White Paper 23-08

Genetic Associations with Traits in 23andMe Customers

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Summary

Purpose: This white paper serves as a companion to 23andMe customer reports, offering more details and scientific support for the reported findings. We hope that the paper may also serve the scientific community to elaborate molecular pathways and contribute to the understanding of basic human biology and disease.
Methods: Customers submitted saliva for DNA extraction and testing using the 23andMe Personal Genome Service® (PGS®). The 23andMe PGS® uses a BeadChip array to probe over half a million genetic variants distributed across the entire human genome. Trait data were gathered through questions presented via the 23andMe website. Anonymized trait and genotype data were then combined to conduct a GWAS. Associations meeting the genome-wide significance criterion for each trait ($p < 5x10^{-8}$) are incorporated into customer reports.
Findings: We report the following trait associations:

- *Cilantro Aversion*: Two genetic loci are significantly associated with aversion to cilantro. Both loci are located in a cluster of olfactory receptor genes that have been linked with the ability to detect aldehyde odorants.
- *Sweet vs. Salty/Savory Taste Preference*: Two genetic loci that are significantly associated with the preference for sweet-tasting foods. These loci are located within the *FGF21* and *FTO* genes, both of which are associated with metabolism and body mass regulation.

Conclusions: We will continue to perform GWAS on a variety of traits and use data reported in this white paper to support customer reports. We will continue adding new trait associations to this white paper as more 23andMe GWAS results become available.

Introduction

The 23andMe Personal Genome Service® (PGS®) uses DNA extracted from customer saliva to give customers access to their genetic information. Customers are invited to answer questions about various traits and health conditions. Their anonymized survey responses and genetic data are combined to perform a genome-wide association study (GWAS).

By combining our large consented customer research database, web-based surveys, and custom GWAS tools, we routinely identify genetic associations for a variety of human traits. Some of these analyses have been used to replicate associations reported in the literature and to publish novel associations in peer reviewed journals [1–11].

This white paper details genetic associations that we have identified with the participation of 23andMe customers. It is intended to support customer reports that provide interpretations of personal genetic results. We will update this white paper over time as we add more customer reports.

Methods

Single-phenotype GWAS were conducted as described previously [6]. Relevant details and changes are described briefly below.

Study Participants

Study participants were 23andMe customers who had been genotyped as part of the 23andMe PGS®, consented to research, and voluntarily responded to web-based surveys. The study protocol and consent form were approved by the external Association for the Accreditation of Human Research Protection Programs-accredited Institutional Review Board, Ethical and Independent Review Services.

All study participants were required to have > 97% European ancestry, as determined by analysis of local ancestry [12]. The reference population data for ancestry analysis were derived from public datasets (the Human Genome Diversity Project, HapMap, and 1000 Genomes) and from 23andMe customers who have reported having four grandparents from the same country. At present, the database has the highest power to detect associations in cohorts of European ancestry.

We also required that participants were unrelated (sharing a smaller percent of the genome than the minimum expected for first cousins), as determined by a segmental identity-by-descent estimation algorithm [13].

Sample collection, DNA extraction, and genotyping

Participants provided their saliva using a specialized collection device, and mailed their samples to a CLIA-certified laboratory contracted by 23andMe. DNA extraction and 23andMe BeadChip genotyping were performed by the contracted laboratory [1,6]. All samples were genotyped on one of four versions of 23andMe BeadChips (produced by Illumina) that probe over half a million single nucleotide polymorphisms (SNPs) distributed across the entire human genome.

Trait data collection

Each GWAS presented in this paper is based on the response to one or more questions presented via the 23andMe website. Each question is designed to collect data about a specific trait or a set of related traits. Questions are typically multiple choice. The 23andMe self-report data gathered through such questions is statistically robust and replicable, as shown by a number of collaborator publications [3,6,9,11,14–16].

GWAS

Single-phenotype GWAS were conducted as previously described [6], except that no phasing or SNP imputation were done. Associations between genotyped SNPs and traits were estimated using logistic regression assuming additive allelic effects for binary traits (to calculate an odds ratio (OR)) and linear regression for quantitative traits (to calculate a regression coefficient β). The analysis was adjusted for age, sex, and the top five principal components to account for population structure. *P* values were computed using a likelihood ratio test. SNPs were excluded from the GWAS analysis if any of the following criteria were met: minor allele frequency < 0.1%, Hardy-Weinberg equilibrium test [17] $p < 10^{-20}$ in people of European ancestry, evidence of laboratory batch effects, or genotype call rate < 95%. SNPs were also excluded if they had large allele frequency discrepancies compared with European 1000 Genomes reference data, identified by computing a 2x2 table of allele counts of European 1000 Genomes samples and 2000 randomly sampled 23andMe customers with European ancestry, and identifying SNPs with a chi squared $p < 10^{-15}$. After GWAS analysis, *p* values were adjusted using genomic control (a factor of 1.092 for cilantro preference data, 1.227 for sweet preference data) to correct for statistical inflation [18]. SNPs with an association $p < 5 \times 10^{-8}$ were considered statistically significant.

Trait selection for reporting

For customer reports, we gave higher priority to associations that had larger effect sizes, identified novel phenotype associations, or had strong evidence for underlying biological mechanisms.

Data presentation

Association *p* values for all genotyped SNPs across all chromosomes are illustrated in a Manhattan plot. Compelling associations will have clusters of significantly associated SNPs at one or more chromosomal loci, with a few SNPs with highly statistically significant *p* values at each locus. Data quality was further assessed in the Q-Q plot, which plots observed quantiles of GWAS *p* values against expected quantiles of *p* values under a null distribution. To identify index SNPs, all SNPs with association $p < 10^{-5}$ were grouped into intervals separated by gaps of at least 250kb. The SNP with the lowest statistically significant *p* value in each interval was considered to be the index SNP for that region, and reported in Table 1. SNP positions are specified according to the NCBI Genome Reference Consortium human genome build 37 (GRCh37).

Associations identified by GWAS

Cilantro taste aversion

The *Coriandrum sativum* plant is commonly known as cilantro or coriander. It is used as an ingredient in various cuisines around the world, with historical references even found in ancient Roman texts [19–21]. However, some people describe cilantro taste as unpleasant and "soapy", and the prevalence of cilantro aversion appears to vary with ancestry [22]. The key chemical components responsible for cilantro aroma are thought to be aldehydes: unsaturated aldehydes are described as smelling "fruity" and (E)-2-alkenals are described as "soapy" [23–25]. These and many other odorants are detected by specialized odorant receptors, products of a family of about 400 functional human genes [26].

Genetic differences in odorant receptors have been shown to affect how we perceive tastes and smells [1,27–33]. To learn more about potential genetic associations, we assessed participants' perception of cilantro taste using a multiple-choice question with 3 answer options (in parentheses):

"Do you like the taste of fresh (not dried) cilantro?" (Yes/No/I'm not sure)

A total of 56,360 participants (74%) answered "Yes" and 19,731 participants (26%) answered "No". Participants who answered "I'm not sure" were excluded.

We identified 2 genomic loci that passed criteria for genome-wide association significance (summarized in Figure 1, detailed data in Table 1). Index SNPs for these loci, rs2741762 and rs3930459, lie in non-coding regions within a cluster of 56 olfactory receptor genes in chromosomal region 11p15.4 [34]. The A allele of rs2741762 ($p = 2.1 \times 10^{-14}$, OR = 1.1) and the C allele of rs3930459 ($p = 4.2 \times 10^{-13}$, OR = 1.1) are associated with higher odds of disliking the taste of cilantro.

We previously published a GWAS on cilantro preference using a smaller cohort of 23andMe customers. In that study, we identified a SNP (rs72921001) within 100kb of the OR6A2 olfactory receptor gene associated with perception of a "soapy taste" in cilantro [35]. The data described here represents a refinement of the earlier study methodology with a larger study cohort. The new GWAS identified SNPs within 10kb of the OR10A2, OR10A4, OR10A6, and OR10A3 genes and within 100kb of the OR6A2 gene (noted in the previous study). *OR6A2* is orthologous to the rat *I7* receptor gene [36–40]. The I7 receptor detects a range of n-aliphatic aldehyde odorants, including aldehyde components of cilantro aroma [25,34,37].

Sweet versus salty/savory taste preference

Human taste perception depends in part on taste receptors in buds on the tongue [41–43]. Sweet taste preference has approximately 50% heritability [44,45], meaning that genetic and non-genetic factors play an equal role. Studies in children and adults have shown that early childhood experiences and long-term exposures to dietary sugar or salt in adulthood influence one's perception and preference for sweeter or saltier foods [46–48]. Cultural differences in taste preferences are likely due to differences in the way sugar and salt are used in each cultural group's cuisine

[49–51]. In addition, there is evidence for interplay between taste preference, food intake, and metabolism, all of which have genetic components [52–56].

To learn more about potential genetic associations with taste preferences, we assessed participants' sweet versus salty/savory food preference using a multiple-choice question with 4 answer options (in parentheses):

"When you're in the mood for a snack, what kind of snack do you usually reach for?"
(Sweet / Salty or savory / Both / Neither)

A total of 54,901 participants (46%) answered "Sweet" and 64,049 participants (54%) answered "Salty or savory". Participants who answered "Both" or "Neither" were excluded.

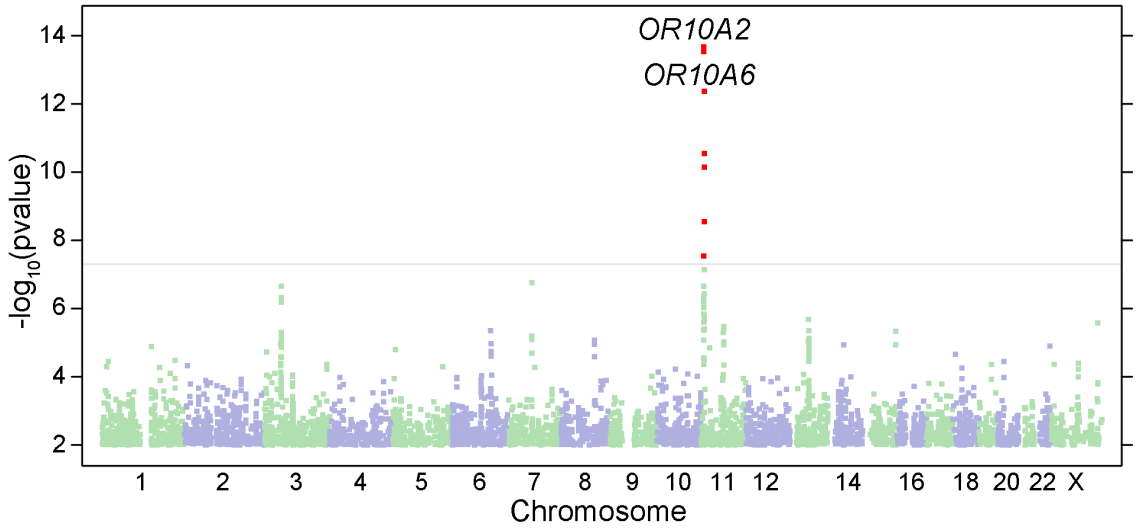
We identified 29 genomic loci that passed criteria for genome-wide association significance (summarized in Figure 2). From these we chose two index SNPs with the lowest *p* values to be incorporated into customer reports (detailed data in Table 1). The index SNP for the first locus, rs838133, lies within an intron of the gene *FGF21* in chromosomal region 19q13.33. The index SNP for the second locus, rs1421085, lies within an intron of the gene *FTO* in chromosomal region 16q12.2. The A allele of rs838133 ($p = 1.9 \times 10^{-49}$, OR = 1.1) and the C allele of rs1421085 ($p = 3.6 \times 10^{-23}$, OR = 1.1) are associated with higher odds of preferring sweet tasting foods.

The *FGF21* gene encodes a hormone that regulates glucose and lipid metabolism. [57–60]. In obese individuals, blood levels of FGF21 are elevated and are predictive of developing diabetes [61,62]. Because of its function as a metabolism regulator, FGF21 has been proposed as a therapeutic target for metabolic diseases [63,64].

The *FTO* locus we report was previously found to be associated with obesity [65,66]. This locus contains long-range elements that regulate the expression of the neighboring homeobox gene *IRX3* [67,68]. In turn, *IRX3* is thought to play an important role in the regulation of body mass and metabolism [67].

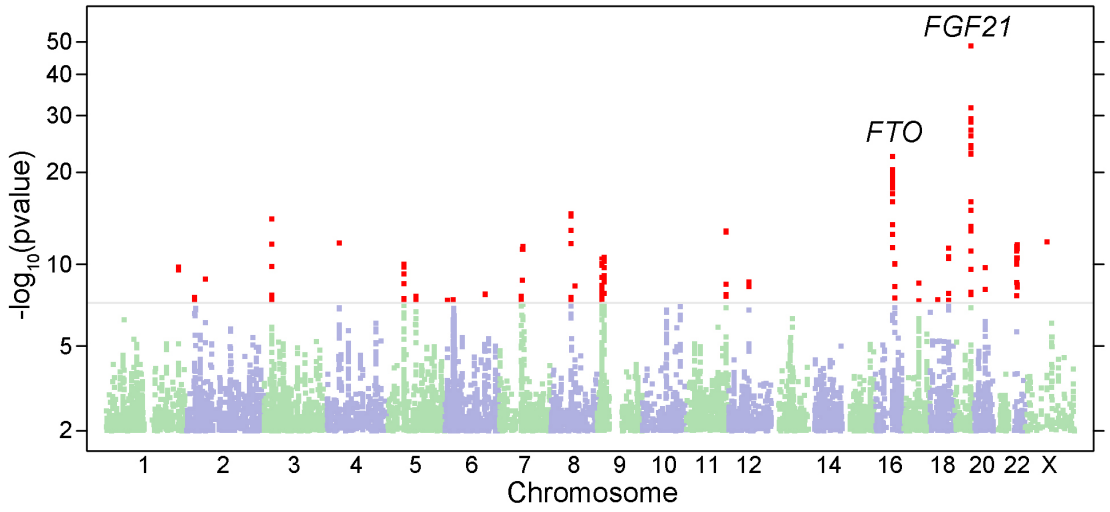
Our findings are consistent with those of Chu et al., who identified an association between the same *FTO* and *FGF21* loci (including SNP rs838133) and dietary macronutrient intake [69].

Figure 1. Cilantro aversion GWAS results



Manhattan plot of GWAS results for the cilantro taste trait. Log-scaled *p* values (y-axis) are plotted against genomic position on chromosomes 1-22 and X (x-axis). Red squares represent SNPs with $p < 5x10^{-8}$ (-log *p* of ~7.3), green and blue squares represent SNPs with $p > 5x10^{-8}$. The horizontal grey line represents the $p = 5x10^{-8}$ cut-off. Labels next to the most significant index SNP locations show the names of the nearest genes.

Figure 2. Sweet vs. salty taste preference GWAS results



Manhattan plot of GWAS results for the sweet taste preference trait. (See legend for Figure 1.)

Table 1. Significant Associations Reported to Customers

Trait	SNP	Region	Position	Alleles (effect/no effect)	EAF	OR (95% CI)	*p* value	Gene context
Cilantro aversion	rs2741762	11p15.4	6892866	A/G	0.62	1.102 (1.075 - 1.130)	2.1×10^{-14}	*OR10A2*[]-*OR10A4*
	rs3930459	11p15.4	7953958	C/T	0.41	1.095 (1.069 - 1.122)	4.2×10^{-13}	*OR10A6*-[]-*OR10A3*
Sweet preference	rs838133	19q13.33	49259529	A/G	0.44	1.147 (1.136 – 1.157)	1.9×10^{-49}	*[FGF21]*
	rs1421085	16q12.2	53800954	C/T	0.41	1.096 (1.076 – 1.117)	3.6×10^{-23}	*[FTO]*

Index SNPs for regions with association $p < 5 \times 10^{-8}$ are reported. Region – cytogenetic band position; Position – SNP position according to the NCBI Genome Reference Consortium human genome build 37 (GRCh37); Alleles – effect/no effect on genomic reference strand; EAF – effect allele frequency across all study participants; OR – odds ratio for the high-risk allele; CI – 95% confidence interval; Gene context – gene(s) spanning or flanking (< 1Mb away from) the index SNP: brackets indicate the position of the SNP, and dashes indicate distance to a flanking gene (- >1 kb; -- >10 kb; --- >100 kb).

Table 2. Demographic characteristics of analyzed data

		Sex (%)		Age distribution (%)			
		Males	**Females**	**≤ 30**	**> 30 and ≤ 45**	**> 45 and ≤ 60**	**> 60**
Cilantro aversion	cases	8309 (42.1%)	11422 (57.9%)	2158 (10.9%)	4645 (23.5%)	5273 (26.7%)	7655 (38.8%)
	controls	26121 (46.3%)	30239 (53.7%)	5983 (10.6%)	16325 (29.0%)	16771 (29.8%)	17281 (30.7%)
Sweet preference	cases	26420 (48.1%)	28481 (51.9%)	8459 (15.4%)	17181 (31.3%)	14677 (26.7%)	14584 (26.6%)
	controls	35108 (54.8%)	28941 (45.2%)	10277 (16.0%)	21054 (32.9%)	17299 (27.0%)	15419 (24.1%)

Numbers (and percentages) of individuals in the analyzed data sets.

Definitions

Allele – A version of a DNA sequence at a specific genomic location (either coding or non-coding). An individual's **genotype** is his/her set of alleles at a specific genomic location.
Ancestry – Characterization of an individual as belonging to a group with a specific historical geographic location and ethnic identity. Determined computationally by comparing the individual's genome to reference datasets for various ancestry groups.
Effect Allele Frequency (EAF) – The frequency in a population of the allele associated with higher odds of having a specific trait.
Genome Wide Association Study (GWAS) – A study that uses an array of SNPs that span the genome to identify loci linked with a particular trait.
Hardy Weinberg Equilibrium (HWE) – An idealized state where the allele frequencies for a specific gene in a population are constant from generation to generation. HWE may be disturbed by natural selection, genetic drift, mutation, and other factors that shift allele frequencies.
Intron – A region of DNA within a gene that is normally removed (spliced) after transcription and before translation to a protein.
Linkage Disequilibrium (LD) – A non-random association between alleles at different locations in the genome indicating shared ancestral origins and a higher likelihood of being inherited together after recombination.
Odds Ratio (OR) – A ratio of the odds of having a trait given one SNP genotype to the odds of having the same trait given another SNP genotype, equivalent to the effect size of a genetic association for a binary trait.
Quantile-Quantile (Q-Q) Plot – A graphical representation of the quantiles of one data set plotted against the quantiles of another (reference) data set. In this white paper the Q-Q plot is used to evaluate whether an experimental data distribution is significantly different from a theoretical null (no SNP-trait association) distribution.
Regression Coefficient (β) – A measure of the strength of the linear relationship between a SNP allele and a trait, used to estimate the effect size of a genetic association.
Single Nucleotide Polymorphism (SNP) – A single-nucleotide variation at a specific location in DNA sequence that may be used as a marker for a specific human trait or traits.
Trait – An easily observable characteristic that can be narrowly defined and identified in multiple individuals. In this white paper "trait" is identical to "phenotype".

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Revision History

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Revision A published February 25, 2015. The following changes were made in Revision A:

- Added new GWAS data for sweet taste preference to Table 1 and new Figure 2
- Corrected EAF values for cilantro preference SNPs in Table 1, which were listed for the wrong allele
- Added Table 2 – Demographic characteristics