations in gene XRCC 1 increased the risk of LRI at the age of 3-5 years
- ➔ The presence of XPD 6 allele AA is associated with increased proportion of children having ever diagnosed acute bronchitis in the first two years of life (1086 dg out of 1544 dg of LRI)
- ➔ Up to our knowledge, this is the first study reporting association between the DNA repair genotypes and respiratory morbidity.

## Acknowledgement

Czech Ministry of Environment (VAV-IC/5/6/04)  
EC QLK4-CT-2002-02198 (CHILDRENGENONETWORK)