Data Article

Dataset of allele, genotype and haplotype frequencies of five polymorphisms CDKN2B-AS1 gene in Russian patients with primary open-angle glaucoma

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\textbf{ABSTRACT}

Data on the allele, genotype and haplotype frequencies of the five single nucleotide polymorphisms (SNPs) such as rs1063192, rs7865618, rs2157719, rs944800 and rs4977756 of the CDKN2B-AS gene in Russian patients with primary open-angle glaucoma (POAG) are provided. These SNPs are found to be associated with the risk of POAG by genome-wide association studies (GWAS). The frequencies of alleles, genotypes and haplotypes of CDKN2B-AS gene were present separately for entire group of patients, females and males, and may be used as reference data of Russian population.

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Specifications Table

| Subject | Biology |
|---------|---------|
| Specific subject area | Genetics |
| Type of data | Table |
| How data were acquired | MALDI/TOF mass spectrometry using Sequenom MassARRAY 4.0 platform (Agena Bioscience™) |
| Data format | Raw and analyzed data |
| Parameters for data collection | About 5 ml of whole blood was collected from each study subject into a plastic vial (Vacutainer®) with 0.5M EDTA (pH=8.0). Genomic DNA was isolated using standard method of phenol-chloroform extraction and purification. DNA samples of good quality (concentration 10-15 ng/mL, purity A260/A280=1.7-2.0) were included for genotyping. About 5% of blind replicate samples were included for quality control of genotyping, and the repeatability test resulted in a 100% concordance rate. |
| Description of data collection | The quality of isolated DNA was assessed by Nanodrop-2000 spectrophotometer. DNA samples were genotyped using Sequenom MassARRAY® iPLEX platform using a method of MALDI-TOF (matrix-assisted laser desorption/ionization time-of-flight) mass spectrometry. Assay Design Suite 1.0 was used to design a multiplex genotyping assay (http://agenabio.com/assay-design-suite-10-software). |
| Data source location | Belgorod, Russia |
| Data accessibility | The data is available with this article |

Value of the Data

- The frequencies of alleles, genotypes and haplotypes for five SNPs such as rs1063192, rs7865618, rs2157719, rs944800 and rs4977756 of the CDKN2B-AS1 gene are presented separately for entire sample, males and females with POAG from Russian population.
- The data on the allele, genotype and haplotypes frequencies represent a resource for conducting meta-analyses of genetic studies on POAG.
- Allele, genotype and haplotype frequencies of the CDKN2B-AS1 gene polymorphisms and linkage disequilibrium values can be used as reference data for further population and genetic association studies of common diseases.

1. Data Description

The dataset represents the raw data (supplementary Table), frequencies of alleles, genotypes (Table 1) and haplotypes (Table 2) for five SNPs (rs1063192, rs7865618, rs2157719, rs944800 and rs4977756) of the CDKN2B-AS gene in Russian patients with POAG. These SNPs are found to be associated with the risk of POAG in previously published GWAS (Table 3) [1-10]. These SNPs possess the regulatory potential (Table 4), as demonstrated by several eQTLs (Table 5) and splicing QTLs (Table 6). The frequencies of alleles, genotypes and haplotypes for the SNPs are provided separately for three groups: entire sample, females and males. No significant differences in the allele, genotype and haplotype frequencies were found between the males and females groups.

2. Experimental Design, Materials, and Methods

2.1. Study subjects

A study sample was comprised of 536 patients with POAG, including 290 females and 246 males. The study participants were examined at the Division of Eye Microsurgery of Saint Joasaph’s Belgorod Regional Clinical Hospital. The patients with POAG were unrelated Russians, residents of the Central Russia [11]. The subjects were enrolled for the study according to criteria described elsewhere [12]. All study participants signed a written informed consent in accordance with the principles of the Helsinki Declaration.
Table 1
The frequencies of alleles and genotypes for SNPs rs1063192, rs7865618, rs2157719, rs944800 and rs4977756 CDKN2B-AS1 gene in Russian patients with POAG.

| SNP genotype or allele | All (n=536) n frequency | Female (n=290) n frequency | Male (n=246) n frequency |
|------------------------|-------------------------|---------------------------|-------------------------|
| rs1063192 GG          | 104 0.1940              | 59 0.2034                 | 45 0.1829               |
| rs1063192 AG          | 256 0.4776              | 134 0.4621                | 122 0.4959              |
| rs1063192 AA          | 176 0.3264              | 97 0.3345                 | 79 0.3212               |
| rs1063192 G           | 464 0.4328              | 252 0.4345                | 212 0.4309              |
| rs1063192 A           | 608 0.5672              | 328 0.5655                | 280 0.5691              |
| rs7865618 GG          | 94 0.1753               | 52 0.1793                 | 42 0.1707               |
| rs7865618 AG          | 263 0.4907              | 139 0.4793                | 124 0.5041              |
| rs7865618 AA          | 179 0.3340              | 99 0.3414                 | 80 0.3252               |
| rs7865618 G           | 451 0.4207              | 243 0.4190                | 208 0.4228              |
| rs7865618 A           | 621 0.5793              | 337 0.5810                | 284 0.5772              |
| rs2157719 GG          | 85 0.1585               | 45 0.1552                 | 40 0.1626               |
| rs2157719 AG          | 249 0.4646              | 135 0.4655                | 114 0.4634              |
| rs2157719 AA          | 202 0.3769              | 110 0.3793                | 92 0.3740               |
| rs2157719 G           | 419 0.3909              | 225 0.3879                | 11 0.3943               |
| rs2157719 A           | 653 0.6091              | 355 0.6121                | 215 0.6057              |
| rs944800 GG           | 64 0.1194               | 32 0.1103                 | 32 0.1301               |
| rs944800 AG           | 241 0.4496              | 130 0.4483                | 111 0.4512              |
| rs944800 AA           | 202 0.3769              | 110 0.3793                | 92 0.3740               |
| rs944800 G            | 419 0.3909              | 225 0.3879                | 11 0.3943               |
| rs944800 A            | 653 0.6091              | 355 0.6121                | 215 0.6057              |
| rs4977756 GG          | 100 0.1866              | 61 0.2104                 | 39 0.1585               |
| rs4977756 AG          | 286 0.5336              | 154 0.5310                | 132 0.5366              |
| rs4977756 AA          | 150 0.2798              | 75 0.2586                 | 75 0.3049               |
| rs4977756 G           | 486 0.4534              | 276 0.4759                | 210 0.4268              |
| rs4977756 A           | 586 0.5466              | 304 0.5241                | 282 0.5732              |

Table 2
The frequencies of haplotypes for SNPs rs1063192, rs7865618, rs2157719, rs944800 and rs4977756 CDKN2B-AS1 gene in Russian patients with POAG.

| Haplotype (rs1063192-rs7865618-rs2157719-rs944800-rs4977756) | All (n=536), frequency | Female (n=290), frequency | Male (n=246), frequency |
|-------------------------------------------------------------|------------------------|---------------------------|-------------------------|
| GGGAG                                                       | 0.2221                 | 0.2197                    | 0.2304                  |
| AGGAG                                                       | 0.0127                 | 0.0125                    | 0.0130                  |
| GAGAG                                                       | 0.0220                 | 0.0189                    | 0.0272                  |
| AAGAG                                                       | 0.0101                 | 0.0137                    | 0.0068                  |
| GGAG                                                        | 0.0120                 | 0.0185                    | 0.0054                  |
| GGAGG                                                       | 0.0505                 | 0.0628                    | 0.0434                  |
| GGAGG                                                       | 0.0373                 | 0.0361                    | 0.0397                  |
| AAAG                                                        | 0.0713                 | 0.0859                    | 0.0641                  |
| GGGGA                                                       | 0.0262                 | 0.0211                    | 0.0359                  |
| AAAA                                                        | 0.0299                 | 0.0265                    | 0.0377                  |
| AGGAA                                                       | 0.0133                 | 0.0178                    | 0.0096                  |
| AAGGA                                                       | 0.0141                 | 0.0155                    | 0.0136                  |
| GGAGA                                                       | 0.0154                 | 0.0117                    | 0.0208                  |
| AGAGA                                                       | 0.0191                 | 0.0189                    | 0.0198                  |
| GAAGA                                                       | 0.0318                 | 0.0424                    | 0.0217                  |
| AAAGA                                                       | 0.3890                 | 0.3779                    | 0.4110                  |
Table 3
The literature data about associations of the studied polymorphisms CDKN2B-AS1 gene with POAG and optic disc characteristics (GWAS data).

| SNP         | Position (hg38) | Phenotype         | Association (significance)/(associated allele) | Reference |
|-------------|-----------------|-------------------|-----------------------------------------------|-----------|
| rs1063192   | 22003368        | POAG Vertical cup-disc ratio | OR= 0.79 (p=5 × 10^{-11}) (T) β=-0.01 mm^2 (p=4 × 10^{-15}) (G) | [1][2]    |
| rs7865618   | 22031006        | POAG Vertical cup-disc ratio | OR= 1.78 (p=9 × 10^{-11}) (A) β=-0.013 unit (p=5 × 10^{-24}) (G) β=-0.023 unit (p=1 × 10^{-21}) (G) | [3][4][5] |
| rs2157719   | 22033367        | POAG Vertical cup-disc ratio | OR= 1.45 (p=2 × 10^{-18}) OR= 1.41 (p= 3 × 10^{-33}) β=-0.013 unit (p=4 × 10^{-35}) | [6][7][8] |
| rs944800    | 22050899        | POAG               | OR= 1.33 (p=4 × 10^{-14}) (G) OR= 1.48 (p= 7 × 10^{-30}) (A) | [9]       |
| rs4977756   | 22068653        | POAG               | OR= 1.45 (p=2 × 10^{-18}) OR= 1.41 (p= 3 × 10^{-33}) β=-0.013 unit (p=4 × 10^{-35}) | [10]      |

2.2. DNA analysis

Whole blood sample (5 ml) from each participant was drawn by a certified nurse into a plastic vial (Vacutainer®) with 0.5M EDTA (pH=8.0). Total DNA was isolated from buffy coat using standard phenol-chloroform extraction method [13]. DNA quality was assessed by Nanodrop-2000 spectrophotometer (Thermo Scientific, Inc.). DNA samples of good quality (concentration 10-15 ng/mL, purity A260/A280=1.7-2.0) were included for genotyping.

Five SNPs such as rs1063192, rs7865618, rs2157719, rs944800 and rs4977756 of the CDKN2B-AS1 gene were selected for the study according to the following criteria [14,15]: 1) SNP showed an association with POAG by GWAS, 2) SNP possesses the regulatory potential, 3) SNP has eQTLs and/or sQTLs, 4) minor allele frequency, MAF > 5%.

All selected SNPs were associated with POAG in previously published GWAS (Table 3). These SNPs have the regulatory potential (Table 4), eQTLs (Table 5) and sQTLs (Table 6), as assessed by the HaploReg v4.1 (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.php) and GT-Exportal recourses (http://www.gtexportal.org).

DNA samples were genotyped using the MALDI-TOF mass spectrometry iPLEX platform (Agena Bioscience Inc, San Diego, CA). Concentration of DNA varied from 10 to 15 ng/mL. Assay Design Suite 1.0 (http://agenabio.com/assay-design-suite-10-software) was used to design a multiplex genotyping assay. About 5% of blind replicate samples were included for quality control of genotyping, and the repeatability test resulted in a 100% concordance rate.

2.3. Statistical analysis

Allele frequencies were estimated by the gene counting method, and the chi-square test was applied to identify significant departures from Hardy–Weinberg equilibrium (HWE). Differences in allele, genotype and haplotype frequencies between the study groups (females and males) were analyzed by the Kruskal-Wallis test. The haplotypes for the SNPs of the CDKN2B-AS1 gene were constructed using an algorithm implemented in the PLINK software, v. 2.050 [16] (http://zzz.bwh.harvard.edu/plink/).
Table 4
Regulatory effects of the 5 SNPs of the CDKN2B-AS1 gene (HaploReg, v4.1, update 05.11.2015) (https://pubs.broadinstitute.org/mammals/haploreg/haploreg.ph)

| chr | pos (hg38) | variant | Ref | Alt | AFR | AMR | ASN | EUR | SiPhy | Promoter | Enhancer | DNAse | Proteins | Motifs | NHGRI/EBI | GRASP | QTL | Selected eQTL | GENCODE | dbSNP |
|-----|------------|---------|-----|-----|-----|-----|-----|-----|-------|---------|----------|--------|---------|--------|--------|---------|--------|--------|----------------|----------|-------|
|     |            |         | freq| freq| freq| freq| cons| histone marks | histone marks | bound | changed | GWAS hits | GRASP hits | QTL hits | Selected eQTL hits | genes | func annot |
| 9   | 22003368   | rs1063192 | G   | A   | 0.99 | 0.79 | 0.82 | 0.57 |       | SKIN    | AIRE,GATA,Tgif1 | 2 hits | 3 hits |        |        |        |        |        |        | CDKN2B | 3'-UTR |
| 9   | 22031006   | rs7865618 | G   | A   | 0.99 | 0.8  | 0.9  | 0.58 |       | BLD, SKIN |        |        | 3 hits | 4 hits |        |        |        |        | RP11-145E5.5 | intronic |
| 9   | 22033367   | rs2157719 | C   | T   | 0.99 | 0.8  | 0.9  | 0.58 |       | BRST, SKIN |        |        | 3 hits | 4 hits |        |        |        |        | CDKN2B-AS1 | intronic |
| 9   | 22050899   | rs944800  | A   | G   | 0.99 | 0.86 | 0.9  | 0.68 |       | 12 tissues |        |        |        |        |        |        |        |        | CDKN2B-AS1 | intronic |
| 9   | 22068653   | rs4977756 | G   | A   | 0.67 | 0.78 | 0.79 | 0.6  |       | BRN     |        |        | 4 hits | 2 hits |        |        |        |        | CDKN2B-AS1 | intronic |
Table 5
The cis-eQTL values of the 4 SNPs of the CDKN2B-AS1 gene, (according to Genotype-Tissue Expression (GTEx) (http://www.gtexportal.org/)).

| SNP            | Gene expression | Reference allele | Alternative allele | Effect Size (β) | P-Value       | Tissue          |
|----------------|-----------------|------------------|-------------------|----------------|---------------|-----------------|
| rs1063192      | CDKN2A          | G                | A                 | 0.33           | 0.000031      | Brain - Cortex  |
| rs7865618      | CDKN2B          | G                | A                 | -0.14          | 0.000051      | Muscle - Skeletal |
| rs2157719      | CDKN2A          | C                | T                 | 0.33           | 0.000045      | Brain - Cortex  |
| rs944800       | CDKN2B-AS1      | A                | G                 | 0.26           | 0.0000026     | Cells - Transformed fibroblasts |

Table 6
The sQTL values of the 5 SNPs of the CDKN2B-AS1 gene (according to Genotype-Tissue Expression (GTEx) (http://www.gtexportal.org/)).

| SNP            | Gene Symbol   | Reference allele | Alternative allele | Intron Id                  | Effect Size (β) | P-Value       | Tissue          |
|----------------|---------------|------------------|-------------------|----------------------------|----------------|---------------|-----------------|
| rs1063192      | CDKN2B-AS1    | G                | A                 | 21995161:22046751:clu_55270 | 0.47           | 7.9e-9        | Pituitary       |
| rs7865618      | CDKN2B-AS1    | G                | A                 | 21995161:22046751:clu_55270 | 0.47           | 7.9e-9        | Pituitary       |
| rs2157719      | CDKN2B-AS1    | C                | T                 | 21995161:22046751:clu_55270 | 0.47           | 1.2e-8        | Pituitary       |
| rs944800       | CDKN2B-AS1    | A                | G                 | 21995161:22046751:clu_55270 | 0.4            | 0.0000004     | Pituitary       |
| rs4977756      | CDKN2B-AS1    | G                | A                 | 21995161:22046751:clu_55270 | 0.4            | 9.3e-8        | Pituitary       |

Declaration of Competing Interest

The authors declare that they have no competing financial interests or personal relationships which have, or could be perceived to have, influenced the work reported in this article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi: 10.1016/j.jdb.2020.105722.

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