A genome-wide association study of deviated nasal septum using UK Biobank cohort

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Research

Keywords: deviated nasal septum, genome-wide association analysis, gene, GTEx

Posted Date: April 2nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-20195/v1

Abstract

Background Deviated nasal septum (DNS) is a common otolaryngology disease. The genetic mechanism underlying DNS remains largely unknown. Methods Totally, 2, 978 DNS patients and 2,978 randomly selected controls from the UK biobank were used in this study. Genotyping was done using the Affymetrix UK BiLEVE Axiom or UK Biobank Axiom array. Genome-wide association study (GWAS) was performed by PLINK 2.0, using age, sex, population structure PC1, PC2 and PC3 as covariates. eQTLs analysis and gene set enrichment analysis (GSEA) were also performed to explore the functional relevance of identified loci with DNS. Results GWAS identified multiple candidate genetic loci for DNS, such as rs75651247 located in DLGAP1 (β=-5.3398, P=9.31×10-8), rs141366706 located in CCND3 (β=-4.7036, P=2.56×10-6), rs76606504 located in FAF1 (β=-4.5013, P=6.76×10-6), and rs142537880 located in SVIL (β= 4.4336, P=9.27×10-6). GSEA detected multiple DNS associated gene sets or pathways, such as KEGG_CALCIUM_SIGNALING_PATHWAY (FDR=3.35×10-3, P=5×10-5) and DAVICIONI_TARGETS_OF_PAX_FOXO1_FUSIONS_UP (FDR=1.60×10-3, P=5×10-5). Conclusions Our study reported multiple candidate genes and gene sets for DNS, providing novel clues for understanding the genetic mechanism of DNS.

Introduction

Deviated nasal septum (DNS) is a kind of common disease during otorhinolaryngology daily practice. The nasal septum, which is made up of bone and cartilage, is a straight one. But in some persons, the septum is deviated or kinked, affecting the nasal airway and causing nasal airflow obstruction(1). Meanwhile, DNS is widespread that there is an incidence of 14.5% in newborns after a one year observation, while nearly 80% in adults reported in recent studies (2, 3). DNS is usually accompanied by some breathing and other problems, including nosebleeds, sinusitis, allergic rhinitis, recurrent nasal discharge, epistaxis and so on, as well as headache(1). The DNS patients with mild symptoms would be relieved by medications, while the severer one would require surgery treatment.

DNS is a multifactorial disease. Multiple risk factors accounted for the bent septum have been reported, including hereditary, trauma, face injury and so on(4). Some of which are congenital, while others develop a DNS after injury or trauma to the nose. Yunusov AS et.al estimated the genetic influences on DNS in a twin study, providing strong evidence that genetic factors attribute greatly to the formation of DNS in the children population(5). Hence, there might be a possibility of a genetic predisposition contributing to the later development of a DNS. However,the genetic pathogenesis underlying the DNS has not been well studied yet.

Recent years, genome-wide association studies (GWAS) have showed great power in mapping novel genes for various human complex diseases and quantitative traits(6, 7). But to the best of our knowledge, few GWAS of DNS have been conducted by now. Furthermore, GWAS focuses on the function of single gene or variant while ignoring the potential integrating of the causal genes. Since most of complex diseases are contributed by the interplay of multiple genetic variants affecting a number of pathways or

biological process, analyzing the pathogenesis of diseases on pathway level is a promising approach. Gene set enrichment analysis can be used to identify the significant gene sets or pathways for GWAS loci. For example, a pathway-based GWAS analysis was performed for obesity and they found the Vasoactive Intestinal Peptide (VIP) Pathway may play an important role in the development of obesity(8).

Although much effort in exploring the risk factors for DNS have been widely reported. However, there is no systematic genetic analysis of the DNS yet. Given the high prevalence and heritability of DNS among population, it is essential to elucidate the molecular mechanisms of DNS. In this study, a GWAS analysis for DNS using UK biobank participants was performed here. To further reveal the biological relevance of identified genetic loci with DNS, gene set enrichment analysis was performed to detect DNS associated gene ontology terms and pathways. Our analysis aims to better elucidate the genetic architecture of DNS, providing novel candidates genes and gene sets for the mechanism studies of DNS.

Materials And Methods

Study populations and Phenotype Definition

The participants in this study were from the UK Biobank cohort (https://www.ukbiobank.ac.uk/). UK biobank is a prospective study cohort, which consists of approximately 500,000 individuals aged between 49 and 60 years old. At the beginning of recruitment, all of the participants were assessed in 22 assessment centers in UK, answering serials of questions about baseline information including socio-demographic, lifestyle and health-related factors, and make some kind of physical measures. The electronic signed consents were included in the participants visit assessment. Ethical approval was granted by the National Health Service National Research Ethics Service (reference 11/NW/0382). Detailed information about participants in UK biobank can be seen in a published study(9).

For this study, a total of 2, 978 DNS patients and 2,978 randomly selected controls were involved in this study. The cases of DNS were determined either from self-report during nurse led interviews or health records using International Classification of Diseases (ICD)-10 codes for DNS (UK biobank ID J34.2). Meanwhile, blood samples were collected by UK Biobank for following SNP genotyping. Individuals were linked retrospectively and prospectively to the National Health Service's Hospital Episode Statistics database.

Genotyping and Quality Control (QC)

Briefly, SNP genotyping was performed by UK Biobank using the Applied Biosystems UK BiLEVE Axiom Array by Affymetrix or the Applied Biosystems UK Biobank Axiom Array. The detailed information about the DNA extraction and genotyping are described in a published study(10). Any samples that did not pass the checks in the process of sample retrieval, DNA extraction, and genotype calling were excluded from the resulting genotype calls. Quality control (QC) was performed using PLINK v1.9 and R v3.3.1. It consists of two parts, namely sample-based QC and marker-based QC. The unrelated subjects were generated with KING software, a rapid algorithm for relationship inference that allows the presence of

unknown population substructure(11). For the sample-based QC, the metrics of missing rate and heterozygosity were used to identify the poor quality samples. For marker-based QC, batch effects, plate effects, departures from Hardy–Weinberg equilibrium, sex effects, array effects, and discordance across control replicates, these are all tested statistically here to identify poor quality markers, checking for consistency of genotype calling across experimental factors.

Imputation

The 1000 Genomes phase 3 dataset, the merged UK10K and 1000 Genomes phase 3 reference panels and the Haplotype Reference Consortium (HRC) data were used as the imputation reference panel, of which HRC data was defined as the main imputation reference panel, for it consisted of the largest available set (64,976) of broadly European haplotypes at 39,235,157 SNPs (12). The process of imputation was conducted using the IMPUTE4 program, a re-coded version of the IMPUTE2. Finally, this imputation process generates a dataset with 93,095,623 autosomal SNPs, short indels and large structural variants.

Statistical analysis

Genome-wide association testing were performed using the logistic regression model of PLINK 2.0 software (13) using age, sex, population structure PC1, PC2 and PC3 as covariates. The subjects with genotype missing rate > 10% and the SNPs with call rate < 99%, Hardy–Weinberg equilibrium (HWE) test $P < 1.0 \times 10^{-3}$, and minor allele frequency (MAF) < 1% were excluded from this study. For eQTLs analysis, we aligned DNS associated variants identified by GWAS with the the eQTLs driven from the GTEx portal GTEx (http://www.GTExportal.org/) (14).

Gene set enrichment analysis

Gene set enrichment analysis (GSEA) for DNS was performed using the GWAS summary data of DNS. GSEA was performed using a modification of the Gene Set Enrichment Algorithm developed by Wang et al. (15). A total of 2850 gene sets or biological pathways extracted from the BioCarta(http://www.biocarta.com/genes), Kyoto Encyclopedia of Genes and Genomes (KEGG) (http://www.genome.ad.jp/kegg/pathway.html), Ambion GeneAssist (http://www.ambion.com/tools/pathway), and Gene Ontology (GO) databases (http://www.geneontology.org) were analyzed. The significant gene sets or pathways were selected with False Discovery Rate (FDR) <0.05.

Results

Study population

Totally, 2, 977 DNS patients, including 1017 females (average age 56.143, range 40-70), 1960 males (average age 56.138, range 40-70) were enrolled. And 2,978 randomly selected controls, including 1575

females (average age 56.488, range 40-70), 1403 males (average age 56.475, range 40-70) were involved in this study.

GWAS of DNS

GWAS identified 235 SNPs corresponding to 39 genes, which showed suggestive association signals with DNS (Additional table 1 and Figure 1). We detected 6 SNPs located or near to DLGAP1 gene. rs75651247 was the most significant one (β=-5.3398, P=9.31×10^{-8}) for DLGAP1(Table 1). Other identified candidate loci include rs141366706 located in the CCND3 gene (β=-4.7036, P=2.56×10^{-6}), rs76606504 located in the FAF1 gene (β=-4.5013, P=6.76×10^{-6}), rs188334775 located in the PLCB1 gene (β=-4.5806, P=4.64×10^{-6}) and rs142537880 located in the SVIL gene (β= 4.4336, P=9.27×10^{-6}).

eQTL analysis

After aligning the candidate loci identified by the GWAS with the GTex eQTLs data, 92 candidate loci were found to be eQTLs. The top candidate eQTLs was rs76606504 (P_{GWAS}=6.76×10^{-6}) for EPS15 region. Furthermore, several interesting eQTLs were also identified in our study, including rs76606504 (P_{GWAS}=6.76×10^{-6}) for DMRTA2 gene, rs2231521 for CHRAC1 gene (P_{GWAS} =1.4×10^{-5}) (Additional table 2).

GSEA analysis

GSEA identified 22 gene sets or pathways for DNS (Table 2), such as DAVICIONI_TARGETS_OF_PAX_FOXO1_FUSIONS_UP (FDR=1.60×10^{-3}, P=5×10^{-5}), KEGG_AXON_GUIDANCE (FDR=2.14×10^{-3}, P=5×10^{-5}) and KEGG_CALCIUM_SIGNALING_PATHWAY (FDR=3.35×10^{-3}, P=5×10^{-5}).

Discussion

DNS is a common disease with multifactorial factors. Normally, hereditability, injury or traumas were all thought to contribute to the cause and the development of DNS. However, the genetic architecture of DNS is lack of attention and largely unknown. To further explore the genetic architecture of DNS, we performed a GWAS of DNS using 5,956 UK Biobank participants of European ancestry. We detected multiple candidate genes and gene sets that may involve in the pathogenesis of DNS.

Multiple candidate genes for DNS have been identified in our study, including CCND3, FAF1, and PLCB1 and so on. Of them, DLGAP1 is the top significant one. DLG associated protein 1 (DLGAP1), also known as Disks large-associated protein 1 (DAP-1), guanylate kinase-associated protein (GKAP), localizes at the postsynaptic density (PSD). DLGAP1 knockout mice exhibited alterations of the postsynaptic density and selective reductions in sociability (16). Additionally, previous literatures showed that DLGAP1 is mainly involved in the neuropsychiatric disorders, such as autism spectrum disorder (ASD), obsessive–compulsive disorder (OCD) and schizophrenia (SCZ). Interesting, a study showed that serious infection in

the paranasal sinuses may show symptoms of neurological disease, indicating that the involvement of nervous system in the development of sinusitis(17). Our data seem to suggest that DLGAP1 is a candidate gene for DNS. Given the important role of DLGAP1 in synaptic junction and nerve system, we supposed that there might be a possibility that DLGAP1 influence the cause and development of DNS via the neuron way.

Another notable gene is FAF1. Fas-associated factor 1 (FAF1) is a binding protein that can induce apoptosis when activated by Fas ligand binding or anti-Fas antibody crosslinking in multiple organ systems. Previous studies focused on the specific function of FAF1 in apoptotic execution. For example, an existing study found that FAF1 is a member of Fas-death-inducing signaling complex (Fas-DISC) acting upstream of caspase-8, explaining the proapoptotic role of FAF1 in Fas-mediated signaling (18). Cell death has been demonstrated to play a vital role in the process of nasal polyposis. A study demonstrated apoptosis occurred in traumatized nasal septal cartilage, suggesting it might be a causal factor for the cartilage resorption, weakness, and warping when used as a graft (19). Normally, abnormal anatomic structure of nasal cavity is one of the important reasons for the cause of sinusitis and nasal polyposis. Moreover, the occurrence of DNS was usually accompanied by various breathing problems, including sinusitis□allergic rhinitis and so on. Valera, Küpper et al observed significantly lower expression of apoptotic factors including p53, caspases 3 and 9 genes in chronic rhinosinusitis with nasal polyps patients compared with control group (20). Another study proved that delayed cellular apoptosis is implicated in the pathogenesis of nasal polyps (21). Based on the fact that close connection between nasal polyposis and DNS, we may draw the similar conclusion for the DNS, which is that the imbalance of cell proliferation and cell apoptosis is related to the development of DNS and FAF1 might be implicated in the pathogenesis of DNS via inducing cell death.

SVIL, also known as supervillin, is an actin-binding protein binding protein localized at a focal adhesion between cell and extracellular matrix. The focal adhesion-regulatory and Lyn-associated protein supervillin are both required for normal cell division, cell motility, and matrix degradation. Furthermore, supervillin may regulate cell survival through decreasing levels of the tumor suppressor protein p53 and its downstream target genes (22). SVIL has been demonstrated to be associated with multiple diseases. For example, Kira C. Taylor et al identified that a potentially novel locus in the supervillin gene is the most significant one to be related with clinical fracture in a GWAS meta study (23). Another study confirmed the important role of SVIL in moderate-to-severe chronic obstructive pulmonary disease (COPD)(24). However, there has been no articles about the role of SVIL in the cause of DNS yet, further studies are required to confirm our results.

Further eQTLs analysis of GWAS results detected EPS15 for DNS. Epidermal growth factor (EGF) receptor substrate 15 (EPS15), characterized as a novel tyrosine kinase substrate, is proved to be involved in the receptor-mediated endocytosis of EGF. The relationship between the EGF receptor (EGF-R) and airway epithelium has been well documented in recent years. For example, the expression of EGF-R was found in many cells in the sinus mucosa of chronic sinusitis patients, including goblet cells, basal cells, and submucosal gland cells, indicating the crucial role of EGF-R in mucus production in the epithelium of the

sinus mucosa (25). Similarity, EGF-R cascade was found to be involved in the regulation of goblet cell mucins in nasal polyposis (26). Based on the previous studies and our results, we hypothesized there was a role of EPS15 in the mucus hypersecretion in DNS.

This study detected several candidate gene sets or pathways for DNS. KEGG_CALCIUM_SIGNALING_PATHWAY is one of the significant pathways. It is a calcium signaling pathway, and totally consists of 177 genes, including ADCY1, CACNA1A, and CALM1 and so on. Calcium is defined as an important chemical messenger that regulates a number of processes in cells. Growing evidence showed that calcium played a vital role in sinusitis and nasal polyps. For example, Ichimura K et al. showed the regulation role of calcium in the smooth-muscle contraction of the nasal blood vessels(27). Furthermore, the therapy value of the calcium cevitamate in otolaryngology has been well documented since 2014 (28). Our study results suggest the involvement of KEGG_CALCIUM_SIGNALING_PATHWAY in the genetic mechanism of DNS, but biological experiments are needed to confirm our results.

In conclusion, we performed a GWAS and reported multiple candidate genes and gene sets for DNS. To the best of our knowledge, this is the first GWAS of DNS. Our study results provide novel clues for understanding the genetic mechanism of DNS. Further studies are needed to confirm our findings and explore the potential mechanism of identified genes and gene sets implicated in the development of DNS.

Abbreviations

GWAS
genome-wide association study
GSEA
gene set enrichment analysis
DNS
Deviated nasal septum
VIP
Vasoactive Intestinal Peptide Pathway
QC
Quality control
HRC
Haplotype Reference Consortium
HWE
hardy–Weinberg equilibrium
MAF
minor allele frequency
KEGG
Kyoto Encyclopedia of Genes and Genomes

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the National Health Service National Research Ethics Service (reference 11/NW/0382)

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declared no conflict of interest.

Funding

This study is supported by the National Natural Scientific Foundation of China (81472925, 81673112, 81772411), and the Key projects of international cooperation among governments in scientific and technological innovation (2016YFE0119100), and the Natural Science Basic Research Plan in Shaanxi Province of China (2017JZ024), and the Fundamental Research Funds for the Central Universities.

Authors' contributions

Conceptualization, Cuiyan Wu and Yan Wen; Data curation, Feng Zhang; Funding acquisition, Feng Zhang; Investigation, Lu Zhang; Methodology, Yan Wen, Shiqiang Cheng, Xin Qi, Mei Ma, Lu Zhang and Chujun Liang; Project administration, Feng Zhang; Software, Xin Qi; Writing – original draft, Li Liu, Cuiyan Wu and Xiaoxia Dai; Writing – review & editing, Bolun Cheng, Ping Li, Xiaomeng Chu, Jing Ye and Yao Yao.

Acknowledgements

We sincerely thank all the participants in the UK biobank cohort for providing genetic and phenotypic information.

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Tables

Table 1. List of the suggestive SNPs mapping to genes for deviated nasal septum

Gene	ID	CHROM	REF	Z_STAT	P
DLGAP1	rs75651247	18	C	-5.33979	9.306E-08
	rs9807505	18	C	-5.30815	1.107E-07
	rs59724684	18	C	-5.18406	2.171E-07
	rs201175298	18	C	-5.11432	3.149E-07
	rs12456597	18	T	-5.08888	3.602E-07
	18:4261320_TCC_T	18	T	-5.05871	4.221E-07
FAF1	rs76606504	1	A	-4.50125	6.755E-06
	rs75876848	1	A	-4.46016	8.19E-06
	rs11587750	1	A	-4.45159	8.524E-06
	rs112247206	1	T	-4.44991	8.591E-06
	rs112810143	1	T	-4.44894	8.63E-06
	rs2896887	1	T	-4.43148	9.359E-06
	rs11587909	1	T	-4.38694	1.15E-05
	rs6679843	1	G	-4.38196	1.176E-05
	rs6679854	1	C	-4.37827	1.196E-05
	rs11577519	1	T	-4.37527	1.213E-05
	rs11587148	1	C	-4.37494	1.215E-05
	rs113815363	1	A	-4.37302	1.225E-05
	rs111604405	1	C	-4.37237	1.229E-05
	rs17387164	1	G	-4.36869	1.25E-05
	rs111358652	1	A	-4.3584	1.31E-05
	rs17387761	1	A	-4.3563	1.323E-05
	rs79521580	1	T	-4.35442	1.334E-05
	rs17383851	1	A	-4.33808	1.437E-05
	rs74080008	1	T	-4.32782	1.506E-05
	rs77236920	1	G	-4.32471	1.527E-05
	rs113348171	1	G	-4.32184	1.547E-05
	rs775103516	1	A	-4.31221	1.616E-05
	rs77733062	1	A	-4.30959	1.636E-05
	rs6692113	1	C	-4.30765	1.65E-05
	rs11584612	1	T	-4.30368	1.68E-05
	rs78625523	1	C	-4.29851	1.719E-05
	rs111632161	1	T	-4.29242	1.767E-05
	rs7522853	1	G	-4.29216	1.769E-05
	rs1849553	1	A	-4.27483	1.913E-05
	rs77082692	1	T	-4.27075	1.948E-05
	rs369598088	1	C	-4.26762	1.976E-05
	rs6672112	1	C	-4.26126	2.033E-05
	rs12565378	1	T	-4.25711	2.071E-05
	rs76215192	1	A	-4.25685	2.073E-05
	rs11205797	1	A	-4.25517	2.089E-05
	rs11589343	1	C	-4.25478	2.093E-05
	rs111949735	1	A	-4.24727	2.164E-05
	rs75504961	1	T	-4.24605	2.176E-05
	rs75069849	1	T	-4.24375	2.198E-05
	rs11585772	1	C	-4.2353	2.283E-05
	rs77914551	1	C	-4.22034	2.439E-05

	rs7525655	1	T	-4.21855	2.459E-05
	rs145341060	1	AC	-4.21602	2.486E-05
	rs12561912	1	C	-4.21578	2.489E-05
	rs547429971	1	T	-4.20259	2.639E-05
	1:51448844_CAT_C	1	C	-4.20007	2.668E-05
	rs565735881	1	T	-4.1943	2.737E-05
	rs752279795	1	A	-4.17921	2.925E-05
	rs149029885	1	TA	-4.17078	3.036E-05
	rs771063789	1	TA	-4.16894	3.06E-05
	rs6700139	1	C	-4.16014	3.181E-05
	rs6588392	1	G	-4.15836	3.205E-05
	rs36071834	1	C	-4.14863	3.345E-05
	rs6698809	1	C	-4.14688	3.37E-05
	rs6673810	1	G	-4.14219	3.44E-05
	rs6668495	1	A	-4.13486	3.552E-05
	rs11588333	1	T	-4.1207	3.777E-05
	rs11576128	1	A	-4.11943	3.798E-05
	rs72690493	1	C	-4.10678	4.012E-05
	rs78738909	1	G	-4.0621	4.863E-05
	rs147647466	1	TTCTCTCTC	-4.05665	4.978E-05
CCND3	rs141366706	6	C	-4.70361	2.556E-06
SVIL	rs142537880	10	C	4.43356	9.269E-06
PLCB1	rs188334775	20	G	-4.58064	4.636E-06

Table 2. List of significant gene sets identified for DNS

Pathway list	NES	P value	FDR
ACEVEDO_LIVER_CANCER_WITH_H3K27ME3_UP	4.631555406	5.00E-05	2.48E-03
DAVICIONI_TARGETS_OF_PAX_FOXO1_FUSIONS_UP	4.967352071	5.00E-05	1.60E-03
KEGG_AXON_GUIDANCE	4.499599129	5.00E-05	2.14E-03
KEGG_CALCIUM_SIGNALING_PATHWAY	4.646588478	5.00E-05	3.35E-03
MCCLUNG_CREB1_TARGETS_DN	4.557259863	5.00E-05	2.06E-03
ONDER_CDH1_TARGETS_2_UP	4.61146757	5.00E-05	1.98E-03
RIGGINS_TAMOXIFEN_RESISTANCE_DN	4.135378517	5.00E-05	7.63E-03
CAIRO_LIVER_DEVELOPMENT_UP	3.910204722	1.00E-04	1.64E-02
HORIUCHI_WTAP_TARGETS_UP	4.134932483	1.00E-04	6.88E-03
RIGGI_EWING_SARCOMA_PROGENITOR_DN	4.191716957	1.00E-04	6.91E-03
ZHANG_TARGETS_OF_EWSR1_FLI1_FUSION	3.668117487	1.00E-04	3.29E-02
DELYS_THYROID_CANCER_DN	3.796189631	1.50E-04	2.16E-02
HUTTMANN_B_CLL_POOR_SURVIVAL_DN	3.635958498	1.50E-04	3.26E-02
MANALO_HYPOXIA_UP	4.218200426	1.50E-04	7.03E-03
CONCANNON_APOPTOSIS_BY_EPOXOMICIN_DN	3.64200389	2.00E-04	3.40E-02
CHEBOTAEV_GR_TARGETS_UP	3.803923221	3.00E-04	2.27E-02
HATADA_METHYLATED_IN_LUNG_CANCER_UP	3.497115229	4.00E-04	4.21E-02
PICCALUGA_ANGIOIMMUNOBLASTIC_LYMPHOMA_DN	3.538789049	4.00E-04	4.19E-02
REACTOME_TRANSMISSION_ACROSS_CHEMICAL_SYNAPSES	3.532722104	4.50E-04	4.07E-02
VECCHI_GASTRIC_CANCER_ADVANCED_VS_EARLY_UP	3.468362744	4.50E-04	4.47E-02
CHARAFE_BREAST_CANCER_BASAL_VS_MESENCHYMAL_DN	3.53012196	5.00E-04	3.90E-02
MASSARWEH_TAMOXIFEN_RESISTANCE_DN	3.56112707	5.00E-04	4.08E-02

Figures

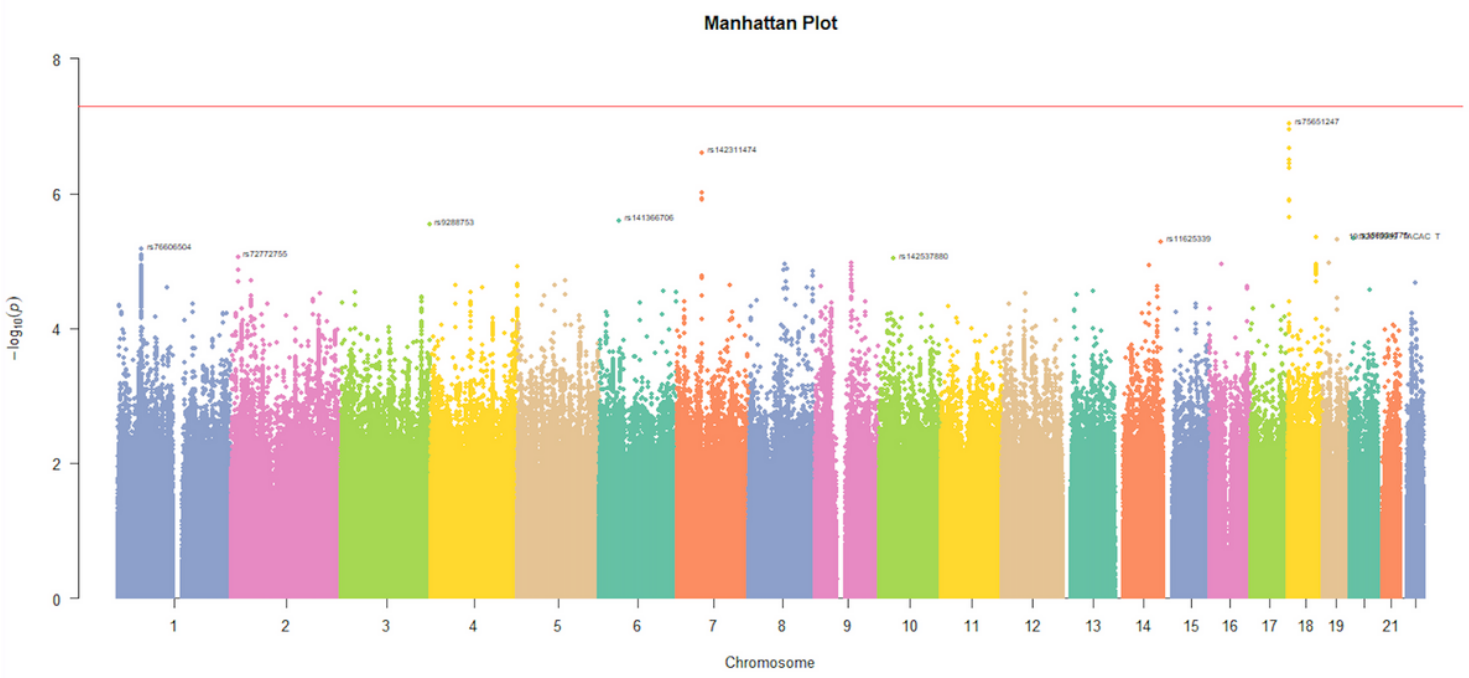

Figure 1

Manhattan plot for genome-wide association analysis of deviated nasal septum. Each point corresponds to a SNP passing quality control, plotted according to genomic position on the x-axis and the strength of association (−log10 P-value) on the y-axis. The red horizontal line indicates genome-wide significance (5×10-8).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionaltable1.xlsx
- Additionaltable2.xlsx