GWAS Identifies 14 Polymorphisms Associated with Motion Sickness

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Introduction

Roughly one in three individuals is highly susceptible to motion sickness and yet the underlying etiology of this condition is not well understood. One theory suggests that motion sickness results from contradictory information the brain receives while traveling. The vestibular system of the inner ear, which senses motion and influences balance, signals "moving" to the brain, while the eye signals "not moving" because the vehicle appears stationary relative to the viewer. Twin studies on motion sickness suggest high heritability (57-70%), but no genetic factors have been significantly associated with motion sickness to date. We conducted the first ever genome-wide association study on this condition in over 36,572 individuals.

About Motion Sickness

Stimuli. Traveling in cars, boats, planes, and spacecraft; amusement park rides; skiing; riding on camels; virtual reality environments.

Symptoms. Dizziness, nausea, vomiting, headache, pallor, sweating, drowsiness, increased salivation, hyperventilation, emotional distress.

Comorbidities. Migraine, vertigo, postoperative nausea and vomiting (PONV), chemotherapy-induced nausea and vomiting (CINV), morning sickness.

Risk Factors. Younger age, female, Asian, physiological factors.

Methods

We performed a GWAS in 36,572 individuals with European ancestry from the customer base of 23andMe, Inc. Motion sickness was assessed by online self-report. Participants responded to questions about their degree of motion sickness during road, air or sea travel; these questions were combined into a motion sickness score of 0 (never), 1 (occasionally), 2 (sometimes), or 3 (frequently) (Figure 1). Participants were genotyped for 586,916 to 1,008,948 SNPs on Illumina-based BeadChips. We imputed 8,058,452 SNPs; 7,087,609 met our thresholds of 0.005 MAF and $r^2 > 0.3$. We also investigated comorbidities with motion sickness within the 23andMe database by looking at the association of 1667 different phenotypes with motion sickness. All analyses were controlled for age, sex, and five principal components.

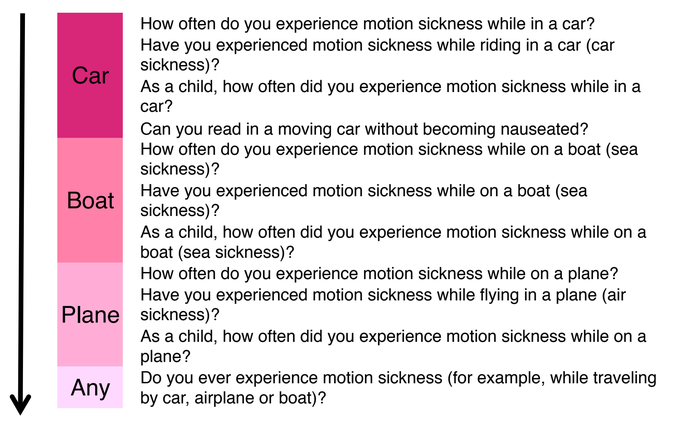

Figure 1. Phenotyping

A motion sickness score was assigned based on 11 different questions. The arrow represents the prioritization of the questions with respect to the customer's score. For example, if data was present on car sickness, then the score for car sickness was the final score.

Summary of Results

The mean motion sickness score was 1.06 in women and 0.71 in men. Motion sickness decreased with advancing age. In our genetic analysis, 14 regions were significantly ($p < 5.0e-08$) and nine regions were suggestively associated with motion sickness ($p < 1.0e-06$). We created a genetic propensity score based on the number of risk alleles for the 14 significant SNPs. Individuals in the top decile of propensity (over 16.05 risk alleles) had an average motion-sickness score 0.47 units higher than those in the bottom decile (under 10.4 risk alleles). The variance in motion sickness explained by the propensity score was 1.7%. In our phenotypic analysis, 39 traits and conditions were significantly associated with motion sickness.

Results

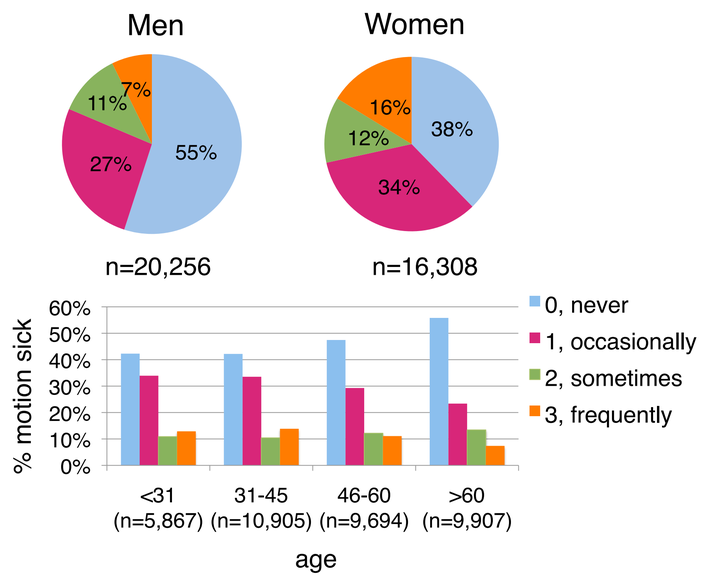

Figure 2. Cohort Statistics

Motion sickness was more severe in women than men. Motion sickness also decreased with advancing age.

SNP	Chr	Pos	Region	Allele	MAF	r^2	Beta	SE	adj p-value
rs56100358	3	109637768	PVRL3	G/A	0.320	0.983	0.090	0.008	4.94e-28
rs376935	2	157394443	(GPD2)	G/T	0.263	0.992	0.080	0.008	1.17e-20
rs10970305	9	31372583	ACO1	C/A	0.495	0.935	0.061	0.008	4.58e-15
rs55968286	3	22597178	UBE2E2	C/A	0.252	0.991	-0.057	0.008	7.60e-11
rs705145	10	125226178	GPR26	C/A	0.364	0.993	0.050	0.008	1.74e-10
rs6064238	20	54136093	CBLN4, DOK5	T/G	0.164	0.992	-0.064	0.010	7.97e-10
rs1502466	3	173400942	NLGN	A/T	0.166	0.855	-0.067	0.011	1.24e-09
rs12111385	6	8370767	MUTED	T/C	0.267	0.988	0.050	0.008	5.84e-09
rs62018380	15	95275917	MCTP2	C/A	0.132	0.958	-0.065	0.011	1.12e-08
rs7049217	9	29360960	LINGO2	G/C	0.381	0.987	0.045	0.008	1.29e-08
rs4891275	18	73102887	TSHZ1	A/G	0.170	0.958	0.058	0.010	1.50e-08
rs9906289	17	46644677	(HOXB3)	C/T	0.047	0.949	0.104	0.018	2.33e-08
rs4076764	1	163441286	NUF2, RGS5	T/C	0.351	0.923	-0.046	0.008	2.58e-08
rs7545959	1	96049429	RWDD3	T/C	0.438	0.961	0.043	0.008	2.74e-08
rs7033837	9	81214202	PSAT1, TLE4	G/C	0.255	0.947	0.049	0.009	5.31e-08
rs12108066	3	72706983	RYBP, SHQ1	C/T	0.407	0.973	-0.041	0.008	1.66e-07
rs7023324	9	121176116	TLR4, DBC1	G/T	0.216	0.908	0.051	0.009	1.95e-07
rs10834	2	177042087	HOXD3, HOXD1	A/G	0.349	0.945	0.042	0.008	3.22e-07
rs572290	6	161938548	(PARK2)	G/A	0.212	0.998	-0.046	0.009	7.04e-07
rs12710974	4	105062514	TACR3, CXXC4	T/C	0.407	0.972	0.038	0.008	9.90e-07
N/A	4	35562364	ARAP2	C/T	0.100	0.678	-0.072	0.015	1.84e-06
rs1758825	10	56296700	(PCDH15)	A/C	0.134	0.983	-0.053	0.011	2.09e-06
rs28695487	4	180318185		G/A	0.306	0.891	-0.041	0.008	2.22e-06

Table 1. SNPs Associated with Motion Sickness

SNPs with $p < 1.0e-06$. Genomic positions are given with respect to NCBI build 37.0. Parentheses mark SNPs in genes; for intergenic SNPs, nearby genes are listed. Alleles are listed as major/minor and are specified for the forward strand. r^2 is a measure of the imputation quality. Beta is the effect per copy of the minor allele. P-values were adjusted for the inflation factor.

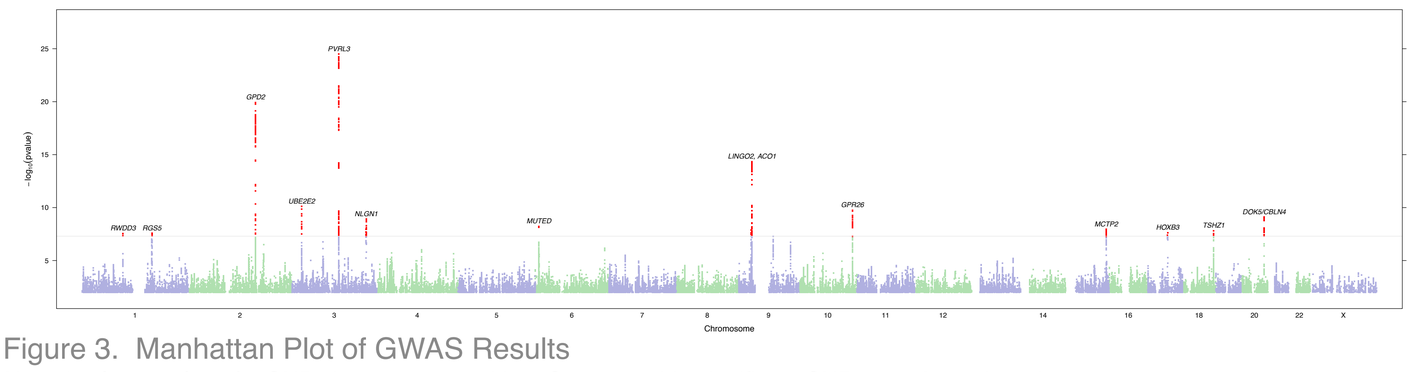

Figure 3. Manhattan Plot of GWAS Results

Negative log p-values for SNPs by genome position. Genome-wide significant SNPs are shown in red.

Phenotype	Type	P-value	Effect	Number
Vertigo	CC	2.2e-44	0.321	34,374
Altitude sickness	CC	1.23e-45	0.302	18,656
Vomiting with codeine	CC	7.11e-31	0.286	17,220
PONV	CC	5.53e-63	0.252	18,199
Nausea and vomiting with antidepressants	CC	7.49e-08	0.204	7,401
Cluster Headaches	CC	3.04e-11	0.189	26,762
Red wine headaches	CC	1.48e-17	0.16	18,432
Migraines	CC	3.72e-22	0.15	39,984
Stomach upset with NSAIDs	CC	1.05e-18	0.15	23,616
Irritable bowel syndrome (IBS)	CC	8.47e-10	0.15	12,698
Severe reaction to mosquito bites	CC	2.38e-19	0.125	23,175
Drowsy with benadryl	CC	1.39e-10	0.121	14,592
Poor circulation	CC	5.68e-08	0.113	18,371
Jittery with sudafed	CC	3.71e-14	0.111	18,768
Allergic asthma	CC	8.38e-10	0.11	31,597
Dizziness	QT	2.83e-20	0.11	4,906
Neuroticism	CC	3.92e-20	0.106	28,537
Morning sickness	QT	1.54e-17	0.103	7,509
Seasonal affective disorder (SAD)	CC	1.89e-08	0.1	10,950
History of surgery	CC	2.82e-11	0.0986	26,907
Food allergies	CC	2.26e-09	0.0983	27,546
GERD	CC	9.76e-10	0.097	33,687
Lightheaded upon exercise	QT	3.51e-15	0.0962	4,641
Freckles	CC	2.45e-10	0.0922	33,824
Asthma	CC	8.26e-09	0.0808	37,538
Crying upon cutting onions	QT	4.4e-19	0.0752	12,445
Hemorrhoids	CC	1.24e-09	0.072	34,078
Yeast infections	QT	1.96e-08	0.0685	7,670
Indigestion with dairy products	QT	4.32e-10	0.0628	7,157
Neuroticism	QT	3.44e-27	0.0627	28,537
Feeling panicky on antidepressants	QT	2.96e-13	0.0551	16,915
Leg jiggle	QT	3.42e-08	0.0551	7,435
Recent history of colds	QT	3.55e-10	0.0513	13,920
Severity of rosacea	QT	2.38e-08	0.0456	148,370
Parkinson's-like symptoms	QT	3.78e-08	0.0413	16,405
Conscientiousness in men	QT	2.81e-08	-0.041	15,313
Feet face straight	CC	7.47e-09	-0.0624	33,215
History of tobacco use	CC	5.16e-16	-0.086	41,914
Sound sleeper	CC	3.04e-13	-0.102	19,903

Established comorbidities or symptoms

GI phenotypes

Other phenotypes of interest

Table 2. Phenotypic Associations

Under our threshold of significance (bonferroni-corrected p-value < 0.001 with 3334 tests), 39 phenotypes were associated with motion sickness. Associations include known symptoms or comorbidities of motion sickness (blue) and gastrointestinal (GI) phenotypes (green). For case control (CC), the effect is for cases; for quantitative traits (QT), the effect is per SD change in the phenotype.

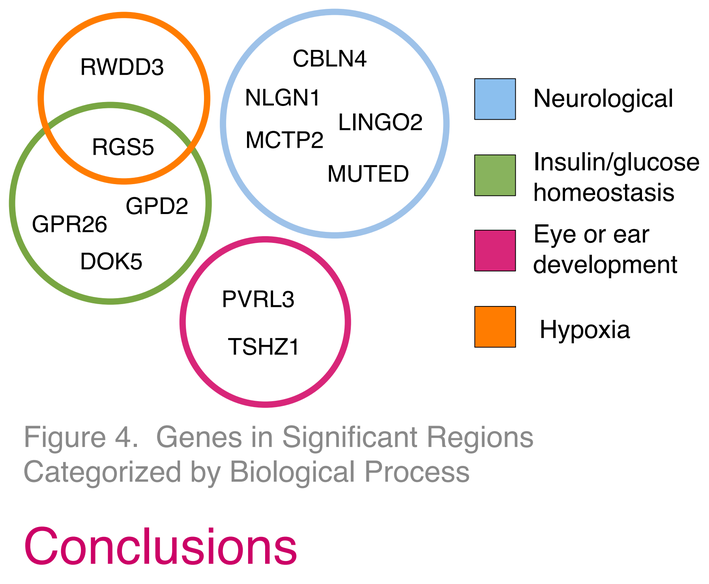

Figure 4. Genes in Significant Regions Categorized by Biological Process

Conclusions

We report 14 novel genome-wide significant associations for motion sickness and nine others with suggestive evidence. Associated regions appear to be involved in ear and eye development, neurological processes including synapse formation and balance, and insulin/glucose homeostasis. Two regions contain hypoxia-inducible genes. We also provide evidence that motion sickness is significantly associated with numerous conditions and traits. Our phenotypic analysis confirmed associations with known comorbidities including vertigo, migraine, and postoperative nausea and vomiting (PONV) and suggested novel associations with poor circulation and altitude sickness. Together, these findings provide clues about the etiology of motion sickness.

Acknowledgments

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References

1. Golding JF. Motion Sickness Susceptibility. Auton Neurosci. 2006;129(1-2):67-76.