INTRODUCTION

While heavy episodic drinking has been shown to be harmful to the heart, moderate alcohol consumption is thought to be protective against cardiovascular disease, through the regulation of rising HDL cholesterol levels. The cardio-protective effect of alcohol is now not thought to vary by beverage type. In fact, evidence for an additional cardio-protective effect of antioxidant polyphenols in red wine is weak.

The study of genetics variants of the alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) genes involved in alcohol metabolism is important to understand the patterns of drinking habits and its effects in stroke susceptibility. The enzyme alcohol dehydrogenase (ADH), which oxidizes alcohol to acetaldehyde, has proven to play an important role in alcohol metabolism. Seven genes encoding ADH are found in a tight cluster on chromosome 4 and some are polymorphic in white European populations. More active variants of ADH cause higher concentrations of acetaldehyde in the body following alcohol consumption and are therefore protective against drinking. Functional variants in both ADH1B and ADH1C have been associated with alcohol consumption or alcohol dependence. The ADH1B variant (rs1229984) has emerged as the most strongly associated with alcohol phenotypes and is therefore the most suitable instrument for Mendelian randomization studies in Europeans. The A allele has an allele frequency of approximately 2.5% in Europeans and plays a protective role against heavy drinking because it confers an higher alcohol metabolic rate and consequent accumulation of toxic acetaldehyde.

Hence we analyzed if a possible association of the SNP rs1229984 with stroke susceptibility is mediated by the patterns of alcohol consumption.

RESULTS

The SNP met quality control criteria and was further evaluated. Genotyping results are shown in Table 2. AA and AG genotypes were taken together for further analysis to enable a better statistical analysis. Association analysis between these two variables was performed and its results are shown in Table 3.

On the associations analysis with significant results (genotype-stroke-alcohol consumption-stroke consumption), we tested whether the third variable (genotype and stroke, respectively) was modifying the observed effect. As Tables 4 and 5 illustrate alcohol consumption modifies the association genotype-stroke (P=0.008) with excessive alcohol consumption playing the largest effect on this modification (P=0.034). Genotype also modifies the association alcohol consumption-stroke (P=0.04).

DISCUSSION AND CONCLUSIONS

(1) In this study we did not find an association between the SNP rs1229984 and alcohol phenotype, further studies in larger populations are needed to confirm these results. Also it would be interesting to observe whether the activity of ADH1B varies within groups of individuals sharing the same genotype, which might influence individual alcohol tolerance.

(2) We tested whether the amount of alcohol consumed was modifying the association genotype-stroke and we observed, as expected, that heavy drinking increases in about four times (OR=4.17) stroke risk in the group of A allele non-carriers. On the other hand, A carriers present a decrease to about half (OR=0.46) stroke risk despite the excessive alcohol consumption, which suggests that the A allele plays a protective role on stroke susceptibility. Further studies are needed to validate the same trend in groups of individuals with lighter alcohol consumption.

(3) We confirmed the importance of alcohol as a stroke risk factor. While moderate consumption appears to be protective (OR=1), heavy drinking is potentially harmful (OR=4), as previously mentioned. However, when testing whether the genotype was modifying the association alcohol consumption-stroke, we observed a protective role of A allele, which is consistent with previous results. In fact, considering individuals with none or moderate alcohol consumption, A carriers show a decreased stroke risk when compared with non-carriers (0.85; OR=0.85 to 0.92; OR=0.92), (A allele carriers are a 9.2% risk reduction). Individuals consuming excessive amounts of alcohol, despite an increased stroke risk, have larger probability of developing an event if they are A non-carriers (A carriers = 1.92 vs OR non-carriers = 4.17).

In conclusion, A allele of the SNP rs1229984 appears to be protective against stroke. However, further studies are needed to replicate these results in other populations. Because the associations analyzed are complex, fundamental studies including other relevant genetic variants, such as ALDH, should be performed. Physiological studies including variables such as hypertension and hypercholesterolemia would also be interesting.