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Short Communication

Genetics, odor perception and food liking: The intriguing role of cinnamon

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ABSTRACT

Humans use a repertoire of > 400 olfactory receptors (ORs) to perceive odorants. The sense of smell is a complex trait whereby genetics and environmental factors interplay. To date, still little is known regarding the genetics of smell, even though the high genetic variability of ORs genes has already been demonstrated. Recently a significant association between cinnamon odorant recognition and the rs317787 polymorphism, located in a cluster of OR genes, has been described. Based on this data, here, we replicated the effect of the same variant (rs317787) on cinnamon odorant identification as well as looked at any possible association with liking for wine whose bouquet frequently smells of cinnamon. Our analysis in a cohort of individuals from two Italian genetic isolates confirmed that rs317787-T allele is associated with an improved cinnamon detection (p-value 5.18×10^{-06} , n = 971) but also with a greater liking for red wine (p-value 0.017, n = 2374). Present results further confirm the association of rs317787 SNP and cinnamon odorants detection and provide additional details about the role of the ORs genes in food liking. Overall, our work contributes to better deciphering the genetic basis of smell and food liking aimed at a more in-depth elucidation of the role of the ORs genes.

1. Introduction

Individual food preferences, being the major drivers of food choice, are important predictors of food intake. They are influenced by many factors such as culture, food availability, nutritional aspects and genetics. Among genetic factors, chemosensory genes play a crucial role and have been well investigated by researchers (Díószegi et al., 2019; Hayes et al., 2013). The most notable example regards *TAS2R38* gene, a major contributor to individual differences in bitter taste perception. In particular, it is well known that variations among *TAS2R38* gene correlate with preferences for different bitter foods such as brassica vegetables, alcoholic beverages, but also spicy foods, sweets and added fat.

Another important factor influencing food liking and preferences could be played by OR genes (Hayes et al., 2013). Although odour perception impacts food preferences, the effect of ORs genetic variation on the sensory perception of food and food preferences remain unclear. Previous studies revealed associations with odors' perception for a few canonical OR loci (Gisladdottir et al., 2020). For example, it is well known the role of two variants (rs61729907 or R88W, and rs5020278 or T133M) within *OR7D4* gene which impair the individual ability to perceive androstenone (5 α -androst-16-en-3-one) (Keller et al., 2007). In

particular, Lunde and colleagues (Lunde et al., 2012) found that *OR7D4* variants are associated with sensory perception and preferences of pork meat containing androstenone (i.e., androstenone is naturally present in the meat of male pigs).

In general, the sense of smell is critical for a variety of functions enabling us to interact with the surrounding environment. The interplay between genes and environment gives everyone a unique sense of smell, and a reduced odor intensity or perception results in a loss of critical information. Human beings use a family of > 400 OR genes to detect odors. These genes are characterised by a high genetic variability which can modulate OR responses. Understanding how the olfactory system detects odorants and translates their features into perceptual information is one of the fundamental questions in olfaction and might have severe implications in associated diseases. In fact, smell dysfunction has been already identified as a potential biomarker of neurodegenerative diseases (e.g., Parkinson's and Alzheimer's) but also as a typical sign for SARS-Cov2 infection (Meinhardt et al., 2021).

Very recently, Gisladdottir and colleagues (Gisladdottir et al., 2020) carried out a genome-wide scan of 11,000 Icelanders, phenotyped through the Sniffin' Sticks smell test, identifying a significant association between the rs317787 polymorphism in *OR51B5* gene and cinnamon odor.

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Here, we analysed 2374 individuals coming from two Italian isolates (i.e., Friuli Venezia Giulia (FVG) and Val Borbera (VBI)) for replication of rs317787 with cinnamon smell perception and we searched for any association with wine preferences. The rationale behind this choice is that a significant proportion of wines are rich in cinnamon fragrance at the olfactory and taste-olfactory level. In particular, the scent and flavour of cinnamon is generated by the corresponding chemical substance “cinnamaldehyde” (<https://cosylab.iitd.edu.in/flavordb/>) due to the wine ageing in wooden barrels. This fragrance/flavour is typical of red grapes varieties such as Dolcetto and Barbera (typical of VBI) or Merlot and Cabernet Sauvignon (FVG), and also of white grapes varieties such as Timorasso (VBI) or Friulano, Chardonnay, Verduzzo, Sauvignon and Ribolla Gialla (FVG).

2. Materials and methods

2.1. Participants

Two thousand three hundred seventy-four individuals belonging to the Italian Network of Genetic Isolates (INGI) were included in the study (i.e., 1240 from FVG and 1134 from VBI). A detailed description of these populations has been previously reported (Cocca et al., 2020). All participants gave written informed consent, and the study was approved by the ethical committees of the Institute for Maternal and Child Health – IRCCS Burlo Garofolo (Trieste, Italy) and IRCCS San Raffaele (Milan, Italy). All research was conducted according to the ethical standard as defined by the Helsinki Declaration.

2.2. Data collection

The smell functionality of each subject was evaluated through the “Sniffin’ Sticks test” (Screening 12 test, Burghardt Messtechnik GmbH, Wedel, Germany) a smell discrimination test which contains 12 “Sniffin’ sticks”, felt-tip pens with precise odorants to be recognized (Hummel et al., 1997). Only information about cinnamon odorant was used in this work.

As regards red and white wine liking, it was assessed through a food and beverages questionnaire (without any tasting), rating the liking on a 9-point scale (Concas et al., 2019).

2.3. Genotyping and imputation

All samples have been genotyped with Illumina 370–700 K high-density SNP array and imputed considering as reference a custom panel generated merging the 1000 Genomes phase 3 (Abecasis et al., 2012) and whole-genome sequences of samples. More details are reported in our previous work (Cocca et al., 2020).

2.4. Statistical analysis

The information about the Single Nucleotide Polymorphism (SNP) rs317787 was extracted.

A binary variable with value 0 for individuals that correctly identified cinnamon and 1 for those that failed has been defined for statistical analysis.

To verify the effect of the SNP on cinnamon discrimination and wine liking, association analyses were conducted in FVG and VBI populations separately, using mixed linear models as implemented in GEMMA (Zhou and Stephens, 2012). An additive model was applied, adjusted by sex and age, and genomic kinship matrices were used as random effects to take into account relatedness. Meta-analysis was performed using an inverse-variance method (METAL) (Willer et al., 2010). To better understand the impact of the SNP on cinnamon recognition error, we transformed the effect size to the Odds Ratio using LMOR (Lloyd-Jones et al., 2018).

The nominal p-value threshold of 0.05 has been considered as a sign

of successfully replication and association.

3. Results

A total of 2374 (1240 for FVG and 1134 for VBI) individuals aged 18–90 years, were included in the study. Table 1 shows the characteristics of the samples.

In our dataset, the rs317787 was imputed and showed an Info Score > 0.96. It is located in the intronic region of *OR51B5* gene and, in agreement with previously published data, it has a Minor Allele Frequency (MAF) (T allele) of 32% in our populations (Gisladdottir et al., 2020).

Results of the genetic analysis aimed at detecting the effect of the SNP on cinnamon errors and wine liking are summarized in Table 2, while Table S1 showed the results in each population separately. The T allele is associated with a better cinnamon odorant discrimination (odds ratio 0.61, p-value 5.18×10^{-06}). Moreover, an additional association between rs317787-T and greater liking for red wine (beta 0.17, p-value 0.017) was found. A similar trend was also observed for white wine (overall beta 0.13, p-value 0.09; VBI: p-value 0.05843 (Table S1)).

Because of the presence of cinnamaldehyde in both cinnamon stick and wine, the relationship between cinnamon errors, liking for wine and SNP genotypes has been investigated. This analysis is limited to 969 individuals for whom the information about the Sniffin’ sticks test and liking for wines were available. No significant association between cinnamon smell errors and red or white wine liking (also splitting the sample by rs317787 genotypes) have been detected (T test or ANOVA p-value > 0.05). The results, summarized in Fig. S1, show that individuals that correctly identified cinnamon odorant compared to the others, presented a lower liking for red wine and a higher for white wine. Splitting the sample according to rs317787 genotypes, the same trend remained for each genotype group, except for heterozygous C/T individuals and white wine preference.

4. Discussion

In this work, the relationship between the rs317787 SNP located within *OR51B5*, a protein coding gene involved in olfactory transduction pathway and expressed in the human olfactory epithelium (Saraiva et al., 2019) and cinnamon odor identification has been replicated from previously published data (Gisladdottir et al. 2020). In addition, considering the presence of cinnamon scent/flavour in drink wines consumed by the investigated populations (FVG and VBI), the association between the same SNP and the liking for wine has also been checked, finding a significant relationship with the liking for red wine and an almost significant for the white wine liking.

In particular, in this study, in agreement with data from Gisladdottir et al., we observed that individuals carrying the T allele for the rs317787 SNP show a better cinnamon perception compared to the other subjects. The same T allele also display a more liking for red wine (p-value 0.017), and a similar trend was also observed for white wine (almost significant, p-value 0.09). Interestingly, the populations here investigated are known for being top wine producers, with many wines with a bouquet rich in cinnamon fragrance. Precisely, most of the wines (both white and red) of these regions are aged in wooden barrels, and this process confers

Table 1
Characteristics of individuals included in the study (n = 2374).

Characteristics	
Sex male, n (%)	1008 (42.5%)
Age, mean (SD)	53.39 (16.60)
Cinnamon odorant error, N (%) (n = 971)	248 (25.59)
Liking for red wine, mean (SD)	6.07 (2.50)
Liking for white wine, mean (SD) (n = 2353)	5.35 (2.48)

SD, standard deviation.

Table 2

Results of the associations between rs317787 and cinnamon odor recognition, red wine liking and white wine liking.

SNP	Chr:position	EA/OA	Gene	Coding effect	EAF	Phenotype	N	Effect (95% CI)	p-value
rs317787	11:5525543	T/C	OR51B5	intron	0.32	Cinnamon errors	971	0.61 (0.49,0.75) ^a	5.18x10 ⁻⁰⁶
						Red wine liking	2374	0.17 (0.03, 0.32) ^b	0.01724
						White wine liking	2353	0.13 (-0.02,0.28) ^b	0.09032

The position of the SNP is referred to Human genome reference build 37 (GRCh37). EA, effect allele; OA, other allele. EAF, effect allele frequency in the combined sample; SD, standard deviation. The effect is presented as odds ratio for cinnamon phenotype (a) and beta coefficients (b) for wine liking. 95% confidence intervals are provided in parenthesis. The p-value for heterogeneity between FVG and VBI was > 0.05 for each analysis.

them the typical scent/flavour of cinnamon corresponding to the chemical substance named cinnamaldehyde. As regards white wine, the almost significant p-value (0.058) detected in VBI cohort might be related to the presence of an autochthonous white grape variety named Timorasso, rich in cinnamon fragrance, that recently has been replanted in this valley.

No significant association between liking for wine and cinnamon odor recognition was found in our populations, suggesting that the SNP influences smell perception and liking for wine in an independent manner.

Our findings confirm the hypothesis of Gisladdottir et al. (2020) that rs317787 SNP, located within OR51B5 gene, could influence the perception of cinnamaldehyde molecule, present both in the cinnamon stick and in the wine (<https://cosylab.iitd.edu.in/flavordb/>). It is still unknown if this specific gene responds to cinnamaldehyde odorant, but eQTL studies showed a correlation between rs317787 SNP and another gene, named OR52D1, which has been already demonstrated as being a receptor for cinnamaldehyde ligand (Zou et al., 2012) (de March et al., 2015).

Here, for the first time, we reported an association between OR genes and liking for wine most likely linked to cinnamon odorant. To date, very few associations with flavour perception in wine were described; thus, it is worth mentioning the individual differences already detected for two particular molecules: *cis*-3-hexen-1-ol, that provides a green or fresh grassy note in white wines, and rotundone, that contributes to wine's peppery notes. As regards the *cis*-3-hexen-1-ol molecule, genetic studies (McRae et al., 2012) described the effect of two amino acid substitutions, T113A and R226Q, within the OR2J3 olfactory gene; these variants seem to impair the ability to respond to *cis*-3-hexen-1-ol. Instead, for rotundone, a molecule discovered in 2008, only few works are available: very recently, Gaby et al. (Gaby et al., 2020) reported the presence of individuals anosmic for this specific substance.

Overall, our findings confirm that variation in olfactory genes influences odor perception and support the role of rs317787 variant and its linked genes (OR51B5/OR52D1) with cinnamon perception. Moreover, we correlated the SNP mentioned above with red wine liking, providing additional evidence of the importance of odor perception in eating habits. Further studies are needed to elucidate the role of rs317787 and OR51B5, OR52D1 genes in cinnamon smell recognition and food liking.

Data availability

A subset of the data is already available on the European Genome-phenome Archive (EGA) at the following links:

FVG cohort: BAM files <https://www.ebi.ac.uk/ega/studies/EGAS00001000252>; sample list, vcf files <https://www.ebi.ac.uk/ega/studies/EGAS00001001597>; <https://www.ebi.ac.uk/ega/datasets/EGAD00001002729> ;

VBI cohort: BAM files <https://www.ebi.ac.uk/ega/studies/EGAS00001000398>; <https://www.ebi.ac.uk/ega/studies/EGAS00001000458>.

Author contributions

PG, GG, MPC: designed the study; MPC: analysed the data; GP collected smell test data; MPC, AM, GG, PG: wrote the manuscript. All

authors: read and approved the manuscript.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.foodqual.2021.104277>.

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