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Genetic determinants of swallowing impairments among community dwelling older population

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ABSTRACT

Background: Swallowing difficulties (dysphagia) affect a significant proportion of community dwelling older individuals, being more prevalent in age-associated neurological conditions such as stroke and Parkinson's disease. The genetic determinants of dysphagia are still being explored and have largely been studied through candidate gene analysis approaches. The aim of the study was to perform a genome-wide association study (GWAS) of common genetic single nucleotide polymorphisms (SNP) and self-reported swallowing impairments in a longitudinal cohort of community dwelling older adults.
Materials and methods: We performed a case–control genome-wide association study of self-reported swallowing symptoms using the Sydney Swallow Questionnaire. The analysis included 555 community dwelling, unrelated, older adults (mean years of age = 81.4; SD = 5.349) with known phenotype and genetic information consisting of 512,806 single nucleotide polymorphisms. Gene-based association analysis of these traits was also conducted.
Results: Analysis of the cohort confirmed European ancestry with no major population stratification. Further analysis for association with swallowing impairment identified one SNP rs17601696 which achieved genome-wide significance (*P*-value = 5×10^{-8}) within a non-coding region of chromosome 10. Gene-based analysis did not result in any genome-wide significant association.
Conclusion: SNP rs17601696 may have an impact on swallowing impairment among elderly individuals. The results require replication in an independent cohort with appropriate phenotype/genotype data.

1. Introduction

The swallowing process is controlled by a coordinated neuromuscular system regulated by areas of the brain stem and the cerebral cortex. Difficulty in the ability to swallow solid or liquid materials is termed dysphagia. Approximately 15% of healthy, ageing population may be affected by swallowing difficulties (Barczi et al., 2000). The presence of stroke, Parkinson's disease and other neurological conditions increases rates of dysphagia (Kalf et al., 2012; Martino et al., 2005). Swallowing impairments are associated with higher risk of pneumonia, dehydration, malnutrition and lowered quality of life due to increased risk of anxiety and depression (Verdonschot et al., 2013). Patients with dysphagia reveal different recovery patterns (Singh and Hamdy, 2006), which often impacts on the effectiveness of existing therapies.

Recent evidence suggests that the swallowing process may in part be affected by genetic variations. Previous studies conducted by Jayasekeran et al. (2011) reported an association between a Brain-Derived Neurotrophic Factor (*BDNF*) (OMIM 113505) gene polymorphism rs6265 and the response to neurostimulation in the area of the brain responsible for swallowing. *BDNF* is a member of the nerve growth factor family, expressed in cortical neurons and is necessary for survival of striatal neurons in the brain. *BDNF* was previously described as being a gene with pleiotropic effect, playing a role in neurological and psychiatric diseases which include depression and schizophrenia (Angelucci et al., 2005). Mentz et al. (2015) performed the first association analysis between self-reported swallowing symptoms among older individuals and a single nucleotide polymorphism (SNP) within the *APOE* gene (OMIM 107741). The *APOE* gene which encodes apoliporotein is

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essential for normal catabolism of triglyceride-rich lipoprotein constituents and has been reported as a risk factor in dementia and cognitive decline in an elderly cohort (Liu et al., 2013; Schiepers et al., 2012).

A potential limitation to current candidate gene based analysis models for swallowing symptoms and dysphagia are that they depend on a-priori assumptions about biological processes in a complex system. A genome-wide association study (GWAS) offers an effective method to identify novel genetic variation which confers susceptibility to complex genetic disorders (Ikegawa, 2012). As yet there have been no GWAS investigations of dysphagia.

The aim of this study was to examine the contribution of SNPs to swallowing impairment in older people using a genome-wide screening approach. We present the results from the first case–control GWAS of self-reported swallowing symptoms related to dysphagia derived from a cohort of non-hospitalised, community dwelling older adults.

2. Methods

2.1. Study cohort

A subset of individuals from the Dyne-Steel DNA archive for cognitive genetics of older adults was used where data on swallowing had been collected. The Dyne-Steel archive is an on-going study established by the "University of Manchester Longitudinal Studies of Cognition in Normal Healthy Old Age" initiated in 1981 (Wallace et al., 2000). This cohort of 6542 healthy older adults aged between 42–92 years comprised community dwelling older adults from Manchester and Newcastle in the United Kingdom with contemporary cognitive, lifestyle and health information. Between 1999 and 2001, approximately 2000 volunteers consented to donating blood samples for genetic studies of cognitive ageing. Only 800 continued the study in 2004 when the Sydney Swallowing Questionnaire was send. The numbers decreased due to death of participants or withdrawing from the study. The swallowing questionnaire was send to all participants from whom 634 completed forms giving response rate of 79%. From 634, 555 had full genetic and phenotypic information used in the following studies.

This study relates to a sample of 555 volunteers from this cohort which had appropriate genetic and clinical data (Table 1).

2.2. Swallowing phenotype

Swallowing phenotype is constructed from participants' answers to the Sydney Swallow Questionnaire (SSQ) (Wallace et al., 2000). The SSQ contains 17 questions, scored from 0 to 100, about the difficulty of swallowing (maximum score from the questionnaire is 1700). For each question a score of 0 means no problem at all whereas 100 indicate severe difficulty. Swallowing impairment was judged to be present, when the total score from the SSQ for each individual was equal or above 180 (based on previous findings presented by Wallace et al. (2000)). Volunteers were classified as being cases when the total score from the SSQ was ≥180 and controls when total score from the SSQ was <180.

2.3. Neurological and depression phenotype

Information about participants' demographics such as age and gender were available from data collected. Advanced age, presence of Parkinson's disease or history of stroke and clinical depression have been described as major risk factors for swallowing symptoms related to dysphagia. Self-reported presence of stroke or Parkinson's disease has been assessed using the Cornel Medical Index (CMI) Health Questionnaire (Pendleton et al., 2004). To measure emotional health in these individuals, responses to the Geriatric Depression Scale (GDS) 15 item version was used (Sheikh and Y.JA., 1986). This information was included in the analysis as confounders.

2.4. Phenotype for 'sensitivity analysis'

For additional, sensitivity analysis was performed in which subjects with stroke (n = 48) and Parkinson's disease (n = 4) or both (n = 1) were excluded and GDS 15 score was not included as a covariate. In this analysis only age and sex were included as confounders.

2.5. Genotyping and quality control

All DNA samples underwent genome-wide genotyping using the Illumina Human 610-Quad v1.0 Genotyping BeadChip (approximately 620000 markers). This was performed at the Edinburgh University Wellcome Trust Clinical Research Facility, Edinburgh, UK.

Genotyping and quality control for the Dyne-Steel cohort which included participants used in the current study have been described elsewhere (Turner et al., 2011). Briefly, corrections of sex differences errors, chromosomal abnormalities, relatedness between individuals and population substructure were corrected with additional analysis using PLINK software (http://pngu.mgh.harvard.edu/purcell/plink) (Purcell et al., 2007). Individuals were excluded from this study based on unresolved gender discrepancy, relatedness, call rate (≤0.95), and evidence of non-Caucasian descent. SNPs were included in the analyses if they met the following conditions: call rate ≥0.98, and Hardy–Weinberg equilibrium test with *P*-value ≥0.001, minor allele frequency (MAF) ≥0.05. The levels of MAF were increased from MAF ≥0.01 in the current GWAS considering the sample size and power for this association analysis.

A total number of 512,806 of the 549,692 SNPs passed quality control procedures and were available for two approaches of the analysis.

2.6. Statistical analysis

To calculate the statistical power of the study the Quanto (http://hydra.usc.edu/gxe/) programme was used. SNP-based GWAS was performed using the PLINK toolset for genotype–phenotype analysis using logistic regression (http://pngu.mgh.harvard.edu/~purcel/plink) (Purcell et al., 2007). Four covariates: age, sex, GDS depression scores and presence/absence of key neurological disorders (stroke and Parkinson's disease) were included in subsequent analyses. A second 'sensitivity analysis' model was performed with only age and sex as covariates on sub-sample of the cohort (see Section 2.4). Tests for association were performed by PLINK v.107 separately for each SNP in the

Table 1
Study cohort characteristic.

	Total	Mean	Percentage	Range
Subjects:				
Male	125	82 ± 5.3 (years)	22.5%	69–98 (years)
Female	430	81 ± 5.4 (years)	77.5%	69–98 (years)
Score ≥180 from SSQ for swallowing impairment	71		12.8%	
Presence of neurological disorder Parkinson's disease and/or stroke	52		9.4%	
GDS score >5	43	1.46	7.45%	0–12