The oxidative phenotype of DBQ was determined by giving a 10 mg Declinax tablet at 22:00 hours. Urine of the following eight hours was collected. DBQ and its main metabolite, 4-OH-DBQ, was measured by chromatography and metabolic ratio (MR = excreted DBQ/excreted 4-OH-DBQ) was calculated. Subjects with MR ≤ 1.2:6 were classified as EM and those with MR > 12:6 were classified as PM of DBQ. Four patients (5.1%) and 42 controls (5.0%) were PM of DBQ (no significant difference). No differences were observed when comparing MR values by gender. When analysing separately EM subjects of both groups (figure), Log10 of MR values were normally distributed (Kolmogorov-Smirnov test) and were significantly lower (p<0.001, U Mann-Whitney’s test) in controls (mean = 0.295, SD = 0.427) than in patients (mean = 0.085, SD = 0.388), indicating a higher hydroxylation ability in the control group.

No relationship exists between oxidative phenotype of DBQ and the risk of developing RA. Nevertheless, the EM phenotype includes two genotype, the heterozygote and the homozygote for the dominant-functioning wild-type allele. Heterozygotes carry one of the three existing non-functioning mutant recessive alleles, A, B, or D. Heterozygote EMs tend to have lower MR values for than heterozygote EMs, indicating that they are more efficient oxidizers than heterozygote EMs, suggesting a gene-dose effect. Nevertheless, there is a broad overlap of Log10 of MR values between both EM genotypes (figure) that makes it impossible to classify individually EMs as homo or heterozygous only in the basis of their values for MR.

Our results suggest that there is an excess of heterozygote EMs patients with RA. The mean age in our control group was much lower than in patients, but age does not influence the metabolic rate of DBQ in otherwise healthy subjects. Many patients were taking NSAIDs and/or low dose prednisolone when they were phenotyped, but these drugs do not seem to modify the oxidation of DBQ.

We conclude that the possible excess of any recessive-mutant allele(s) of the CYP2D6 gene we have detected among patients with RA should be confirmed by using genotyping procedures to establish which, if any, allele is linked to the risk of RA.

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