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Original Research

Frequency of Polymorphisms in Gene-Coding Xenobiotic Metabolizing Enzymes and DNA Repair Proteins in Young, Healthy Polish Individuals

M. M. Sasiadek[1]*, I. Laczmanska[1], P. Karpinski[1], J. Gil[1], A. Trusewicz[1], K. Pesz[1], D. Ramsey[2], N. Blin[3]

[1]Department of Genetics, Wroclaw Medical University, Marcinkowskiego 1, 50-367 Wrocław, Poland
[2]School of Mathematics and Statistics, University of Limerick, Limerick, Ireland
[3]Division of Molecular Genetics, University of Tuebingen, Institute of Human Genetics, Wilhelmstr. 27, D-72074 Tuebingen, Germany

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Abstract

The association between polymorphism in both DNA repair and xenobiotic metabolism genes and cancer risk has been reported by many authors. Recent studies have revealed the genetic heterogeneity of various populations. Therefore, the aim of our study was to evaluate the frequency of selected polymorphisms/mutations in 17 minor susceptibility genes and to analyze the pattern of their distribution in a group of 146 healthy, young Polish individuals.The results of our study show that the distribution of studied polymorphisms displayed a distinct pattern.

Keywords: XME (xenobiotic metabolising enzymes), DNA repair, frequency of polymorphism, SNPs

Introduction

Many authors have observed a correlation between polymorphisms in gene coding for either DNA repair proteins or xenobiotic metabolizing enzymes (XMEs) and susceptibility to various environmental mutagens, as well as the risk of cancer [1-4]. Numerous recent studies have enabled the identification of a variety of single nucleotide polymorphisms (SNPs) that influence the structure and function of proteins, and in this way modulate an individual's susceptibility to environment-related diseases.

However, analysis of recently published data has revealed differences in the distribution of SNPs in various populations, as well as differences in the associations between SNPs and the risk of cancer among the studies [2, 3, 5-8]. These controversies may be partially explained either by the low penetration of "minor impact" genes, differences in the structure of the groups examined, such as ethnic origin and strength of social ties within a group, or by the differences between laboratory procedures. Taioli et al. concluded from their study on the significance of allele frequency estimates in epidemiology that "in order to study a genetic-disease association, it is vital to know the true allele frequencies of the pathway related genes in the healthy population" [9]. Their analyses also indicated that only large studies of either one huge group or studies on pooled, already published data could provide sufficiently rich information on allelic frequencies in control populations.

*e-mail: sasiadek@gen.am.wroc.pl

Such groups should be even larger in studies on gene-gene or gene-environment interactions; for example, the expected frequency of associated polymorphisms in genes employed in the metabolism of polycyclic aromatic hydrocarbons is about $7x10^{-5}$ [9]. Furthermore, in testing for linkage disequilibrium among genes involved in a variety of pathways that modulate mutagen sensitivity, the analysis of SNP distribution should be performed on one defined group. This will eliminate the possible influence of a variety of confounding factors, such as ethnicity, non-homogenous genetic composition [9], and any other factors which differ among the groups studied by different authors [3, 10].

Therefore, the aim of our study was to analyse "minor impact" genes such as DNA-repair and xenobiotic metabolising genes, which are involved in the modulation of individual susceptibility to xenobiotics with respect to the distribution of SNPs and possible associations between them, in healthy, non-smoking, young inhabitants of the Lower Silesia region in Poland.

Experimental Procedures

The study protocol was approved by the University Ethics Committee. The allele frequencies were determined for 146 healthy volunteers, 94 women and 52 men, students of the 3rd year of Medical Faculty, Wrocław Medical University. The students were included to the study group after a selection based on detailed interviews and pedigree analysis. Individuals with a family history of cancer were excluded (at least one cancer in the family to the 3rd degree of relationship). The mean age of the group was 22.54 with a standard deviation of 1.56 years.

Analysis of Polymorphisms

For the analysis of the distribution of SNPs in DNA-repair genes, we chose the genes involved in the main DNA-repair pathways, which had been observed to be associated with susceptibility to xenobiotics such as: *XRCC1* $Arg^{399}Gln$, *XRCC1* $Arg^{194}Trp$ (base excision repair; BER); *XPA* $A^{23}G$, *XPA* $G^{709}A$, *XPC* $Lys^{939}Gln$, *XPC* C/A intron 11 (i11), *XPD* $Asp^{312}Asn$, *XPD* $Lys^{751}Gln$, *XPD* $Ile^{199}Met$, *XPG* $Asp^{1104}His$, *XPF* $Arg^{415}Gln$, *ERCC1* $C^{118}T$, *ERCC1* $C^{8092}A$ (nucleotide excision repair; NER); *BRCA1* ^{5382}insC, *BRCA1* $C^{61}G$, *RAD51* ^{135}C, *NBS1* $Glu^{185}Gln$, *XRCC2* $Arg^{188}His$, and *XRCC3* $Thr^{241}Met$ (homologous recombination; HR). For the analysis of genes coding for XMEs, we also chose genes recently revealed to be significant in the modulation of mutagen sensitivity: *CYP1A1* $T^{6235}C$ (*2A), $T^{5639}C$ (*3), $A^{4889}G$ (*2C) and $C^{4887}A$ (*4), *CYP2E1* c1/c2 (involved in the activation of xenobiotics) and *NAT2* $C^{481}T$, $G^{590}A$, $G^{857}A$, *GSTT1*(+/-), *EPHX* $Tyr^{113}His$ (exon 3) and $His^{139}Arg$ (exon 4) (involved in the detoxification of xenobiotics).

The analysis of the polymorphisms was performed as previously described [11]. The accuracy of genotyping was confirmed using RFLP by repeating the analysis of 10% of the samples tested. In all cases the results revealed 100% of concordance.

Statistical Analysis

The chi-squared goodness of fit test was used to test whether the genotype frequencies at a locus were in agreement with the Hardy-Weinberg equilibrium. The maximum likelihood chi-squared test for independence was used to test whether genotypes at separate loci were in linkage equilibrium or not. Due to the very large number of tests, the Bonferroni correction for multiple testing was used, as well as standard p-values.

Results

The following genes showed no variability and hence were not analyzed: *BRCA1* ^{5382}insC, *BRCA1* $C^{61}G$, *XPD* $Ile^{199}Met$, *NAT2* $G^{857}A$. The frequency of polymorphisms in *XRCC1* $Arg^{194}Trp$, *XPA* $G^{709}A$, *XPF* $Arg^{415}Gln$, *RAD51* ^{135}C, *XRCC2* $Arg^{188}His$, *CYP1A1* *2C/*4 (m2/m4) (*2C and *4 polymorphisms were grouped together), *CYP1A1* *2A/*3 (m1/m3) (MspI), *CYP2E1* c1/c2, *GSTT1* (+/-) was below the sensitivity of the goodness of fit test, thus they were not tested for agreement with the Hardy-Weinberg (H-W) equilibrium.

Consequently, the frequency of SNPs in the remaining genes was tested for their agreement with the H-W equilibrium: *XRCC1* $Arg^{399}Gln$, *XPA* $A^{23}G$, *XPC* $Lys^{939}Gln$, *XPC* C/A (i11), *XPD* $Asp^{312}Asn$, *XPD* $Lys^{751}Gln$, *XPG* $Asp^{1104}His$, *ERCC1* $C^{118}T$, *ERCC1* $C^{8092}A$, *NBS1* $Glu^{185}Gln$, *XRCC3* $Thr^{241}Met$, *NAT2* $C^{481}T$, *NAT2* $G^{590}A$, *EPHX* $Tyr^{113}His$ (exon 3), and $His^{139}Arg$ (exon 4) (Table 1).

Two of the polymorphisms tested were found not to fit the H-W equilibrium: more *XPA* $A^{23}G$ heterozygotes and less *EPHX* $Tyr^{113}His$ (exon 3) heterozygotes were observed than expected at the H-W equilibrium (Table 1).

The maximum likelihood chi-squared test for independence was used to test whether genotypes at separate loci were in linkage equilibrium or not. The following 4 pairs of loci: *XPC* $Lys^{939}Gln$ and *XPC* C/A (i11), *ERCC1* $C^{118}T$ and *ERCC1* $C^{8092}A$, *NAT2* $C^{481}T$ and *NAT2* $G^{590}A$, *XPD* $Asp^{312}Asn$ and *XPD* $Lys^{751}Gln$ showed linkage disequilibrium at a significance level of 1%, even when the Bonferroni correction was used (Table 2).

The following 3 pairs of loci exhibited linkage disequilibrium at a significance level of 1%: *CYP1A1* (exon 7) *2C/*4 and *NBS1* $Glu^{185}Gln$, *ERCC1* $C^{8092}A$ and *XPD* $Asp^{312}Asn$, *ERCC1* $C^{118}T$ and *XPA* $A^{23}G$. However, after using the Bonferroni correction this was not significant. Hence, in these cases we do not have clear evidence of linkage disequilibrium (Table 2).

Twelve pairs of polymorphisms in genes located on different chromosomes exhibited linkage disequilibrium at a significance level of 5%, as follows:

1) homozygotes of *XRCC1* $Arg^{399}Gln$ have non-wild type alleles of *RAD51* ^{135}C more often than expected under linkage equilibrium (p=0.01168),
2) T and G alleles of *NAT2* $C^{481}T$ and *XPA* $A^{23}G$ are associated together, analogously C alleles with A alleles (p=0.01270),

Table 1. Distribution of genotypes and allele frequencies in the study group.

Gene/SNP [chromosomal location] biological significance of polymorphism	Genotype/Allele	n	Observed freq (%)	Expected freq ** (%)	p
1	2	3	4	5	6
XRCC1 Arg^{399}Gln	Arg/Arg	51	34.69	36.66	
(BER)	Arg/Gln	76	51.70	47.78	
[19q31.2]	Gln/Gln	20	13.61	15.57	n.s.
Lower repair capacity [34, 35]	**Arg** **Gln**		**60.54** **39.46**		
XPA A^{23}G (non-coding sequence)	G/G A/G	46	31.72	38.53	
(NER)	A/A	88	60.69	47.09	
[9q22.3]		11	7.59	14.39	P<0.001
Modulation of the protein level in cell [36]	**A** **G**		**37.93** **62.07**		
XPC Lys^{939}Gln	Lys/Lys	49	34.03	33.22	
(NER)	Lys/Gln	68	47.22	48.83	
[3p25]	Gln/Gln	27	18.75	17.94	n.s.
Important in bladder cancer [27]	**Lys** **Gln**		**57.64** **42.36**		
XPC C/A intron 11	C/C	41	29.50	28.73	
(NER)	C/A	67	48.20	49.74	
[3p25]	A/A	31	22.30	21.53	n.s.
Important in lung cancer [28]	**C** **A**		**53.60** **46.40**		
XPD Asp^{312}Asn	Asp/Asp	65	49.24	47.01	
(NER)	Asp/Asn	51	38.64	43.11	
[19q13.3]	Asn/Asn	16	12.12	9.88	n.s.
Important in lung cancer [12]	**Asp** **Asn**		**68.56** **31.44**		
XPD Lys751Gln	Lys/Lys	61	41.78	42.79	
(NER)	Lys/Gln	69	47.26	45.25	
[19q13.3]	Gln/Gln	16	10.96	11.96	n.s.
Important in BCC, lung cancer [12,37]	**Lys** **Gln**		**65.41** **34.59**		
XPG Asp^{1104}His	Asp/Asp	91	62.33	62.58	
(NER)	Asp/His	49	33.56	33.05	
[13q22]	His/His	6	4.11	4.36	n.s
Important in lung cancer [38]	**Asp** **His**		**79.11** **20.89**		
ERCC1 C^{118}T (silent)	C/C	69	47.92	45.84	
(NER)	C/T	57	39.58	43.73	
[19q13.2-q13.3]	T/T	18	12.50	10.43	n.s.
Modulation of transcript level, important in lung cancer and gliomas [39,40]	**C** **T**		**61.71** **32.29**		

Table 1. continued

1	2	3	4	5	6
ERCC1 C^{8092}A (non coding sequence)	C/C	92	64.34	64.67	n.s.
(NER)	C/A	46	32.17	31.49	
[19q13.2-q13.3]	A/A	5	3.50	3.83	
Modulation of transcript level, important in lung cancer and gliomas [39, 40]	**C** **A**		**<u>80.42</u>** **<u>19.58</u>**		
NBS1 Glu^{185}Gln	Glu/Glu	49	37.93	37.11	n.s.
(HR)	Glu/Gln	75	51.03	47.62	
[8q21-q24]	Gln/Gln	18	12.68	15.28	
Important in bladder cancer [41]	**Glu** **Gln**		**<u>60.92</u>** **<u>39.08</u>**		
XRCC3 Thr^{241}Met	Thr/Thr	55	37.93	40.26	n.s.
(HR)	Thr/Met	74	51.03	46.38	
[14q32.3]	Met/Met	16	11.03	13.36	
important in colon cancer, melanoma, bladder cancer [42, 43]	**Thr** **Met**		**<u>63.45</u>** **<u>36.55</u>**		
NAT2 C^{481}T (silent)	C/C	42	29.37	31.30	n.s.
(XME – Phase II)	C/T	76	53.15	49.29	
[8p23.1-p21.3]	T/T	25	17.48	19.41	
Important for protein activity [44]	**C** **T**		**<u>55.94</u>** **<u>44.06</u>**		
NAT2 G^{590}A (Arg^{197}Gln)	G/G	58	40.56	41.84	n.s.
(XME – Phase II)	G/A	69	48.25	45.69	
[8p23.1-p21.3]	A/A	16	11.19	12.47	
Important for protein activity [44]	**G** **A**		**<u>64.69</u>** **<u>35.31</u>**		
EPHX	Tyr/Tyr	71	49.31	42.61	P<0.001
Tyr^{113}His (exon 3)	Tyr/His	46	31.94	45.33	
(XME – Phase II)	His/His	27	18.75	12.06	
[1q42.1]					
Important for protein activity [33]	**Tyr** **His**		**<u>65.28</u>** **<u>34.72</u>**		
EPHX	His/His	85	58.62	58.60	n.s.
His^{139}Arg (exon 4)	His/Arg	52	35.86	35.90	
(XME – Phase II)	Arg/Arg	8	5.52	5.50	
[1q42.1]					
Important for protein activity [33]	**His** **Arg**		**<u>76.55</u>** **<u>23.45</u>**		

*n.s. - non significant
**expected frequency - calculated according to Hardy-Weinberg equilibrium.

Table 2. Alleles exhibiting linkage disequilibrium at a significance level of 1% (chi-squared test for independence).

Pair of loci [chromosomal location]	P	Comment
XPC Lys^{939}Gln and XPC C/A (i11) [3p25]	***p=0.00000***	A alleles at *XPC* Lys^{939}Gln linked with C alleles at *XPC* C/A (i11) [C alleles at *XPC* Lys^{939}Gln with C alleles at *XPC* C/A (i11)]
ERCC1 C^{118}T and *ERCC1* C^{8092}A [19q13.2-q13.3]	***p=0.00000***	C alleles at *ERCC1* C^{118}T linked with C alleles at *ERCC1* C^{8092}A [T alleles at *ERCC1* C^{118}T with A alleles at *ERCC1* C^{8092}A]
NAT2 C^{481}T and *NAT2* G^{590}A [8p21.3-p23.1]	***p=0.00000***	C alleles at *NAT2* C^{481}T linked with A alleles at *NAT2* G^{590}A [T alleles at *NAT2* C^{481}T with G alleles at *NAT2* G^{590}A]
XPD Asp^{312}Asn and *XPD* Lys^{751}Gln [19q13.3]	p=0.00001	D alleles at *XPD* Asp^{312}Asn linked with A alleles at *XPD* Lys^{751}Gln [N alleles at *XPD* Asp^{312}Asn with C alleles at *XPD* Lys^{751}Gln]
CYP1A1 *2C/*4 [15q22-q34] and *NBS1* Glu^{185}Gln [8q21-q24]	p=0.00211*	Wild type alleles at *CYP1A1* *2C/*4 linked with G alleles at *NBS1* Glu^{185}Gln [Non-wild type alleles at *CYP1A1* *2C/*4 with C alleles at *NBS1* Glu^{185}Gln
ERCC1 C^{8092}A [19q13.2-q13.3] and *XPD* Asp^{312}Asn [19q13.3]	p=0.00456*	C alleles at *ERCC1* C^{8092}A linked with D alleles at *XPD* Asp^{312}Asn [A alleles at *ERCC1* C^{8092}A with N alleles at *XPD* Asp^{312}Asn]
ERCC1 C^{118}T [19q13.2-q13.3] and *XPA* A^{23}G [9q22.3]	p=0.00637*	A larger number of C/C, A/A double homozygotes than expected under a lack of linkage disequilibrium.

*Using the Bonferroni correction these results were shown to be insignificant

3) variant alleles of *XPD* Asp^{312}Asn and *ERCC1* C^{118}T (p=0.01389) display a positive correlation,

4) *ERCC1* C^{8092}A and *XRCC1* Arg^{399}Gln (low frequency of double heterozygotes, p=0.02066),

5,6,7) *CYP1A1* *2A/ *3 (MspI) and *CYP1A1* *2C/ *4 (exon 7), *NBS1* Glu^{185}Gln and *CYP1A1* *2A/*3 (MspI), *XPD* Lys^{751}Gln and *ERCC1* C^{8092}A (p=0.02233, p=0.0251, and p=0.04157, respectively) show a positive association,

8,9) *RAD51* ^{135}C and *CYP2E1* c1/c2 (p=0.0377), *XPF* Arg^{415}Gln and *XRCC1* Arg^{194}Trp (p=0.03846) (a slight negative association between the appearance of non-wild type alleles at these loci),

10) *XPC* Lys^{939}Gln and *XPA* A^{23}G (high frequency of the G/G and A/A genotype pairs, p=0.04382),

11) *CYP1A1* *2C/*4 (exon 7) and *XRCC1* Arg^{399}Gln (p=0.04768) (low frequency of Arg/Arg and variant genotype),

12) association of G/G *NAT2* G^{590}A and *GSTT1* null genotype (p=0.04897).

However, after using the Bonferroni correction these results were not significant. Hence, in these cases we definitely do not have any clear evidence of linkage disequilibrium (Table 3).

Discussion of Results

Our advancing knowledge about the etiology of environment-related diseases (including cancers) has revealed how important polymorphisms in genes involved in DNA-repair and xenobiotic metabolism are for an individual's susceptibility to environmental mutagens [1, 2, 10]. Despite the huge number of papers that have been published presenting data on the frequency and distribution of SNPs in a variety of genes and their associations with both mutagen susceptibility and risk of cancer, most of these studies come to conflicting conclusions. This probably results, to a large extent, from the insufficient attention paid to characterizing the genetic variation in controls [9]. Therefore, there is a strong need to precisely define the pattern of the distribution of SNPs in appropriately defined populations, which could be used as a golden standard. In our study, a group of 146 students, homogeneous with respect to ethnic background, age, smoking habits, and without a history of cancer in the family, were analyzed with regard to the frequency of SNPs and the associations between them. In the group tested, no variant alleles of *BRCA1* ^{5382}insC, C^{61}G, *XPD* Ile^{199}Met, or *NAT2* G^{857}A were found. This observation is consistent with the data of other authors [12-15] and results from the relatively small size of the group tested. Also, the very low frequency of the *XPA* G^{709}A allele is in agreement with other studies on healthy individuals in the Polish population [12]. However, the frequencies of the *XRCC2* ^{188}His variant and Arg^{188}His polymorphism revealed in our study (0.003) are much lower than those reported by other authors (typically 0.06–0.07) [16, 17]. Also, the frequency of the *CYP2E1* c2 allele (c1/c2, RsaI) noted by us differs from data obtained by other authors. In our study no homozygous c2/c2 genotype was observed, while the c2 allele was present with a frequency of 0.08. Cichoz-Lach et al. found the *CYP2E1* c2 allele (frequency of 0.015) in a Polish study; however, in a heterozygous state and only among male alcohol abusers [18]. Other studies have indicated that the frequency of the c2 allele in Caucasians is 0.024-0.038 [1, 19, 20]. The discrepancy between our results and the results of other authors probably results from the size of the groups tested. It may be due to the variability in the frequency of SNPs in different groups. In Asian populations the c2 frequency is about 0.2-0.8 [1, 21, 22]. The frequency of the variant alleles in the other genes examined coincides with other data for Caucasians: *RAD51* ^{135}C [23], *XRCC3*

Table 3. Alleles exhibiting linkage disequilibrium at a significance level of 5%.

No.	Pairs of loci	p	comment
1	*XRCC1* Arg^{339}Gln and *RAD51* ^{135}C	p=0.01168	an association between the homozygotes of *XRCC1* Arg^{339}Gln and variant allele of the *RAD51* ^{135}C
2	*NAT2* C^{481}T and *XPA* A^{23}G	p=0.01270	T associated with G and C with A.
3	*XPD* Asp^{312}Asn and *ERCC1* C^{118}T	p=0.01389	a positive association between the number of variant alleles at each locus
4	*ERCC1* C^{8092}A and *XRCC1* Arg^{339}Gln	p=0.02066	low frequency of double heterozygotes,
5	*CYP1A1* *2A/*3 (MspI) and *CYP1A1* *2C/*4 (exon 7),	p=0.02233,	a positive association between variant genotypes
6	*NBS1* Glu^{185}Gln and *CYP1A1* *2A/*3 (MspI),	p=0.0251	a positive association between variant genotypes
7	*XPD* Lys^{751}Gln and *ERCC1* C^{8092}A	p=0.04157	a positive association between variant genotypes
8	*RAD51* ^{135}C and *CYP2E1* c1/c2	p=0.0377	a slight negative association
9	*XPF* Arg^{415}Gln and *XRCC1* Arg^{194}Trp	p=0.03846	a slight negative association
10	*XPC* Lys^{939}Gln and *XPA* A^{23}G	p=0.04382	high frequency of the G/G and A/A genotype pairs,
11	*CYP1A1* *2C/*4 (exon 7) and *XRCC1* Arg^{339}Gln	p=0.04768	Low frequency of Arg/Arg and variant pair of genotypes.
12	*NAT2* G^{590}A and *GSTT1* (+/-)	p=0.04897	G/G *NAT2* G^{590}A is associated with *GSTT1* null genotype

Thr^{241}Met [16, 24, 25], *NBS1* Glu^{185}Gln [26, 27], *XPD* Asp^{312}Asn, Lys^{751}Gln [12, 25], *XPA* A^{23}G [7], *XPC* Lys^{939}Gln and *XPC* C/A (intron 11) [27-29], *XPG* Asp^{1104}His [27], *XRCC1* Arg^{194}Trp, Arg^{399}Gln [24, 25], *XPF* Arg^{415}Gln [24], *ERCC1* C^{118}T, C^{8092}A [30], *CYP1A1* [31, 32], *NAT2* [14], and *EPHX* [33].

Two of the genes tested in our study do not fit the H-W equilibrium: more *XPA* A^{23}G heterozygotes and fewer *EPHX* Tyr^{113}His (exon 3) heterozygotes were observed than expected at the H-W equilibrium (Table 1). Even after using the Bonferroni correction for multiple testing to account for the likelihood of false positives, these results were still found to be significant at a level of 1%. Thus, we have strong evidence that these two genes do not fit the H-W equilibrium frequencies.

When analyzing the associations between the allele variants in each pair of the genes tested, 4 pairs of alleles, respectively:

1) *XPC* Lys^{939}Gln and *XPC* i11 C/A,
2) *ERCC1* C^{118}T and *ERCC1* C^{8092}A,
3) *NAT2* C^{481}T and *NAT2* G^{590}A,
4) *XPD* Asp^{312}Asn and *XPD* Lys^{751}Gln

...showed very clear evidence of linkage disequilibrium (at a significance level of 1%, even when the Bonferroni correction was used). In each of these cases, both associated genes lie on the same chromosome. Alleles of genes located on different chromosomes exhibited linkage disequilibrium at a significance level of either 1% or 5%. However, using the Bonferroni correction these results were shown to be insignificant. Hence, in these cases we do not find clear evidence of linkage disequilibrium.

Conclusion

Therefore, even if a population of 146 individuals may not suffice to assess the allelic frequencies of some rare variants e.g. *BRCA1* ^{5382}insC, *C61G*, *XPD* Ile^{199}Met or *NAT2* G^{857}A, our results clearly revealed that the distribution of SNPs in the control population shows distinct patterns. These facts underline the necessity to choose a well-conceived control population.

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