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RESEARCH ARTICLE

Effects of DNA repair gene polymorphisms on DNA damage in human lymphocytes induced by a vinyl chloride metabolite *in vitro*

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Abstract

Background: Epidemiologic studies suggest that variability in DNA damage from vinyl chloride monomer (VCM) may be partially mediated by genetic polymorphisms in DNA repair. This study aimed to corroborate these observations with controlled experiments *in vitro* using cell lines from individuals with differing DNA repair genotypes to determine damage following VCM metabolite exposure.
Methods: Matched pairs of lymphoblast cell lines (homozygous wild-type versus homozygous variant for either XRCC1 399 or XPD 751 polymorphism) were exposed to chloroacetaldehyde and analyzed by the cytokinesis-block micronucleus assay.
Results: All cell lines demonstrated a dose–response of increasing micronuclei with increasing exposure, but for both XRCC1 and XPD, the polymorphic cells peaked at higher micronucleus frequencies and declined at a slower rate to baseline than the wild-type cells.
Conclusion: This supports the findings that XRCC1 and XPD polymorphisms may result in deficient DNA repair of VCM-induced genetic damage.

Keywords

DNA repair, micronuclei, polymorphisms

History

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Introduction

Vinyl chloride monomer (VCM) is one of the highest production volume chemicals globally (approximately 16 billion pounds annually) used primarily for the production of polyvinyl chloride plastics (ATSDR, 2006). The carcinogenicity of VCM in humans has been well established since at least 1974 based on its association with angiosarcoma of the liver in occupationally exposed workers (Creech & Johnson, 1974; Heath et al., 1975; Lange et al., 1974). As a result, the International Agency for Research on Cancer classified VCM as a group I carcinogen in 1987 and re-affirmed this conclusion in 2008 (IARC, 2008). Additional epidemiological studies of exposed workers provided further support for this link (Lelbach, 1996; Mundt et al., 2000; Ward et al., 2001), and the mechanism of VCM-related carcinogenesis has been at least partially elucidated (Brandt-Rauf et al., 2000). Early studies demonstrated that VCM is primarily metabolized in the liver by a cytochrome P450 (CYP2E1) into the reactive intermediates chloroethylene oxide (CEO) and chloroacetaldehyde (CAA) (Bartsch et al., 1979). Both of these metabolites interact with DNA to form mutagenic etheno-DNA adducts that can result in various types of DNA damage, including micronuclei formation, sister chromatid exchanges and mutations in oncogenes and tumor suppressor genes (ATSDR, 2006). These various types of DNA damage have been seen with increased frequency in different cohorts of VCM-exposed workers (Brandt-Rauf et al., 2012). However, not all workers with the same levels of VCM exposure are found to have the same levels of DNA damage indicating variable susceptibility to its mutagenic effects. One possible contributing factor to this variability could be inherited differences in DNA repair capability due to polymorphisms in the genes encoding proteins involved in the repair pathways. Two proteins that have been studied in this regard are the X-ray cross complementing 1 (XRCC1) protein and the xeroderma pigmentosum D (XPD) protein (Brandt-Rauf et al., 2013). XRCC1 is critical in base excision repair (BER), which is known to be involved in the repair of etheno-DNA adducts, so its potential importance in VCM carcinogenesis is not unexpected. On the other hand, XPD is critical in nucleotide excision repair (NER), which might not normally be expected to have an impact on the repair of etheno-DNA adducts. However, although BER is known to be efficient in the repair of etheno-A and etheno-C adducts, it is much less efficient for the repair of etheno-G adducts (Dosanjh et al., 1994), and the epidemiologic studies of VCM-exposed workers found that polymorphisms in XRCC1 had an apparent impact on biomarkers of etheno-A induced DNA damage but not

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on biomarkers of etheno-G induced DNA damage, whereas polymorphisms in XPD did have an apparent impact on biomarkers of etheno-G induced DNA damage (Brandt-Rauf et al., 2013). Thus, polymorphisms in both XRCC1 and XPD have been examined in subsequent studies of VCM carcinogenesis.

XRCC1 is mapped to human chromosome 19q13.2 (Thompson, 1991). As a part of the BER machinery, XRCC1 acts as a scaffold for complexing with apurinic/apyrimidinic endonuclease (APE1), DNA polymerase β (Pol β), DNA ligase III (Lig III), and poly-ADP-ribose polymerases (PARP-1 and PARP-2) in the repair of abasic sites that result from the removal of damaged DNA bases (such as VCM-induced etheno-DNA adducts) by specific DNA glycosylases (Caldecott, 2003; Thompson & West, 2000). There are several polymorphic variants of XRCC1, including at codons 194, 280 and 399, with the codon 399 variant being the most common and best studied. In this variant, the normal Arg at codon 399 is replaced by Gln. Several studies have associated the XRCC1 399 variant with an increased risk for cancers, including head and neck cancer (Sturgis et al., 1999), lung cancer (Divine et al., 2001), colorectal cancer (Abdel-Rahman et al., 2000) and breast cancer (Duell et al., 2001), although the results overall have been mixed (Hu et al., 2005; Hung et al., 2005). In addition, *in vitro* studies have observed evidence of potentially decreased DNA repair activity following micro-irradiation in cells with the XRCC1 399 variant compared to those that are wild-type (Hanssen-Bauer et al., 2012).

XPD is mapped to human chromosome 19q13.2-13.3 (Chen & Suter, 2003; Lehmann, 2001). In NER, XPD acts as an ATP-dependent 5′-3′ helicase that functions as a subunit of the transcription factor IIH complex (TFIIH) to promote DNA bubble formation at the damaged site (usually bulky DNA adducts) by unwinding the DNA (Wood et al., 2001). As with XRCC1, there are several polymorphic variants of XPD, including at codons 199, 312 and 751, with the codon 751 variant being the most common and best studied. In this variant, the normal Lys at codon 399 is replaced by Gln. Several studies have associated the XPD 751 variant with an increased risk for cancers, including head and neck cancer (Sturgis et al., 2000) and lung cancer (Chen et al., 2002), although the results overall have been mixed (Manuguerra et al., 2006; Wang et al., 2008). In addition, *in vitro* studies have observed evidence for potentially decreased DNA repair activity following UV exposure in cells with the XPD 751 variant compared to those that are wild-type (Qiao et al., 2002).

Molecular epidemiology studies in China have investigated genetic polymorphisms of DNA repair genes, including XRCC1 and XPD, and DNA damage in VCM-exposed workers by using the cytokinesis-block micronucleus (CBMN) assay as the biomarker (Qiu et al., 2011; Wang et al., 2013). The frequency of micronuclei (MN) in peripheral blood lymphocytes has been extensively used as a biomarker of chromosomal damage in workers occupationally exposed to many different carcinogens and shown to be a reliable method for measuring such DNA damage (Bonassi et al., 2005; Hagmar et al., 2001). Similarly, the results of the studies in Chinese VCM workers have suggested an increased frequency of MN in peripheral lymphocytes with VCM exposure, and this effect appeared to be increased in individuals with common genetic polymorphisms in XRCC1 (such as Arg → Gln at amino acid residue 399) and XPD (such as Lys → Gln at amino acid residue 751).

The aim of the current study was to provide the biological plausibility for these epidemiologic observations using controlled experiments *in vitro* by examining the frequency of MN formation following CAA exposure in cultured lymphoblasts from individuals who are either homozygous wild-type or homozygous polymorphic for codon 399 of XRCC1or codon 751 of XPD.

Materials and methods

Cell culture

Immortalized human lymphoblast cell lines established by routine transformation techniques with Epstein-Barr virus were obtained from two sources. One source was the previously described cohort of VCM-exposed workers in France who had been genotyped for XRCC1 and XPD polymorphisms (Li et al., 2009; Smith et al., 1998). From these worker cell lines, 10 lines were selected for study: five were homozygous wild-type (Arg-Arg) and five were homozygous polymorphic (Gln-Gln) for XRCC1 codon 399. These two genotype groups were otherwise similar in terms of demographic characteristics (age, gender, ethnicity) and other relevant genotypes, i.e. CYP2E1, XPD codons 312 and 751, and XRCC1 codons 194 and 280 (all homozygous wild-type except for one wild-type XRCC1 cell line that was heterozygous for XPD). The second source of cells was a previously described cohort of participants in the Metropolitan New York Registry of Breast Cancer Families (Kennedy et al., 2005; Machella et al., 2008). From these registry cell lines, six lines were selected for study: three that were homozygous wild-type (Lys-Lys) and three that were homozygous polymorphic (Gln-Gln) for XPD codon 751. These two genotype groups were otherwise similar in terms of demographic characteristics (age, gender, ethnicity) and other relevant genotypes, i.e. CYP2E1, XRCC1 and XPD codon 312 (all wild-type). All cell lines were cultured in RPMI 1640 medium (Cellgro, Manassas, VA) supplemented with 10% fetal bovine serum (FBS; Gibco, Grand Island, NY) and 1% penicillin/streptomycin (Cellgro, Manassas, VA) at 37 °C in a humidified atmosphere containing 5% CO_2.

CAA treatment

For each cell line, 1×10^6 cells were suspended in 1 ml RPMI 1640 medium and exposed to CAA (Sigma-Aldrich, St. Louis, MO) at concentrations of 0, 1.5 and 2.0 μg/ml at 37 °C for 1 h; these exposure levels were adapted from those used previously (Chiang et al., 1997) to achieve maximal mutagenic effect. Following exposure, the media was removed and the cells were rinsed twice with phosphate-buffered saline (PBS). The cells were then seeded into six-well plates with a density of 0.5×10^6 cells and cultured in RPMI 1640 medium supplemented with 10% FBS and 1% penicillin/streptomycin at 37 °C with a humidified atmosphere containing 5% CO_2 for 1–6 d to allow for recovery and repair prior to assaying for DNA damage.

Cytokinesis-block micronucleus (CBMN) assay

Cells were analyzed for DNA damage by the CBMN assay performed according to standard methods as described previously (Fenech, 2000) at seven time points: pre-exposure baseline, 1, 2, 3, 4, 5 and 6 d post-exposure. In brief, recovered cells were seeded into a 48-well plate at a density of 1×10^6 cells per well and incubated at 37 °C with 5% CO_2. Cytochalasin-B (Enzo, Farmingdale, NY) was added to each cell culture at a final concentration of 4.5 μg/ml to block cytokinesis. Twenty four hours after the addition of the cytochalasin-B, cells were harvested by cytocentrifugation onto slides (with two wells per slide for each sample collection), treated with 0.075 M KCl hypotonic solution for 15 min and fixed using methanol and acetic acid at a ratio of 3:1. Slides were air-dried and stained with 10% Giemsa (Sigma-Aldrich, St. Louis, MO) in PBS, pH 6.8, for 5 min. For each slide, 1000 bi-nucleated lymphocytes with well-preserved cytoplasm were scored blindly by the same reader.

Statistical methods

All statistical analyses were done using SPSS software package (version 16.0, Chicago, IL). Statistical differences were calculated by the Wilcoxon Signed Rank test or the Mann–Whitney test, and $p < 0.05$ was considered to be statistically significant.

Results

MN frequencies of cells induced at different CAA levels

In general, for all cell types, there was an apparent dose–response of increasing MN frequencies with increasing CAA levels. The MN frequencies of the XRCC1 wild-type and polymorphic cells for the low-level (1.5 μg/ml) and high-level (2.0 μg/ml) CAA treatment groups are shown in Figure 1. The MN frequencies of the XRCC1 wild-type cells were statistically significantly elevated compared to the controls ($p < 0.05$) on day 1 for the high-level treatment group and on days 2 and 3 for both treatment groups. The MN frequencies of the XRCC1 polymorphic cells were statistically significantly elevated compared to the controls ($p < 0.05$) on days 1, 2 and 3 for both treatment groups and on day 4 for the high-level treatment group. The MN frequencies of XRCC1 wild-type and polymorphic cells at both CAA doses reached a maximum at 1–2 d post-recovery at a level that was approximately 2-fold higher than control cell levels for the low-level treatment group and approximately three to 4-fold higher for the high-level treatment group (with the polymorphic cells peaking at higher levels than the wild-type cells in both groups). The MN frequencies of the XPD wild-type and polymorphic cells treated with CAA at different levels are shown in Figure 2, and similar trends are apparent. For example, the MN frequencies of the XPD wild-type cells were statistically significantly elevated compared to the controls ($p < 0.05$) on day 1 for the high-level treatment group, on day 2 for both treatment groups, and on day 3 for the low-level treatment group. The MN frequencies of the XPD polymorphic cells were statistically significantly

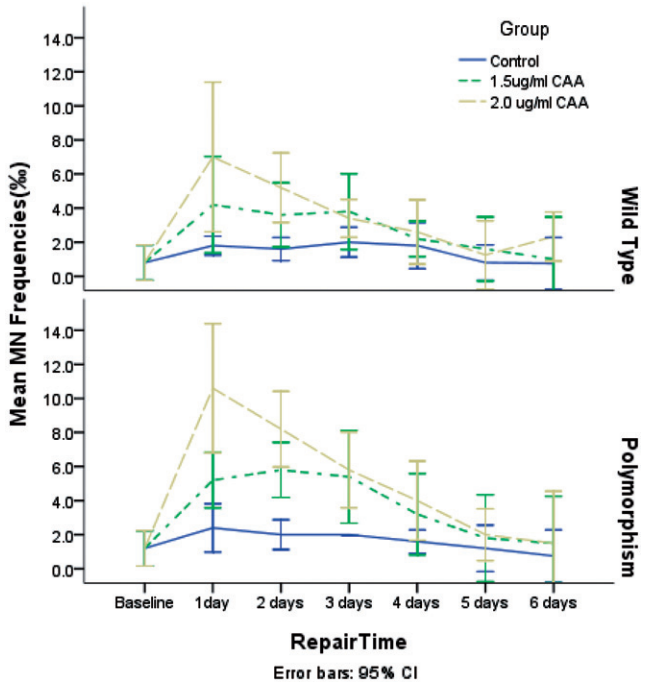

Figure 1. MN frequencies of XRCC1 wild-type and polymorphic cells treated with CAA at different levels.

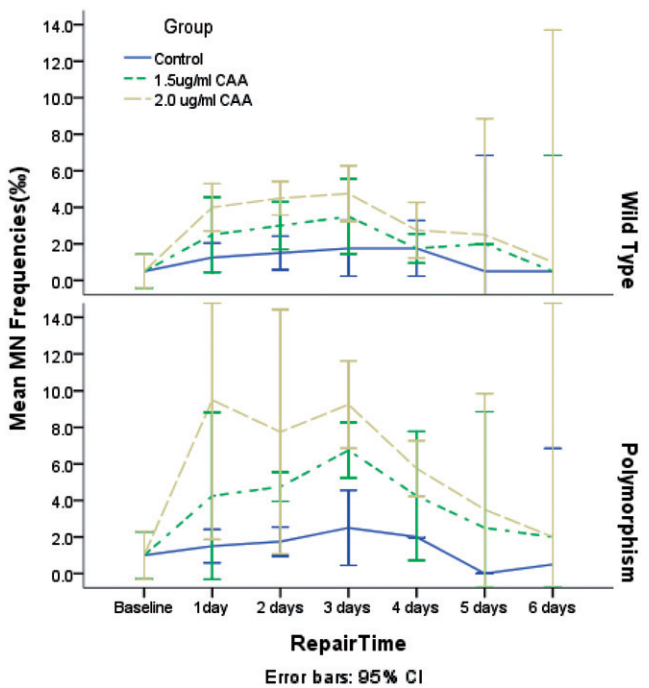

Figure 2. MN frequencies of XPD wild-type and polymorphic cells treated with CAA at different levels.

elevated compared to the controls ($p < 0.05$) on days 1, 2 and 3 for both treatment groups and on day 4 for the high-level treatment group. The MN frequencies of XPD wild-type and polymorphic cells at both CAA doses reached a maximum at 1–3 d post-recovery at a level that was approximately 2.5-fold higher than control cell levels for the low-level treatment group and three to 6-fold higher than control cell levels for the high-level treatment group (with the polymorphic cells peaking at higher levels than the wild-type cells in both groups).

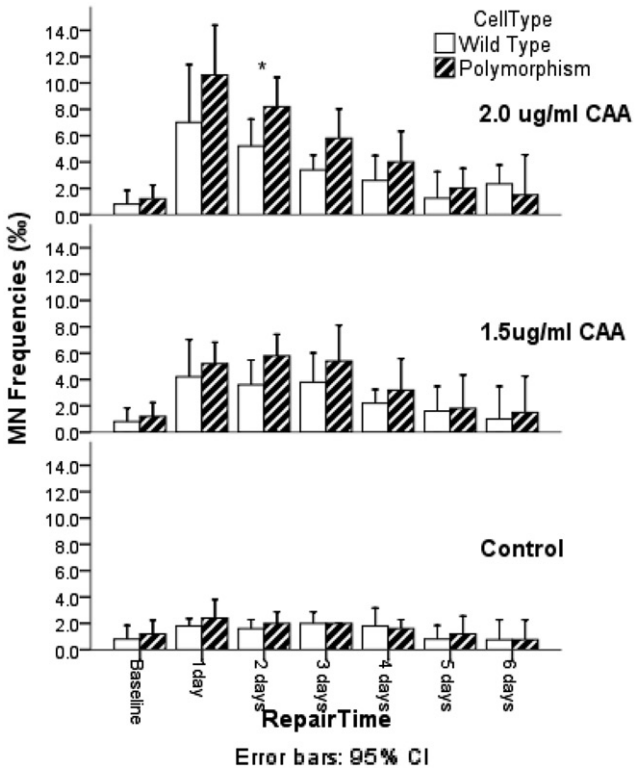

Figure 3. MN frequencies of XRCC1 wild-type and polymorphic cells treated with CAA at different levels (*$p < 0.05$ compared with the wild-type using the Mann–Whitney test).

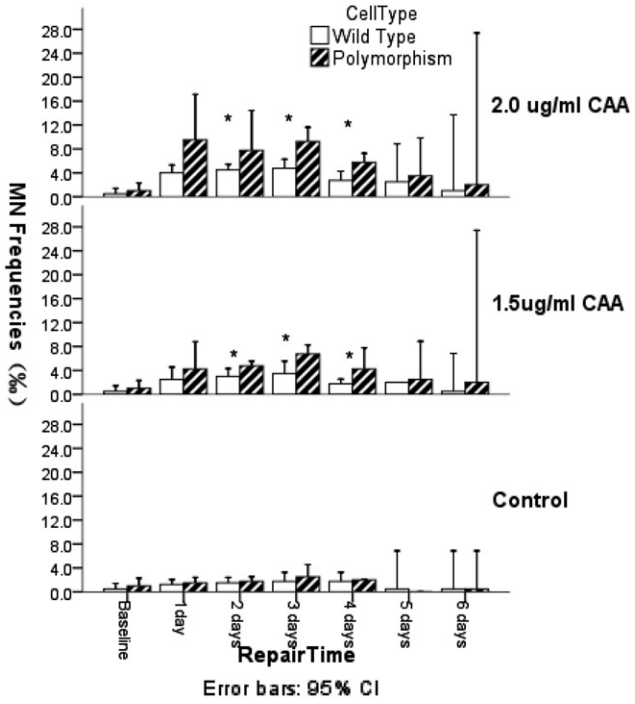

Figure 4. MN frequencies of XPD wild-type and polymorphic cells treated with CAA at different levels (*$p < 0.05$ compared with the wild-type using the Mann–Whitney test).

MN frequencies of polymorphic compared with wild-type cells

In general for all cases, the polymorphic cells reached higher maximum MN levels and declined to baseline MN levels over longer time periods than the wild-type cells. These differences between wild-type and polymorphic cells are underscored by comparisons of MN levels at individual time points. The results for XRCC1 are presented in Figure 3. At the 1.5 μg/ml CAA level, the MN frequency of the XRCC1 polymorphic cells after 2 d of recovery was greater than that of the wild-type cells, but this was not quite statistically significant ($p = 0.055$). However, at the 2.0 μg/ml CAA level, the MN frequencies of the XRCC1 polymorphic cells after 2 d and 3 d of recovery were borderline or statistically significantly higher than those of the wild-type cells, ($p = 0.033$ and $p = 0.053$, respectively). The results for XPD are presented in Figure 4. The MN frequencies of the XPD polymorphic cells after 2, 3 and 4 d of recovery were statistically significantly higher than those of the wild-type cells at both the 1.5 μg/ml CAA level ($p = 0.025$, $p = 0.020$, $p = 0.046$, respectively) and the 2.0 μg/ml CAA level ($p = 0.036$, $p = 0.019$, $p = 0.019$, respectively).

Discussion

These results suggest that the XRCC1 and XPD polymorphisms can have a significant effect on the ability of cells to repair DNA damage caused by an active metabolite of VCM. These results are consistent with both epidemiologic and experimental studies of the effect of DNA repair polymorphisms on genetic damage from exposure to VCM or its metabolites.

Epidemiologic studies of VCM-exposed workers have demonstrated these effects on the occurrence of several general biomarkers of DNA damage as well as specific mutational biomarkers induced by VCM. For example, the XRCC1 399 polymorphism has been associated with increased DNA damage as detected by sister chromatid exchange (homozygous polymorphic versus heterozygous + homozygous wild-type, $p = 0.03$) (Wong et al., 2003) or by CBMN as noted (homozygous polymorphic versus homozygous wild-type, FR = 1.23, 95% CI = 1.08–1.40) (Wang et al., 2013) in VCM-exposed workers. Similarly, the XPD 751 polymorphism has been associated with increased DNA damage as detected by single strand breaks (heterozygous + homozygous polymorphic versus homozygous wild-type: OR = 2.21, 95% CI = 1.01–5.13) (Zhu et al., 2005), the Comet assay (heterozygous + homozygous polymorphic versus homozygous wild-type, $p < 0.05$) (Ji et al., 2010), and CBMN as noted (heterozygous + homozygous polymorphic versus homozygous wild-type, FR = 1.2, 95 %CI = 0.98–1.45) (Qiu et al., 2011) in VCM-exposed workers.

VCM exposure has also been associated with more specific mutational biomarkers of the K-ras and p53 oncoproteins which are also affected by XRCC1 and XPD polymorphisms (Brandt-Rauf et al., 2012, 2013). For example, as noted CAA and CEO are known to generate etheno-DNA adducts, and the etheno-G adduct produces an oncogenic mutation (G → A) in the K-ras protein while the etheno-A adduct produces oncogenic mutations (A → T) in the p53 protein, both of which are detectable as circulating biomarkers in VCM-exposed workers. In these workers, the XPD 751

polymorphism has been shown to have a statistically significant independent effect on the K-ras mutational biomarker (homozygous polymorphic versus homozygous wild-type: OR = 2.6, 95% CI = 1.5–4.6), and the XRCC1 399 polymorphism has been shown to have a statistically significant independent effect on the p53 mutational biomarker (homozygous polymorphic versus homozygous wild-type: OR = 1.9, 95% CI = 1.1–3.3).

These finding have been further supported by laboratory studies. For XRCC1, molecular modeling studies demonstrate that the 399 substitution produces significant conformational changes in the protein, including the loss of secondary structural features such as α-helices, that could affect its ability to interact with other components of the BER complex; studies of cultured lymphoblasts from individuals of different genotypes exposed to the reactive metabolites of VCM showed that cells with the homozygous polymorphic 399 genotype have an approximate 4-fold decrease in efficiency of repair of etheno-A DNA adducts compared to homozygous wild-type cells, resulting in a 1.8-fold increase in the mutation frequency in the polymorphic cells as measured by the HPRT assay as well as a change in the mutational spectrum to increased A → T transversions (50% in the polymorphic cells versus 19% in the wild-type) similar to the patterns in the exposed workers. For XPD, molecular modeling studies similarly demonstrated conformational changes in the polymorphic protein which could affect its function by interfering with its interaction with other components of the NER complex; also, studies of cultured lymphoblasts from individuals of different genotypes exposed to the reactive metabolites of VCM showed that cells with the homozygous polymorphic 751 genotype have an approximate 5-fold decrease in efficiency of repair of etheno-G DNA adducts compared to homozygous wild-type cells, resulting in a 4.8-fold increase in the mutation frequency similar to the patterns in the exposed workers.

Taken together, these prior studies strongly suggest an important role for BER and NER in the pathogenic pathway of VCM-induced genetic damage, and the potential significance of polymorphisms in these pathways, particularly XRCC1 and XPD, in the mediation of the carcinogenic effects of VCM exposure. Our current results are consistent with these studies and specifically provide biologic plausibility to support the findings of epidemiologic studies, indicating this modulating genetic effect on the occurrence of the CBMN biomarker in VCM-exposed workers. Furthermore, since these DNA repair polymorphisms are quite common in most human populations, these results could have much broader significance for understanding susceptibility to many other mutagenic exposures and risk of occurrence of many other human cancers.

Declaration of interest

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