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Influence of DNA repair gene polymorphisms of *hOGG1*, *XRCC1*, *XRCC3*, *ERCC2* and the folate metabolism gene *MTHFR* on chromosomal aberration frequencies

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Abstract

We have studied the effect of genetic polymorphisms in the DNA repair genes *hOGG1*, *XRCC1*, *XRCC3*, *ERCC2* and the *MTHFR* gene in the folate metabolism on the frequencies of cells with chromosomal aberrations (CA), chromosome-type aberrations (CSA), chromatid-type aberrations (CTA), chromatid breaks (CTB) and chromatid gaps (CTG) scored in peripheral blood lymphocytes from 651 Norwegian subjects of Caucasian descendant. DNA was extracted from fixed cell suspensions. The log-linear Poisson regression model was used for the combined data which included age, smoking, occupational exposure and genotype for 449 subjects.

Our results suggest that individuals carrying the *hOGG1* 326Cys or the *XRCC1* 399Gln allele have an increased risk of chromosomal damage, while individuals carrying the *XRCC1* 194Trp or the *ERCC2* 751Gln allele have a reduced risk regardless of smoking habits and age.

Individuals carrying the *XRCC1* 280His allele had an increased risk of CSA which was only apparent in non-smokers. This was independent of age.

A protective effect of the *XRCC3* 241Met allele was only found in the older age group in non-smokers for CA, CSA and CTA, and in smokers for CSA. In the youngest age group, the opposite effect was found, with an increased risk for CA, CTA and CTG in smokers. Carrying the *MTHFR* 222Val allele gave an increased risk for chromosome and chromatid-type aberrations for both non-smokers and smokers, especially for individuals in the older age group, and with variable results in the youngest age group. The variables included in the different regression models accounted, however, for only 4–10% of the variation. The frequency ratio for CTG was significantly higher than for CTA and CTB for only 7 of the 43 comparisons performed. Some of the gap frequencies diverge from the trend in the CA, CSA, CTA and CTB results.

Keywords: Chromosomal aberrations; *hOGG1*; *XRCC1*; *XRCC3*; *ERCC2*; *MTHFR*; DNA repair polymorphism

1. Introduction

Chromosomal aberrations (CA) in lymphocytes from peripheral blood have been used as a biomarker for predicting cell damage caused by exposure to carcinogens that could eventually lead to development of cancer since the late 1960s. The first cohort study connecting

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cancer incidence to CA frequencies was published in 1994 on the Nordic cohort [1]. This was confirmed by an Italian study in 1995 [2]. A follow-up study of the combined cohort, the European Study Group on Cytogenetic Biomarkers and Health (ESCH) cohort; strengthened the previous results [3]. A nested case–control study within the ESCH cohort [4] showed that CA frequency could predict cancer independently of exposure to major carcinogens in occupational settings and to tobacco smoke, making the point that the predictivity of high rates of CA does not require such exposures. The time lapse between the CA analysis and cancer detection had no influence on the cancer predictivity of CA, indicating that a possible effect of undetected cancer on CA frequency could not explain the findings either [3].

The above results refer to the frequency of metaphase-stage cells with structural CA in peripheral blood lymphocytes as the genotoxicity biomarker. CA include all types of visible chromosomal breaks and exchanges and is usually divided into chromosome-type aberrations (CSA), involving the same locus on both sister chromatids, and chromatid-type aberrations (CTA) involving one sister chromatid. CSA are induced by S-independent agents in the first metaphase post-exposure for cells damaged in G1. Cells damaged in S/G2 lead to CTA. S-dependent agents require DNA synthesis before being expressed in the first metaphase post-exposure and lead to CTA [5].

The paper by Hagmar et al. [6] addressed the question whether a significantly elevated cancer risk could be observed in subjects with high CSA and/or high CTA at test, and these variables showed equally strong cancer predictivity in the Nordic cohorts. The authors concluded that individual characteristics as yet not identified are probably behind the CA/cancer risk association. Polymorphisms in DNA repair genes were indicated as one likely candidate.

DNA is repaired by different pathways depending on the nature of the damage. Oxidation and alkylation of the nucleobases are typically repaired by base excision repair (BER), whereas bulky adducts are repaired by nucleotide excision repair (NER). Unrepaired lesions may be associated with single strand breaks (SSB), also named chromatid-type aberrations (CTA). Two major pathways, homologous recombination (HR) and non-homologous end joining (NHEJ) are involved in the elimination of double strand breaks (DSB or CSA) where HR is most active in the late S/G_2 phase of the cell cycle [7]. Methylenetetrahydrofolate reductase (MTHFR), a key enzyme in folate metabolism, is thought to influence DNA methylation and synthesis leading to single and double strand breaks. Two common functional polymorphisms are known in the *MTHFR* gene (for review see [8]).

Within the CancerRiskBiomarkers framework (EU contract No. QLKA-CT-2000-00628) it was decided to study the influence of polymorphic genes on the repair of CTA and CSA when controlling for *MTHFR* polymorphism.

Information about the possible influence of genetic polymorphism of DNA repair genes on cytogenetic endpoints are emerging [9–16], but more information is still needed to verify the findings on larger populations. We report the effect of polymorphisms in the BER genes *hOGG1* (Ser^{326}Cys) and *XRCC1* (Arg1^{196}Trp, Arg^{280}His and Arg^{399}Gln), the NER gene *ERCC2* (Lys^{751}Gln), and the HR gene *XRCC3* (Thr^{241}Met) in addition to *MTHFR* (Ala^{222}Val) on CA, CSA, CTA, CTB (chromatid breaks not including exchanges) and CTG (chromatid gap) frequencies in a Norwegian population of 651 male subjects of Caucasian descent included in the CancerRiskBiomarker study. Some reports have shown an association with polymorphisms in these genes and the risk of cancer [17–22].

2. Materials and methods

2.1. Subjects

The study population included 310 male subjects from the ESCH cohort, and another 341 male subjects who were scored for CA after the ESCH data base was closed, altogether 651 subjects. Of the 310 subjects, 29 had a cancer diagnosis at the latest follow-up in year 2000. For the remaining 341 subjects no information on cancer is available. Age, smoking habits, occupations and date of sampling were recorded. The mean age of the subjects was 41 years (range 18–71). Only 9 subjects were below 20 and 8 were above 65 years of age. Fifty percent were smokers, and 47% of the participants were included because of possible exposure to clastogenic/carcinogenic agents at work. Some of these studies were performed in order to verify that the exposure level was so low that no CA could be expected to be caused by the exposure. The main occupational exposures, with number of subjects in brackets, were: stainless steel welding fumes (114) [23,24], vinyl chloride (35) [25,26], vapours of naphthenic oils of low and high viscosity (30) [27], electromagnetic field exposure (37) [28,29], acrylamide (25) [30], mercury vapour (30) [31], aluminium (27), lead (8), styrene (19) [32], and various solvents (21). Written informed consent was obtained from all subjects. The Regional Ethics Committee and the Data Inspectorate approved the study.

2.2. Cytogenetic analysis

Phytohemagglutinin stimulated lymphocyte cultures from heparinized whole blood were used according to methods