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ORIGINAL ARTICLE

Genetic variants associated with motion sickness point to roles for inner ear development, neurological processes and glucose homeostasis

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Abstract

Roughly one in three individuals is highly susceptible to motion sickness and yet the underlying causes of this condition are not well understood. Despite high heritability, no associated genetic factors have been discovered. Here, we conducted the first genome-wide association study on motion sickness in 80 494 individuals from the 23andMe database who were surveyed about car sickness. Thirty-five single-nucleotide polymorphisms (SNPs) were associated with motion sickness at a genome-wide-significant level ($P < 5 \times 10^{-8}$). Many of these SNPs are near genes involved in balance, and eye, ear and cranial development (e.g. PVRL3, TSHZ1, MUTED, HOXB3, HOXD3). Other SNPs may affect motion sickness through nearby genes with roles in the nervous system, glucose homeostasis or hypoxia. We show that several of these SNPs display sex-specific effects, with up to three times stronger effects in women. We searched for comorbid phenotypes with motion sickness, confirming associations with known comorbidities including migraines, postoperative nausea and vomiting (PONV), vertigo and morning sickness and observing new associations with altitude sickness and many gastrointestinal conditions. We also show that two of these related phenotypes (PONV and migraines) share underlying genetic factors with motion sickness. These results point to the importance of the nervous system in motion sickness and suggest a role for glucose levels in motion-induced nausea and vomiting, a finding that may provide insight into other nausea-related phenotypes like PONV. They also highlight personal characteristics (e.g. being a poor sleeper) that correlate with motion sickness, findings that could help identify risk factors or treatments.

Introduction

Motion sickness is provoked by exposure to a variety of motions (e.g. traveling in cars, boats or planes; amusement park rides; skiing; and riding on camels) (1). Simulators and virtual reality environments can also induce motion sickness (2). Symptoms of motion sickness include dizziness, nausea, vomiting, headache and pallor (3). Sweating, drowsiness, increased salivation, hyperventilation and emotional distress may also occur. Motion sickness is associated with other conditions including migraines, vertigo, postoperative nausea and vomiting (PONV) and chemotherapy-induced nausea and vomiting (CINV) (1,4).

Roughly one in three individuals is highly susceptible to motion sickness and the rest of the population may experience motion sickness under extreme conditions (5). The underlying etiology of motion sickness, however, is not well understood. One theory suggests that motion sickness results from contradictory information the brain receives during motion (1,5). The

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vestibular system of the inner ear, which senses motion and body position and influences balance, signals 'moving' to the brain, while the eye signals 'stationary' because the car or boat appears stationary relative to the viewer. The vestibular system is also thought to serve as a sensor of disequilibrium-causing neurotoxins (i.e. a toxin detector) and is believed to trigger the emetic response in order to rid the body of toxins. Thus, motion sickness may be an aberrant trigger of the emetic response. Evidence for the involvement of the vestibular system comes from the observation that individuals with complete loss of the vestibular apparatus, a component of the vestibular system, are immune to motion sickness (1).

A variety of factors influence risk for motion sickness. Women are more susceptible than men (6–9) and younger individuals are at increased risk (6,8). Ancestry may also play a role; there is some evidence that motion sickness occurs more frequently in individual with Asian ancestry compared with European ancestry (10,11). Some variables are situational and/or behavioral. For instance, one study showed that passengers without a view of the road ahead were about three times more likely to experience illness (8) and another report suggested that adopting a wider stance may reduce motion sickness (12). There is also evidence that diet and eating behavior influence risk (7).

Perhaps the most important and least understood variable is the underlying physiological susceptibility of the individual. In women, increased cortisol levels are predictive of motion sickness (13) and susceptibility to motion sickness changes as a function of the menstrual cycle, suggesting that levels of estrogen and other hormones might play a role (14). In both sexes, hyperglycemia is implicated in motion-induced nausea and vomiting (15). There is also some evidence that lower baseline levels of adrenocorticotropic hormone (16), also known as corticotropin, and low sympathetic nervous system activity (17) increases susceptibility. Finally, since antihistamines (e.g. Dramamine), anticholinergics (e.g. scopolamine) and sympathomimetics (e.g. d-amphetamine and ephedrine) are effective treatments, altered baseline activity of the receptors these drugs bind to might influence risk for motion sickness.

Although heritability estimates for motion sickness range from 57–70% (18), genome-wide association studies (GWAS) on this phenotype have not been reported. Here, we describe a large GWAS in which we find 35 regions significantly associated with motion sickness.

Results

Genome-wide association study of motion sickness

We performed a GWAS in 80 494 individuals from the customer base of 23andMe, Inc., a personal genetics company. Participants were of primarily European ancestry and were at most distantly related to each other (i.e. first cousins and closer were excluded). Motion sickness was assessed using online self-report. Participants responded to questions about their degree of car sickness on a scale of 0 (never motion sick), 1 (occasionally), 2 (sometimes) or 3 (frequently) as described in the Materials and Methods. Details about the cohort can be found in Table 1 and in the Materials and Methods. All analyses were controlled for age, sex and five principal components of genetic ancestry. Manhattan and quantile–quantile plots are provided in Figure 1 and Supplementary Material, Figure S1. The genomic control inflation factor was 1.156.

Table 1. Cohort statistics for motion sickness GWAS

Group	Total	Male	Female	≤30	31–45	46–60	≥61
Never	40 042	25 137	14 905	5510	10 707	10 592	13 233
Occasionally	24 902	11 855	13 047	4597	8451	6459	5395
Sometimes	6723	3067	3656	1175	2015	1759	1774
Frequently	8827	3011	5816	1784	3173	2310	1560
Total	80 494	43 070	37 424	13 066	24 346	21 120	21 962

Degree of motion sickness stratified by sex and age. Females and younger people tend to be more motion sick.

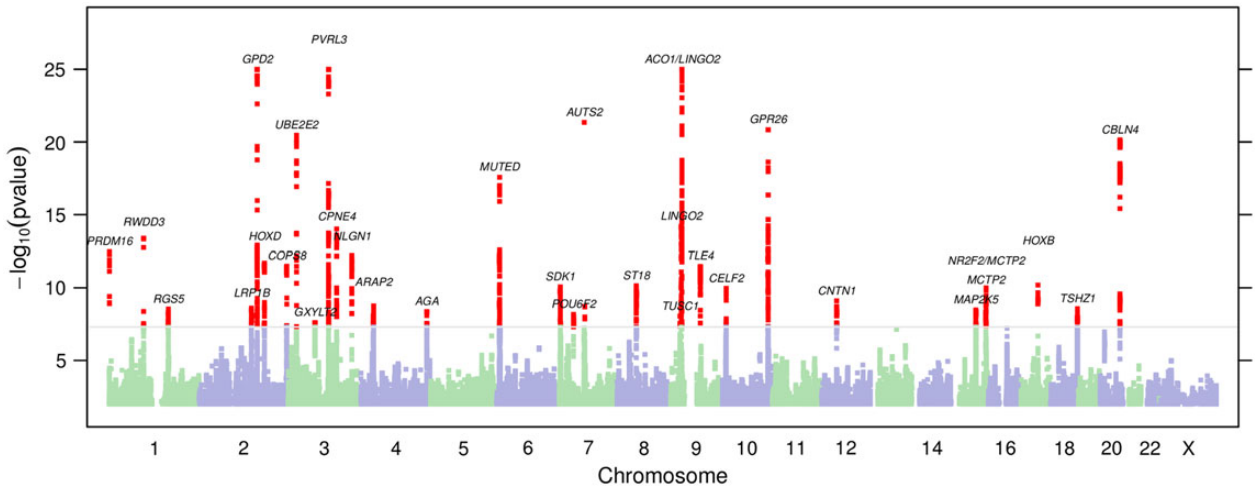

Figure 1. Manhattan plot. The 35 genome-wide-significant regions are listed with the proposed candidate gene; regions that are close together share a label.

Lead SNPs with P-values under 5×10^{-8} for motion sickness are shown in Table 2; 35 regions were significant (Supplementary Material, Fig. S2). The entire dataset is shown in Supplementary Material, Table S1. We created a genetic propensity score based on the number of risk alleles for the 35 index SNPs. Individuals in the top 5% of the distribution (allele dosage of 40.25 or more risk alleles) had an average motion-sickness score 0.546 units higher than those in the bottom 5% (28.37 or fewer risk alleles). The top 5% had 6.37 times increased odds of being 'frequently' motion sick as opposed to 'never' motion sick as compared with the bottom 5%. The variance in motion sickness explained by the propensity score (which may be inflated as it was assessed in the discovery population) was 0.029.

A few associated SNPs are in regions implicated in eye and ear development or balance. For example, our most significant association is with rs66800491 ($P = 4.2 \times 10^{-44}$), located roughly 1 Mb upstream of PVRL3, which encodes the cell adhesion protein Nectin-3. Loss of PVRL3 expression in both humans and mice results in ocular defects (19). The SNP rs10514168 ($P = 2.7 \times 10^{-9}$) is located downstream of TSHZ1, a gene involved in inner ear development in the mouse (20). Another association is with rs2153535 ($P = 2.7 \times 10^{-18}$), located upstream of MUTED, which is implicated in balance (21). Three additional associated SNPs are near genes with major roles in early development: rs2551802 ($P = 2 \times 10^{-12}$) between HOXD3 and HOXD4; rs9906289 ($P = 6.4 \times 10^{-11}$) in HOXB3; and rs149951341 ($P = 3.4 \times 10^{-12}$) near TLE4. The HOXD SNP is in linkage disequilibrium (LD) ($r^2 \approx 0.9$) with rs2072590, which is associated with ovarian cancer (22).

Several other associated SNPs are located near genes involved in neurological processes including synapse development and function: rs11713169 ($P = 5.9 \times 10^{-13}$) in NLGN1 encoding neuroligin; rs6069325 ($P = 7.2 \times 10^{-21}$) upstream of CBLN4 encoding a member of the cerebellin precursor protein family; rs62018380 ($P = 1.7 \times 10^{-9}$) downstream of MCTP2, a gene involved in intercellular signal transduction and synapse function; rs7957589 in PDZRN4 ($P = 7.9 \times 10^{-10}$) near CNTN1 (contactin 1), which plays a role in axon guidance during neural development (23); and two independent SNPs, rs4343996 and rs34912216 ($P = 8.7 \times 10^{-11}$ and 2.7×10^{-8}, respectively) in SDK1 encoding sidekick-1, a cell adhesion molecule that localizes to synapses. The SNP rs2150864 ($P = 6.3 \times 10^{-15}$) is located ~1.5 Mb upstream of LINGO2, a gene implicated in essential tremor (24). Additional associated SNPs in or

Table 2. Genome-wide significant index SNPs

SNP	Band	Position	Alleles	P-value	Effect	95% CI	Frequency	Quality	Gene
rs66800491	3q13.13	109 634,127	A/G	4.2×10^{-44}	−0.078	(−0.089, −0.067)	0.683	0.982	*PVRL3*
rs56051278	2q24.1	157 381 754	A/G	1.5×10^{-29}	0.066	(0.055, 0.078)	0.265	0.992	*GPD2*
rs10970305	9p21.1	31 372 583	A/C	1.0×10^{-27}	−0.057	(−0.068, −0.047)	0.505	0.956	*ACO1*
rs1195218	7q11.22	68 624 342	A/G	4.5×10^{-22}	0.095	(0.076, 0.114)	0.916	1.000[a]	*AUTS2*
rs705145	10q26.13	125 226 178	A/C	1.4×10^{-21}	−0.051	(−0.062, −0.041)	0.638	0.997	*GPR26*
rs11129078	3p24.3	22 592 321	A/G	3.4×10^{-21}	0.057	(0.045, 0.069)	0.751	0.984	*UBE2E2*
rs6069325	20q13.2	54 139 486	G/T	7.2×10^{-21}	0.069	(0.054, 0.083)	0.841	0.933	*CBLN4*
rs2153535	6p24.3	8 369 679	C/G	2.7×10^{-18}	0.046	(0.035, 0.056)	0.480	0.969	*MUTED*
rs2150864	9p21.1	29 363 265	A/G	6.3×10^{-15}	0.042	(0.032, 0.053)	0.348	1.000	*LINGO2*
rs9834560	3q22.1	131 716 105	A/C	9.7×10^{-15}	−0.041	(−0.051, −0.031)	0.610	1.000	*CPNE4*
rs1858111	1p21.3	96 089 731	A/G	4.1×10^{-14}	−0.039	(−0.050, −0.029)	0.567	0.999	*RWDD3*
rs61759167	1p36.32	3 091 587	C/T	3.5×10^{-13}	0.047	(0.034, 0.059)	0.231	0.918	*PRDM16*
rs11713169	3q26.31	173 384 589	A/C	5.9×10^{-13}	−0.052	(−0.067, −0.038)	0.160	0.918	*NLGN1*
rs2551802	2q31.1	177 022 158	C/G	2.0×10^{-12}	0.040	(0.029, 0.052)	0.697	0.951	*HOXD*
rs2318131	2q37.3	237 933 966	A/C	3.3×10^{-12}	0.038	(0.027, 0.049)	0.343	0.999	*COPS8*
rs149951341	9q21.31	81 268 149	A/C	3.4×10^{-12}	−0.050	(−0.064, −0.036)	0.798	0.794	*TLE4*
rs9906289	17q21.32	46 644 677	C/T	6.4×10^{-11}	0.083	(0.058, 0.108)	0.046	0.944	*HOXB*
rs2360806	8q11.23	53 125 734	A/C	7.2×10^{-11}	0.047	(0.033, 0.061)	0.162	0.958	*ST18*
rs4343996	7p22.2	3 362 642	A/G	8.7×10^{-11}	0.034	(0.023, 0.044)	0.451	0.994	*SDK1*
rs7170668	15q26.2	96 014 143	C/T	1.0×10^{-10}	0.035	(0.024, 0.045)	0.632	1.000	*NR2F2*
rs10752212	10p14	10 917 121	A/G	1.1×10^{-10}	0.034	(0.024, 0.044)	0.532	0.974	*CELF2*
rs7957589	12q12	41 874 282	A/T	7.9×10^{-10}	−0.047	(−0.061, −0.032)	0.146	0.930	*CNTN1*
rs62018380	15q26.2	95 275 917	A/C	1.7×10^{-9}	0.047	(0.032, 0.062)	0.869	0.960	*MCTP2*
rs6833641	4p15.1	35 563 786	C/G	1.8×10^{-9}	0.046	(0.031, 0.062)	0.852	0.870	*ARAP2*
rs6946969	7q11.22	70 211 027	A/G	1.9×10^{-9}	0.033	(0.022, 0.043)	0.658	0.996	*AUTS2*
rs17515225	2q22.1	141 545 755	C/T	2.5×10^{-9}	0.032	(0.021, 0.042)	0.445	0.958	*LRP1B*
rs10514168	18q22.3	73 098 949	A/C	2.7×10^{-9}	−0.047	(−0.062, −0.031)	0.854	0.861	*TSHZ1*
rs4076764	1q23.3	163 441 286	C/T	2.9×10^{-9}	0.033	(0.022, 0.044)	0.649	0.933	*RGS5*
rs997295	15q23	68 016 343	G/T	3.3×10^{-9}	−0.033	(−0.044, −0.022)	0.588	0.994[a]	*MAP2K5*
rs1378552	4q34.3	180 356 846	C/T	4.3×10^{-9}	−0.032	(−0.043, −0.022)	0.322	0.998	*AGA*
rs60464047	7p14.1	39 418 538	A/T	6.7×10^{-9}	−0.043	(−0.057, −0.028)	0.850	0.956	*POU6F2*
rs34311235	2q22.2	142 767 433	C/T	7.9×10^{-9}	0.032	(0.021, 0.042)	0.368	0.955	*LRP1B*
rs1782032	9p21.2	25 804 285	A/G	9.0×10^{-9}	−0.031	(−0.042, −0.020)	0.544	0.920	*TUSC1*
rs1847202	3p13	72 934 371	C/T	2.5×10^{-8}	0.031	(0.020, 0.042)	0.644	0.945	*GXYLT2*
rs34912216	7p22.2	4 118 377	A/G	2.7×10^{-8}	−0.035	(−0.047, −0.023)	0.727	0.849	*SDK1*

Alleles are reported in alphabetical order with respect to the positive strand of build 37 of the human genome. The effect is the change per copy of the second allele on a four-point scale of increasing motion sickness. Frequency is the frequency of the alphabetically second allele in the cohort. Quality is imputation r2 for imputed SNPs, call rate for genotyped SNPs. Gene is a proposed candidate gene in the region.

[a]Genotyped SNPs.

near genes in neurological pathways include: rs9834560 ($P = 9.7 \times 10^{-15}$) in CPNE4 encoding copine-4, and two independent SNPS in or near AUTS2 (rs1195218 and rs6946969 ($P = 4.5 \times 10^{-22}$ and 1.9×10^{-9}, respectively).

Other associated SNPs are in regions involved in glucose and insulin homeostasis. For example, the second most significant association we found is with rs56051278 ($P = 1.5 \times 10^{-29}$) in GPD2 that encodes glycerol-3-phosphate dehydrogenase 2, an enzyme implicated in glucose homeostasis. This SNP is in high LD ($r^2 \approx 0.8$) with rs2116665 (the non-synonymous substitution H264R in GPD2) that was previously associated with free fatty acid and glycerol levels (25). The SNP rs11129078 ($P = 3.4 \times 10^{-21}$) is located downstream of UBE2E2, which encodes a component of the ubiquitin–proteasome system. This system is implicated in the autophagy of pancreatic β-cells that produce insulin and plays important roles in insulin homeostasis (26). In addition, rs705145 ($P = 1.4 \times 10^{-21}$) is located just upstream of GPR26, encoding a G protein-coupled receptor. Mice with a deletion of the GPR26 gene develop hyperphagia and diet-induced obesity, which leads to metabolic complications linked to obesity including glucose intolerance, hyperinsulemia and dyslipidemia (27). The SNP rs4076764 ($P = 2.9 \times 10^{-9}$) is located upstream of RGS5, a regulator of G protein signaling. Loss of RGS5 in the mouse is also associated with hyperphagia (28). Finally, rs7170668 ($P = 1 \times 10^{-10}$) is located upstream of NR2F2 encoding COUP-TFII (chicken ovalbumin upstream promoter transcription factor II), a protein with roles in glucose homeostasis and energy metabolism (29). The remaining associated SNPs are in regions implicated in hypoxia (rs1858111 near RWDD3, $P = 4.1 \times 10^{-14}$); iron homeostasis (rs10970305 near ACO1, $P = 1 \times 10^{-27}$); brown adipose tissue (rs61759167 in PRDM16, $P = 3.5 \times 10^{-13}$); and other less characterized processes: rs2360806 ($P = 7.2 \times 10^{-11}$) in ST18, rs2318131 ($P = 3.3 \times 10^{-12}$) near COPS8, rs60464047 ($P = 6.7 \times 10^{-9}$) in POU6F2, rs10752212 ($P = 1.1 \times 10^{-10}$) near CELF2, rs6833641 ($P = 1.8 \times 10^{-9}$) near ARAP2, rs17515225 and rs34311235 (independently associated, $P = 2.5 \times 10^{-9}$ and 7.9×10^{-9}, respectively) in LRP1B, rs1378552 ($P = 4.3 \times 10^{-9}$) in a gene desert on 4q34.3; and rs1782032 ($P = 9 \times 10^{-9}$) near TUSC1, and rs1847202 near SHQ1 and GXYLT2. Finally, rs997295 in MAP2K5 ($P = 3.3 \times 10^{-9}$) is in LD with rs2241423 ($r^2 \approx 0.36$), which is associated with body mass index (BMI) (30). Some of these SNPs are in or near genes (PRDM16, NRF2, MAP2K5, NLGN1, RGS5) that have also been implicated in the vascular system (31–38).

Enrichment

Analysis of all regions with $P < 10^{-5}$ using GREAT (39) showed a significant enrichment in regions containing genes involved in fusion of atlas and occipital bones (FDR = 0.002) and abnormal arcus anterior morphology (FDR = 0.038) in mouse. The genes/gene families annotated with one or both of these processes were HOXB, HOXD, TSHZ1 and RARB regions (the SNP near RARB is rs2067120, $P = 8.2 \times 10^{-6}$).

Phenotypic study of motion sickness

We investigated comorbidities with motion sickness within the 23andMe database. Briefly, we looked at partial correlations between each of 695 different phenotypes and motion sickness, controlling for age, sex (where applicable) and five principal components. Table 3 shows selected large correlations exceeding the Bonferroni threshold of $P < 6 \times 10^{-5}$. The maximum P-value for correlations included in the table was 4×10^{-24}. Some of the associated phenotypes are known symptoms of motion sickness (e.g. headache) or established comorbidities (migraines, vertigo, PONV and morning sickness). In addition to PONV, other gastrointestinal (GI) phenotypes were also associated with motion sickness [e.g. irritable bowel syndrome (IBS); acid reflux; stomach upset with antidepressants, codeine and non-steroidal anti-inflammatory drugs (NSAIDs); and indigestion with dairy products]. Other associations include poor sleep, poor circulation, altitude sickness, hay fever and neuroticism. Phenotypes associated with lower risk for motion sickness include a history of tobacco use, a good sense of direction, higher BMI and a better ability to handle stress.

Table 3. Selected partial correlations with motion sickness

Phenotype	ρ	N
Dizziness	0.119	24 606
PONV	0.117	25 223
Lightheaded during exercise	0.114	23 434
Vomiting from codeine	0.114	12 176
Altitude sickness	0.111	41 661
Morning sickness	0.108	13 285
Daytime sleepiness	0.080	29 384
Indigestion due to dairy products	0.071	29 659
Hay fever	0.069	22 242
Headache after red wine	0.066	42 485
Vertigo	0.065	54 934
Back pain frequency	0.065	28 808
Neuroticism	0.063	38 711
Rosacea	0.063	24 635
IBS	0.062	34 348
Mosquito bites itching more	0.061	51 292
Greater perceived stress	0.060	32 486
More colds last year	0.060	34 759
Drowsiness from Benadryl	0.055	19 307
Migraines	0.055	72 901
Seasonal affective disorder	0.051	32 273
GI pain from NSAIDs	0.047	29 846
More sleep needed	0.046	39 115
Nausea from antidepressants	0.046	12 079
Adventurous	−0.033	34 532
BMI	−0.034	75 217
Punctuality	−0.035	37 486
Good sense of direction	−0.039	46 440
Positive attitude towards self	−0.040	34 082
Pack years (cigarettes)	−0.046	66 381
Sound sleeper	−0.047	48 339
Ability to handle stress	−0.072	30 965

Partial correlations (ρ) are controlled for age, sex and five principal components. N refers to the number of people with data for both motion sickness and the second trait. Traits are sorted by partial correlation (ρ).

Genetic correlations between motion sickness and related phenotypes

We determined if any of the 35 SNPs associated with motion sickness were also associated with six correlated and clinically important phenotypes (PONV, migraines, hay fever, altitude sickness, morning sickness and vertigo) (Supplementary Material, Table S2). Table 4 shows SNPs associated with these phenotypes with a (Bonferroni-corrected) P-value under $0.05/35 \approx 0.0014$ [under a more stringent threshold of $0.05/(35 \times 6) \approx 0.0002$ only the first two are significant]. One motion sickness-associated SNP was significantly associated with migraines: rs61759167 in

Table 4. Significant associations between motion sickness-associated SNPs and other phenotypes

Phenotype	SNP	N	P-value	Effect	95% CI
Migraine	rs61759167	72 901	1.1×10^{-6}	0.08	(0.051, 0.119)
PONV	rs1195218	25 223	0.00012	−0.14	(−0.213, −0.069)
PONV	rs6069325	25 223	0.00079	0.09	(0.038, 0.143)
PONV	rs6833641	25 223	0.00101	0.09	(0.037, 0.148)

N is the number of people with data for motion sickness and migraines or PONV.

PRDM16 ($P = 1.1 \times 10^{-6}$). A previous study (40) reported an association between migraines and another SNP in PRDM16, rs2651899, which is in weak LD with rs61759167 ($r^2 \approx 0.44$). Three motion sickness-associated SNPs were also significantly associated with PONV: rs6833641 near ARAP2, rs1195218 near AUTS2 and rs6069325 near CBLN4. For all four examples, the higher risk allele for migraines or PONV is also the higher risk allele for motion sickness. We see an excess of associations with consistent direction of effect for PONV (27 consistent, $P = 0.001$) and vertigo (27 consistent, $P = 0.001$) and a similar trend for migraine ($N = 23$, $P = 0.06$). We did not detect individually significant associations between motion sickness-associated SNPs and altitude sickness, hay fever, morning sickness or vertigo. While these data suggest some shared etiology for motion sickness and PONV or migraines, it is difficult to assess whether or not this is due to shared causal SNPs.

Sex-specific effects

Motion sickness is much more common in women than in men (Table 1) and several of our SNPs show much stronger effects in women than in men. The SNP rs66800491 has a 1.5× larger effect in women (–0.097 versus –0.062) and rs1847202 has a 3× larger effect in women (0.048 versus 0.016) (both SNPs $P < 0.05$ for interaction, corrected for 35 tests). Overall 26 of the 35 SNPs have estimated larger effects in women than men (binomial $P < 0.003$; Supplementary Material, Table S3).

Discussion

Here we report 35 novel genome-wide-significant associations for motion sickness (Table 2). Genes in regions associated with motion sickness appear to play roles in eye and ear development, balance and other neurological processes and glucose homeostasis. Two of the genome-wide-significant regions contain hypoxia-inducible genes. We also provide evidence that motion sickness is phenotypically associated with numerous conditions and traits (Table 3).

Since motion sickness is thought to stem from the brain receiving contradictory signals from the inner ear versus the eye (e.g. the inner ear signals 'moving' while the eye signals 'stationary'), it is interesting that a region implicated in eye development (rs56100358 near PVRL3) is our most significant association. Chromosomal rearrangements that lead to loss of PVRL3 expression have been associated with ocular defects in humans and the PVRL3 knockout mouse exhibits lens and other vision problems (19). The associations with regions involved in the inner ear (rs12111385 near MUTED and rs1435985 near TSHZ1) are also interesting since disturbances in the vestibular system of the inner ear, which senses motion and body position and influences balance, are thought to play a central role in motion sickness. It has been suggested that the mouse homolog of MUTED controls the synthesis of otoliths of the vestibular labyrinth of the inner ear (21). Otoliths are sensitive to gravity and linear acceleration and play a role in balance. Mutations in TSHZ1 and deletions in the 18q22.3 region that includes TSHZ1 are associated with congenital aural atresia (41), a spectrum of ear deformities that involve malformation of the external auditory canal. More generally, our enrichment analysis suggests that genes involved in certain aspects of cranial developmental may play an important role in motion sickness. Associations with SNPs in or near genes involved in synapse formation and function (NLGN1, CBLN4, MCTP2, PDZRN4, CNTN1 and SDK1) and other neurological pathways (LINGO2, CPNE4, AUTS2) point to the importance of the brain in motion sickness.

Five associated SNPs are in or near genes implicated in glucose and insulin homeostasis or BMI. Although these SNPs are not in LD with SNPs reported in GWAS of type 2 diabetes (42–47), rs56051278 is in high LD ($r^2 \approx 0.8$) with rs2116665, a nonsynonymous substitution (H264R) in the GPD2 gene. H264R has been associated with increased plasma glycerol and free fatty acid concentrations in a French Canadian population (25). Increased free fatty acid levels are indicative of glucose intolerance and hyperinsulinemia. Although it is unclear why genes involved in glucose and insulin regulation might also play a role in motion sickness, one study suggested that hyperglycemia may be related to the gastrointestinal symptoms of motion sickness (15). In this study, individuals who experienced motion-induced nausea and vomiting had lower levels of insulin than people who did not experience gastrointestinal symptoms. The study further suggested that stable glucose levels might help to relieve motion-induced gastrointestinal upset.

At least two of our associated SNPs are near hypoxia-inducible genes: RGS5 and RWDD3 (encoding the RSUME protein). RSUME promotes the activity of hypoxia-inducible factor 1 (HIF-1α), a master regulator of the hypoxic response (48); RGS5 is an apoptotic stimulator induced by hypoxia in endothelial cells (49). These data suggest a potential relationship between motion sickness and hypoxia. Motion sickness might lead to hypoxia or individuals predisposed to hypoxia might also be more susceptible to motion sickness. Both possibilities are intriguing since our phenotypic analysis suggested an association between motion sickness and altitude sickness, which occurs when individuals become hypoxic at higher altitudes (Table 3).

Among the regional association plots (Supplementary Material), one SNP in particular stands out: rs1195218 near AUTS2. This genotyped SNP has a *P*-value under 10^{-20} and no other SNPs in the region have $P < 10^{-6}$. This lack of signal from LD is not terribly surprising, as none of the three proxy SNPs ($r^2 > 0.2$) for this SNP in 1000 Genomes pass imputation quality control in our data. As the clusters for this SNP look excellent and the call rate is 99.98%, we believe this is a true signal.

Certain phenotypic associations are interesting given what is known about motion sickness. PONV is an established comorbidity of motion sickness (50) and is thought to stem from the anesthetics that are administered for surgery. It may not, therefore, be surprising that motion sickness was also associated with vomiting and/or nausea with use of codeine, antidepressants and NSAIDs. Additional gastrointestinal phenotypes (e.g. IBS, acid reflux and indigestion with dairy products) as well as other drug-related phenotypes like being drowsy when taking Benadryl and feeling jittery when taking Sudafed were also associated with motion sickness. Interestingly, our findings suggest shared genetic susceptibility for both motion sickness and PONV (Table 4).

Some phenotypic associations might provide clues about the etiology of motion sickness (e.g. poor circulation and becoming light headed with exercise) or they might suggest simple remedies for motion sickness such as improving sleep quality.

A number of associated phenotypes were related to personality (e.g. neuroticism) or behavior (e.g. smoking). We note, however, that it is difficult to assess causality for these phenotype–phenotype associations. For example, does being a sound sleeper make one less susceptible to being motion sick, or vice versa, or are both related to a third condition? The validity of these novel phenotypic findings is bolstered by the fact that we also detected associations with known symptoms (dizziness and headache) and established comorbidities (PONV, migraines, vertigo and morning sickness) of motion sickness. In some cases we even identified shared genetic factors for motion sickness and related comorbidities (e.g. PONV and migraines). Some of the correlated phenotypes are not established comorbidities or symptoms of motion sickness, however, and do not have an obvious biological relationship to motion sickness.

Our web-based method of capturing phenotypic information allows us to build a very large cohort (e.g. 80 494 individuals in our study), but we may not have obtained a complete picture of an individual's susceptibility to motion sickness. For finding SNPs, the gain in power from having a large sample more than makes up for the reduction in power due to possible misclassification. An additional potential limitation is that we only surveyed individuals about car sickness; future studies should investigate these SNPs in populations phenotyped for other forms of motion sickness. An advantage of our web-based phenotypic collection method is that we can easily investigate whether seemingly related traits have shared underlying genetics. We identified four SNPs simultaneously associated with motion sickness plus PONV or migraines. These findings may provide clues into the etiology of all three conditions and may point to overlapping risk factors or treatments.

Materials and Methods

Human subjects

All participants were drawn from the customer base of 23andMe, Inc., a consumer genetics company. This cohort has been described in detail previously (51,52). Participants provided informed consent and participated in the research online, under a protocol approved by the external AAHRPP-accredited IRB, Ethical & Independent Review Services (E&I Review). Participant data are shared according to community standards that have been developed to protect against breaches of privacy. Currently, these standards allow for the sharing of summary statistics for at most 10 000 SNPs. Association data for a total of 8459 SNPs ($P < 1 \times 10^{-5}$) are shared in this publication (Table 2 and Supplementary Material, Table S1). Data for SNPs that did not reach this threshold are available upon request.

Phenotype collection

Participants were invited to fill out web-based questionnaires, which included four questions about motion sickness during road travel, whenever they logged into their 23andMe accounts. The responses to each question were translated into a motion sickness score of 0 (never), 1 (occasionally), 2 (sometimes) or 3 (frequently). Responses of 'I am not sure' or 'Do not know' were excluded from the analysis. The questions were prioritized (1–4) and a participant's final score was based on the question they answered that had the highest priority. The questions were:

1. 'How often do you experience motion sickness while in a car? (Never/Occasionally/Sometimes/Frequently/I am not sure)'
2. 2. 'Have you experienced motion sickness while riding in a car (car sickness)? (Yes, I do now frequently/Yes, I did frequently, but only as a child/Yes, occasionally/No/Do not know)'
3. 'As a child, how often did you experience motion sickness while in a car? (Never/Occasionally/Sometimes/Frequently/I am not sure)'
4. 'Can you read in a moving car without becoming nauseated? (Never/Sometimes/Always/I am not sure)'

Responses to the final question were scored as Never = 3, Sometimes = 1 and Always = 0. The four questions were developed over a period of several years, and customers could have encountered different questions depending on when and how they used the 23andMe product web site. The prioritization was not validated and was chosen to give preference to responses that were more general and current (i.e. giving lower priority to questions about childhood symptoms or the ability to read in a car).

Genotyping and imputation

Participants were genotyped and additional SNP genotypes were imputed against the August 2010 release of the 1000 Genomes data as described previously (53). Briefly, they were genotyped on at least one of three genotyping platforms, two based on the Illumina HumanHap550+ BeadChip, the third based on the Illumina Human OmniExpress+ BeadChip. The platforms included assays for 586 916, 584 942 and 1 008 948 SNPs, respectively. Genotypes for a total of 11 914 767 SNPs were imputed in batches of roughly 10 000 individuals, grouped by genotyping platform. Imputation was performed as given in ref. (53). Prior to the imputation we discarded genotyped SNPs that were not present in the imputation panel. For the GWAS, we added such SNPs back (if they passed quality control), for a total of 7 428 049 SNPs (7 378 897 imputed and 49 152 genotyped). To filter SNPs whose imputation results had changed over time, we performed an analysis of variance test for frequency differences across batches. The quality control criteria for imputed SNPs were a batch effect P-value of at least 10^{-50}, average r^2 across batches of at least 0.5, and minimum r^2 across batches of at least 0.3. The batch effect filter eliminated SNPs for which the imputation batch explained >0.1% of variance in the imputed dosage. For genotyped SNPs, we required a MAF of at least 0.001, a Hardy–Weinberg P-value of at least 10^{-20}, and a call rate at least 0.9.

Statistical analysis

In order to minimize population substructure while maximizing statistical power, the study was limited to individuals with European ancestry. Ancestry was inferred from the genome-wide genotype data and a principal component analysis that was performed as given in ref. (51,54). The cohort was filtered by relatedness to remove participants at a first cousin or closer relationship. More precisely, no two participants shared >700 cM of DNA identical by descent (IBD; approximately the lower end of sharing between a pair of first cousins). IBD was calculated using the methods described in ref. (55). All P-values were adjusted for genomic control.

The GWAS was performed using likelihood ratio tests for the linear regression

$$C \sim G + A + S + \sum_{i=1}^{5} P_i$$

of car sickness on genotype, age, sex and five principal components of genetic ancestry. Genotypes were coded as a dosage from 0–2 (counting the estimated number of minor alleles

present for imputed SNPs) or as a count 0, 1 or 2 (also number of minor alleles, for genotyped SNPs). Significant SNPs were grouped into regions with at least 500 Kb between pairs of significant SNPs; the SNP with the lowest *P*-value in each region was chosen to be the index SNP. As some of the regions were under 1 Mb apart, a joint regression with all index SNPs was run to make sure that they all represented independent signals. To further verify that none of the associations were substantially influenced by batch effects, we computed association tests including additional covariates representing genotyping date. Specifically, we divided participants into 20 equal sized groups based on when their genotype data was generated in order to capture information about genotyping platform as well as temporal variability in platform performance. For the SNPs in Table 2, none of the *P*-values changed by more than a factor of 10 and all of the associations remained genome-wide significant.

Partial correlation between car sickness C and a phenotype Y were computed by computing the correlation between the residuals produced by regressing both C and Y on age, sex and five principal components, using linear regression even if Y was a binary trait. We did not attempt to quantify the significance of these regressions nor any causality.

Tests of SNPs associated with motion sickness against other correlated traits were done using logistic or linear regressions as appropriate with the same covariates as in the GWAS (except for morning sickness, which dropped sex). The phenotypes studied (PONV, migraines, hay fever, altitude sickness, morning sickness and vertigo) were all case control except for morning sickness, which was scored on a five point scale: None; Mild (occasional bouts of queasiness or nausea, but did not require treatment); Moderate (nausea and some vomiting, but did not require treatment); Severe (severe nausea and vomiting that required treatment); Very severe (requiring hospitalization and intravenous fluid (IV) therapy).

Enrichment analysis using GREAT was conducted on all regions with an index SNP with $P < 10^{-5}$, where regions were enforced to be 500 Kb apart. Windows of 500 Kb on either side of each index SNP were uploaded into GREAT using default settings.

Supplementary Material

Supplementary Material is available at *HMG* online.

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Conflict of Interest statement. The authors are or have been employed by 23andMe and own stock options in the company.

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