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BRIEF COMMUNICATION

# A genome-wide association study on photic sneeze syndrome in a Japanese population

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## Abstract

Photic sneeze syndrome (PSS) is characterized by a tendency to sneeze when the eye is exposed to bright light. Recent genome-wide association studies (GWASs) have identified single-nucleotide polymorphisms (SNPs) associated with PSS in Caucasian populations. We performed a GWAS on PSS in Japanese individuals who responded to a web-based survey and provided saliva samples. After quality control, genotype data of 210,086 SNPs in 11,409 individuals were analyzed. The overall prevalence of PSS was 3.2%. Consistent with previous reports, SNPs at 3p12.1 were associated with PSS at genome-wide significance ($p < 5.0 \times 10^{-8}$). Furthermore, two novel loci at 9q34.2 and 4q35.2 reached suggestive significance ($p < 5.0 \times 10^{-6}$). Our data also provided evidence supporting the two additional SNPs on 2q22.3 and 9q33.2 reportedly associated with PSS. Our study reproduced previous findings in Caucasian populations and further suggested novel PSS loci in the Japanese population.

## Introduction

Photic sneeze syndrome (PSS), or autosomal dominant compelling helio-ophthalmic outburst syndrome, is characterized by a tendency to sneeze when the eye is exposed to bright light. Age at onset is usually before 30 years, with more than half having childhood onset [1, 2]. Previous studies reported no significant difference in gender distribution [1, 2]. PSS is a harmless benign condition except in a situation where a sneeze could lead to an accident [3]. PSS prevalence appears to vary among racial and ethnic groups. Semes et al. [1] reported prevalences of 38.2% and 8.2% in white and black populations, respectively, while Everett [4] reported 23.1% in white and 2.3% in black students. However, little is known for Asian populations.

PSS often occurs in families and is considered an autosomal dominant disorder [2]. The ethnic differences in PSS prevalence may be caused, at least in part, by differences in genetic variants that confer susceptibility to PSS. Recent genome-wide association studies (GWASs) [5, 6] ($N =$ 5390 and 99,695, respectively) identified several single-nucleotide polymorphisms (SNPs) associated with PSS in Caucasian populations. To our knowledge, however, studies on Asian populations are lacking, which prompted us to perform a GWAS on PSS in a Japanese population.

## Subjects and methods

### Subjects

The subjects were 11,922 Japanese individuals who participated in the HealthData Lab project administered by Yahoo! Japan Corporation (Tokyo, Japan). The participants received a kit for saliva collection and answered a questionnaire survey via the Internet. They were shown a list of medical conditions/diseases and were asked to check the conditions/diseases that apply to them. Individuals who checked “light sneeze reflex” were treated as PSS cases. All

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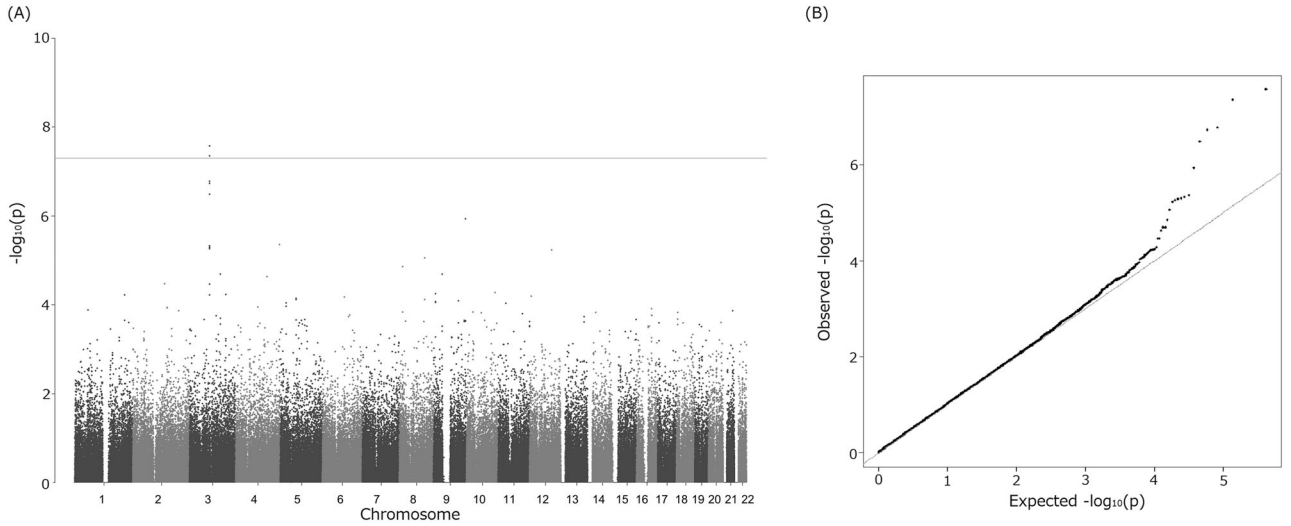


**Fig. 1 a** Manhattan plot for the genome-wide logistic regression analysis of photic sneeze syndrome in a dominant model adjusted for age and sex. Plots show -$\log_{10}$ ($p$-value) for all single-nucleotide polymorphisms (SNPs) by chromosomal positions. **b** Quantile–quantile plot for the genome-wide logistic regression analysis of photic sneeze syndrome in a dominant model adjusted for age and sex. The diagonal line shows the null expected distribution of $p$-values

**Table 1** SNPs significantly associated with PSS under a dominant model adjusted for age and sex

| Chr | Base position | SNP | Allele (effect/ref) | OR [95%CI] | $p$-Value |
|---|---|---|---|---|---|
| 3p12.1 | 84,954,203 | rs1691483 | C/A | 0.5466 [0.4418, 0.6764] | $2.71 \times 10^{-8}$[a] |
| 3p12.1 | 84,951,716 | rs1694933 | A/C | 0.5519 [0.4461, 0.6829] | $4.48 \times 10^{-8}$[a] |
| 3p12.1 | 84,961,750 | rs1614844 | T/C | 0.5702 [0.4619, 0.7038] | $1.69 \times 10^{-7}$[b] |
| 3p12.1 | 84,940,927 | rs452496 | A/G | 0.5713 [0.4629, 0.7052] | $1.87 \times 10^{-7}$[b] |
| 3p12.1 | 84,891,973 | rs401242 | G/A | 0.5768 [0.4670, 0.7125] | $3.30 \times 10^{-7}$[b] |
| 9q34.2 | 136,305,275 | rs2073933 | C/T | 1.713 [1.379, 2.128] | $1.18 \times 10^{-6}$[b] |
| 4q35.2 | 187,247,089 | rs7349633 | T/G | 1.776 [1.390, 2.270] | $4.46 \times 10^{-6}$[b] |

*Chr* chromosome, *OR* odds ratio, *CI* confidence interval, *PSS* photic sneeze syndrome

[a] Genome-wide significance

[b] Suggestive significance

participants gave written consent for the use of their genotype data and survey responses for research purposes. The study was approved by the Ethics Review Committees of Genequest Inc. and the National Center of Neurology and Psychiatry, Japan.

## Genotyping

Saliva DNA extraction and genotyping were performed by Genequest Inc. (Tokyo, Japan). After quality control, 210,086 SNPs in 11,409 participants were used for analyses. Association between genotypes and PSS was examined by logistic regression analysis under a dominant model and an additive model. SNPs with $p < 5 \times 10^{-8}$ were considered genome-wide significant, and those with $p < 5 \times 10^{-6}$ were considered suggestive. Detailed information on genotyping, quality control, population stratification and statistical analyses are shown in Supplementary Methods.

## Results

PSS was present in 360 subjects (176 men and 184 women, mean age [standard deviation]: 46.3 [12.7] years) and absent in 11,049 subjects (5849 men and 5200 women, mean age: 50.0 [13.2] years). Figure 1 shows the Manhattan and quantile–quantile plots for the genome-wide logistic regression analysis of PSS in a dominant model. Table 1 shows significantly associated SNPs in the dominant model analysis. Five SNPs on 3p12.1, all in linkage disequilibrium (LD) with one another ($r^2 = 0.61$–$1.0$), were significantly associated with PSS at genome-wide or suggestive

significance. SNPs on 9q34.2 and 4q35.2 were also suggestively associated with PSS.

Table S1 shows the associations of previously identified SNPs in Caucasian populations [5, 6] with PSS in our sample. Because the two associated SNPs reported by Eriksson et al. [5] were in absolute LD ($r^2 = 1$) with two of the SNPs reported by Pickrell et al. [6], only the SNPs reported by Pickrell et al. [6] were included in Table S1. For SNPs not included in our GWAS platforms, we selected a surrogate SNP in highest LD ($r^2 > 0.5$) in the Japanese population, using a web-based application [7], from the Phase 3 data of the 1000 Genomes Project [8]. Table S1 shows that 11 of the 40 SNPs examined under an additive model were significantly associated with PSS in the same allelic direction as reported by Pickrell et al. [6] at the nominal $p < 0.05$ level. Among them, three SNPs (rs1533426 on 2q22.3, rs1146751 on 3p12.1 and rs887807 on 9q33.2) were significant at the Bonferroni-corrected $p < 0.05$ level (corrected for 40 examined SNPs).

## Discussion

We identified significant genome-wide associations of SNPs on 3p12.1 with PSS in a Japanese population. This locus was previously reported in a Caucasian population [6], among a total of 50 loci associated with PSS to date. We examined 40 of the SNPs at these previously reported 50 loci and found 11 of them to be significantly associated with PSS in the same allelic direction as originally reported, at the nominal $p < 0.05$ level in our Japanese sample. Among them, three SNPs showed highly significant associations, unlikely to be attributable to chance. Our results suggest that at least three loci contribute to the predisposition to PSS in both Caucasian and Japanese populations.

Conversely, the other PSS-associated loci with suggestive significance were not reported in the previous GWASs of Caucasian populations [5, 6]. These association might be novel findings suggesting that PSS in Caucasian and Japanese populations may have partially different genetic bases.

How the PSS-associated SNPs affect human traits remains to be elucidated. Previous studies have examined the association of genetic variants with gene expression levels [9–11] and protein levels [12, 13] in diverse biological samples, and recent evidence indicates that various human traits are associated with expression quantitative trait locus (eQTL) and protein quantitative trait locus (pQTL) SNPs [13, 14]. Indeed, the most significant five SNPs at 3p12.1 associated with PSS have been reported as eQTLs for *CADM2* [8] and rs2073933 on 9q34.2 as an eQTL for *SURF1* and *SURF6* [8, 10] and a pQTL for ADAMTS13 protein [12].

A limitation of the present study is that PSS was determined based on self-report. Only self-observant individuals may recognize their photic sneeze reflexes. The relatively low prevalence of PSS in a Japanese population revealed in this study needs to be confirmed in future studies with independent PSS evaluation.

In conclusion, the present study reproduced some of previous findings in Caucasian populations and suggested novel PSS loci in the Japanese population. Further studies are warranted to investigate how these SNPs affect susceptibility to PSS.

## Compliance with ethical standards

**Conflict of interest** This work was supported by internal funding from Genequest Inc. and an NCNP Intramural Research Grant for Neurological and Psychiatric Disorders (HK, grant number 27-1). These sources provided financial support only. KS and ST are board members, and SA and SN are employees of Genequest Inc. The remaining authors declare that they have no conflict of interest.

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