Evaluation of CNTNAP2 gene polymorphisms for exfoliation syndrome in Japanese

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Purpose: To investigate the contactin-associated protein-like 2 (CNTNAP2) gene for single-nucleotide polymorphisms (SNPs) in Japanese patients with the exfoliation syndrome (XFS).

Methods: One hundred and eight unrelated Japanese patients with the XFS, and 199 normal controls were studied. Genomic DNA was extracted from the leukocytes of the peripheral blood, and 8 SNPs, rs826802, rs1404699, rs7803992, rs700308, rs4725736, rs2107856, rs2141388, and rs6970064, were amplified by polymerase chain reaction (PCR), directly sequenced, and genotyped.

Results: The allele frequencies of rs1404699 (p=8.57XE-3, odds ratio (OR)=1.59, 95% confidential intervals (CI); 1.12–2.24) and rs7803992 (p=5.43XE-4, OR=1.86, 95% CI; 1.31–2.65) were statistically significantly different between XFS and controls. In addition, there were significant differences in these genotype frequencies (p=0.0197 and 1.75XE-3). The allele and the genotype frequencies of rs2107856 and rs2141388, which were statistically significant SNPs in an earlier study, were not significantly different.

Conclusions: The variants, rs1404699 and rs7803992, of CNTNAP2 should be associated with XFS in the Japanese population.

The exfoliation syndrome (XFS; OMIM 177650) is a generalized disorder of the extracellular matrix and is characterized clinically by the pathological accumulation of abnormal fibrillar material in the anterior segment of the eye [1-3]. This predisposes the eye to glaucomatous optic neuropathy. The XFS has also been associated with lens zonule weakness, severe chronic secondary open-angle glaucoma, cataract formation, and also a spectrum of other serious spontaneous and surgical intraocular complications.

The prevalence of XFS varies markedly between populations being highest in Scandinavian countries, while the Anglo-Celtic Caucasians have a markedly lower prevalence [4-7]. The incidence increases with age and is highest in the age group between 70 and 80 years [5]. The prevalence of XFS in Japan was reported to be 1.1% in one study [8] and 4.8% in another study [9].

Thorleifsson et al. [10] found a strong association between single-nucleotide polymorphisms (SNPs) in the lysyl oxidase-like 1 (LOXL1) gene and XFS in the Swedish and Icelandic populations using a genome-wide association study (GWAS). This association was replicated in the United States of America [11-13] and also in other populations [14-23].

LOXL1 is a member of the lysyl oxidase family of proteins that catalyzes the oxidative deamination of lysine residues of tropoelastin [24]. The homeostasis of elastic fibers requires the lysyl oxidase-like 1 protein [25], and LOXL1 plays an important role in elastogenesis. Thus, it is quite possible that defects in LOXL1 can cause features of XFS that result from an aberrant production of elastin and accumulation of fibrillar materials in the anterior segment of the eye.

A GWAS was recently performed using a DNA-pooling approach, and a single genotype at the contactin-associated protein-like 2 (CNTNAP2) locus had significant associations between XFS and exfoliation glaucoma and two SNPs (rs2107856 and rs2141388). These findings were confirmed in an independent German cohort but not in an Italian cohort [26]. CNTNAP2 is a large gene spanning 2.3 mb of DNA on chromosome 7 and has 24 exons, and codes for the contactin-associated protein-like 2 (CNTNAP2, also called Caspr2). CNTNAP2 is member of the neurexin superfamily [27,28] and is possibly involved in stabilizing the location of the potassium channels in the juxtaparanodal region of the neuron [27]. It has been suggested to be a candidate gene for various neuropsychiatric disorders, e.g., the cortical dysplasia-focal epilepsy syndrome [29] and Pitt-Hopkins-like mental retardation [30]. However, its exact function and regulation are not known.

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The purpose of this study was to investigate 8 SNPs variations in \textit{CNTNAP2} in Japanese patients with the XFS.

**METHODS**

One hundred and eight unrelated Japanese patients with XFS (mean age 73.61±6.75 years; 57 men, 51 women) and 199 controls (mean age 69.7±11.3 years; 101 men, 98 women) were studied. The controls were matched by age and gender. The XFS group included 85 exfoliation glaucoma (XFG) patients. They were examined at the ophthalmic clinic of the Tohoku University Hospital, Sendai, Japan, and the Ehime University Hospital, Ehime, Japan. The purpose and procedures were explained to all patients, and an informed consent was obtained. This study was approved by the Institutional Review Boards of the Tohoku University and Ehime University, and the procedures used conformed to the tenets of the Declaration of Helsinki.

Routine ophthalmic examinations were performed on all patients. The criteria used to classify a patient as having XFS was an open anterior chamber angle with accumulation of abnormal fibrillar material in the anterior segment of the eye. In addition, three other criteria for XFG had to be met: 1) applanation intraocular pressure (IOP) >22 mmHg in each eye; 2) glaucomatous cupping in each eye including a cup-to-disc ratio >0.7; and 3) visual field defects determined by Goldmann perimetry and/or Humphrey field analyzer consistent with the glaucomatous cupping in at least one eye. The control subjects had the following characteristics: 1) IOP less than 22 mmHg; 2) normal optic discs; and 3) no family history of glaucoma.

Genomic DNA was extracted from the leukocytes of peripheral blood and purified with the Qiagen QIAamp Blood Kit (Qiagen, Valencia, CA). Genomic DNA was extracted from the leukocytes of the peripheral blood, and the 6 SNPs, rs1404699, rs700308, rs4725736, rs2107856, rs2141388, and rs6970064, were chosen from the earlier studies. Two newly identified SNPs, rs826802 and rs7803992, were designed around intron 9 of the gene. The \textit{CNTNAP2} gene structure with the location of the 8 SNPs is shown in Figure 1. They were amplified by polymerase chain reaction (PCR), directly sequenced, and genotyped. The amplifications were performed at 60 °C annealing temperature. The PCR fragments were purified with ExoSAP-IT (USB, Cleveland, OH), sequenced by the BigDye™ Terminator v3.1 Cycle Sequencing Kit (Perkin-Elmer, Foster City, CA) by an automated DNA sequencer (ABI PRISM™ 3100 Genetic Analyzer, Perkin-Elmer). The allele frequencies, genotypes, and haplotypes of the \textit{CNTNAP2} SNPs were determined.

**Statistical analysis:** The significance of associations between the phenotype and SNPs were determined by contingency table analysis using chi-square or Fisher's exact test. The odds ratios, approximating to relative risks, were calculated as a measure of the association between the \textit{CNTNAP2} allele frequency and the phenotype. For each odds ratio, the 95% confidence intervals were calculated. The inferred haplotypes, quantified between all pairs of biallelic loci, were estimated using the SNPalyze program version 7.0 (Dynacom, Yokohama, Japan). Additionally, a permutation test was performed to test the deviations of allelic frequencies of the SNPs and haplotypes. The Hardy–Weinberg equilibrium was analyzed using gene frequencies obtained by simple gene counting and the chi-square test with Yates' correction for comparing observed and expected values.

**RESULTS**

The allele frequencies and genotypes of the 8 \textit{CNTNAP2} SNPs, rs826802, rs1404699, rs7803992, rs700308, rs4725736, rs2107856, rs2141388, and rs6970064, were determined in the XFS patients.

![Figure 1. CNTNAP2 gene structure. The 8 SNPs studied were; 1. rs826802, 2. rs144699, 3. rs7803992, 4. rs700308, 5. rs4725736, 6. rs2107856, 7. rs2141388, and 8. rs6970064. SP, signal peptide; DISC, discoidin-like domain; LamG, laminin-G domain; EGF, epidermal growth factor like domain; FIB, fibrinogen-like domain; TM, transmembrane region; PDZBD, PDZ-domain binding site.](http://www.molvis.org/molvis/v18/a145)
Distribution of CNTNAP2 variants in XFS patients and control subjects:

The allele frequencies of rs1404699 (p=8.57XE-3, odd ratio (OR)=1.59, 95% confidential intervals (CI); 1,12–2.24) and rs7803992 (p=5.43XE-4, OR=1.86, 95% CI; 1.31–2.65) were statistically significant between the XFS group and the control group (Table 1). There were also significant differences in these genotype frequencies (p=0.0197 and 1.75XE-3; Table 2). Only the rs7803992 was significantly different between the XFG group and the control group (p=0.016; Table 1). Compared with the allele frequencies of rs2107856 and rs2141388 statistically significant SNPs in a previous study [26], our results showed no significantly difference between the XFS group and normal controls (Table 1). Also, the genotype frequencies of those in CNTNAP2 were not significantly higher in the two groups than in the control group (Table 2).

The genotype frequencies of rs700308 and rs6970064 were statistically significant (p=0.016 and 0.0017), but the allele frequencies were not significantly different (p=0.522 and 0.637) between the XFS group and control group. All SNPs adhered to the Hardy–Weinberg expectations (p>0.05).

Haplotype analyses at CNTNAP2 LD block in the Japanese population:
The inferred haplotypes between all pairs of biallelic loci on rs1404699 and rs7803992 were estimated (Table 3). The haplotype-based associations were tested with a 1,000 iterated permutation test. Four major haplotypes; C-A, T-G, T-A, C-G (each frequency >5%) were found in the XFS subjects and normal controls. T-G was over-represented in the XFS subjects with a highly significant difference in frequency compared to the control group (0.327 versus 0.202; p=0.003). In addition, the C-A haplotype was significantly less represented in the XFS subjects (0.522 versus 0.637; p=0.003).

Two locus analyses: A strong correlation between variants in LOXL1 and XFS has been reported [10], LOXL1 common risk haplotype is T-G (the major alleles T of the coding SNPs rs1048661 and major alleles G of the coding SNPs rs3825942) in Japan, instead of G-G in Europeans. We investigated how the variants in LOXL1 gene were related to CNTNAP2. We sorted our subjects for carriers and non-carriers of the risk haplotype T-G (Table 4). The numbers in the subgroup of non-T-G carriers was quite small, and there was no association of CNTNAP2 SNPs with the LOXL1 non-risk haplotype (Table 4; p=0.522 versus 0.637; p=0.003).

DISCUSSION

Association between CNTNAP2 and XFS: We compared the findings of Krumbiegel and colleagues [26] to that obtained

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**Table 1. CNTNAP2 allele frequencies in patients with exfoliation syndrome and in controls in Japanese.**

| dbSNP     | Allele | MAF in this study | MAF in previous study* |
|-----------|--------|-------------------|------------------------|
|           |        | XFS (n=108)       | XFG (n=85)             | Control (n=199) | p-value | XFS (n=770) | Control (n=444) | p-value |
| rs826802  | T      | 0.435 0.429       | 0.372 0.0884           | N/A N/A         | 0.0884 0.0198 |
| rs1404699 | T      | 0.412 0.388       | 0.307 0.0581           | 8.57XE-3 0.016  |
| rs7803992 | G      | 0.394 0.359       | 0.259 0.553            | N/A N/A         | 0.545 0.397 0.0225 |
| rs700308  | A      | 0.407 0.412       | 0.432 0.093            | 0.385 0.653     |
| rs4725736 | A¹     | 0.472 0.441       | 0.402 0.093            | 0.0138 0.103 0.0117 |
| rs2107856 | G²     | 0.450 0.441       | 0.432 0.687            | 0.709 0.776 0.003 |
| rs2141388 | C³     | 0.444 0.441       | 0.437 0.863            | 0.709 0.777 0.002 |
| rs6970064 | A⁴     | 0.181 0.182       | 0.123 0.0524           | 0.418 0.463 0.0306 |

*reported by Krumbiegel et al. [26]. MAF; minor allele frequency, XFS; Exfoliation Syndrome, XFG; Exfoliation Glaucoma. The significance of the association was determined by a contingency table analysis using the χ² test. Upper columns show XFS data, and lower columns show XFG data. 1. There was a difference between the Caucasian and Japanese. Minor allele in previous study was C. 2. Minor Allele in previous study was T. 3. Minor Allele in previous study was T. 4. Minor Allele in previous study was G.

**Distribution of CNTNAP2 variants in XFS patients and control subjects:** The allele frequencies of rs1404699 (p=8.57XE-3, odd ratio (OR)=1.59, 95% confidence intervals (CI); 1,12–2.24) and rs7803992 (p=5.43XE-4, OR=1.86, 95% CI; 1.31–2.65) were statistically significant between the XFS group and the control group (Table 1). There were also significant differences in these genotype frequencies (p=0.0197 and 1.75XE-3; Table 2). Only the rs7803992 was significantly different between the XFG group and the control group (p=0.016; Table 1). Compared with the allele frequencies of rs2107856 and rs2141388 statistically significant SNPs in a previous study [26], our results showed no significantly difference between the XFS group and the control group (Table 1). Also, the genotype frequencies of those in CNTNAP2 were not significantly higher in the two groups than in the control group (Table 2).

The genotype frequencies of rs700308 and rs6970064 were statistically significant (p=0.0402 and 0.0315), but the allele frequencies were not significantly different (p=0.553 and 0.0524) between the XFS group and control group. All SNPs adhered to the Hardy–Weinberg expectations (p>0.05).

Haplotype analyses at CNTNAP2 LD block in the Japanese population: The inferred haplotypes between all pairs of biallelic loci on rs1404699 and rs7803992 were estimated (Table 3). The haplotype-based associations were tested with a 1,000 iterated permutation test. Four major haplotypes; C-A, T-G, T-A, C-G (each frequency >5%) were found in the XFS subjects and normal controls. T-G was over-represented in the XFS subjects with a highly significant difference in frequency compared to the control group (0.327 versus 0.202; p=0.003). In addition, the C-A haplotype was significantly less represented in the XFS subjects (0.522 versus 0.637; p=0.003).

Two locus analyses: A strong correlation between variants in LOXL1 and XFS has been reported [10], LOXL1 common risk haplotype is T-G (the major alleles T of the coding SNPs rs1048661 and major alleles G of the coding SNPs rs3825942) in Japan, instead of G-G in Europeans. We investigated how the variants in LOXL1 gene were related to CNTNAP2. We sorted our subjects for carriers and non-carriers of the risk haplotype T-G (Table 4). The numbers in the subgroup of non-T-G carriers was quite small, and there was no association of CNTNAP2 SNPs with the LOXL1 non-risk haplotype (Table 4; p=0.522 versus 0.637; p=0.003). Besides the subgroups risk of T-G carriers, there was no significant association (Table 4; p=0.072 and 0.084, respectively).
from our Japanese cohorts. We found that two SNPs in CNTNAP2 were strongly associated with XFS. In an earlier study [26], the frequencies of rs2107856 and rs2141388 SNPs in CNTNAP2 were confirmed in an independent German cohort but not in the Italian cohort. Although neither the rs2107856 or rs2141388 SNPs was significant in our study, rs1404699 and nearby rs7803992 were statistically significant between the XFS group and the control group. Thus, it is possible that CNTNAP2 could be associated with XFS. Like other susceptible variants of a complex disease, the OR in the earlier study was modest at about 1.4. In our study, the highest OR was 1.86 for rs7803992. This difference can be explained by racial differences and heterogeneities. Because the number of XFG patients was small, it seemed that the statistical power was weak.

**Table 2. Frequency of genotypes CNTNAP2 gene in patients with exfoliation syndrome and in controls in Japanese.**

| dbSNP    | Allele | XFG (n=108) | p value* | XFG (n=85) | p value* | Control (n=199) |
|----------|--------|-------------|----------|------------|----------|-----------------|
| rs826802 | G/G    | 36 (33.3)   | 0.224    | 27 (31.8)  | 0.425    | 77 (38.7)       |
|          | G/T    | 50 (46.3)   |          | 43 (50.6)  |          | 96 (48.2)       |
|          | T/T    | 22 (20.4)   |          | 15 (17.6)  |          | 26 (13.1)       |
| rs1404699| C/C    | 38 (35.2)   | 0.0197   | 32 (37.6)  | 0.121    | 93 (46.7)       |
|          | C/T    | 51 (47.2)   |          | 40 (47.1)  |          | 90 (45.2)       |
|          | T/T    | 19 (17.6)   |          | 13 (15.3)  |          | 16 (8.1)        |
| rs7803992| A/A    | 38 (35.2)   | 1.75XE-3 | 31 (36.5)  | 6.22XE-3 | 112 (56.3)      |
|          | A/G    | 55 (50.9)   |          | 47 (55.3)  |          | 71 (35.7)       |
|          | G/G    | 15 (13.9)   |          | 7 (8.2)    |          | 16 (8.0)        |
| rs700308 | G/G    | 45 (41.7)   | 0.0402   | 33 (38.8)  | 0.282    | 63 (31.7)       |
|          | G/A    | 38 (35.2)   |          | 34 (40.0)  |          | 100 (50.3)      |
|          | A/A    | 25 (23.1)   |          | 18 (21.2)  |          | 36 (18.1)       |
| rs4725736| C/C    | 34 (31.5)   | 0.0659   | 27 (31.8)  | 0.385    | 69 (34.7)       |
|          | C/A    | 46 (42.6)   |          | 41 (48.2)  |          | 100 (50.3)      |
|          | A/A    | 28 (25.9)   |          | 17 (20.0)  |          | 30 (15.1)       |
| rs2107856| T/T    | 39 (36.1)   | 0.091    | 29 (34.1)  | 0.541    | 63 (31.7)       |
|          | T/G    | 41 (38.0)   |          | 37 (43.5)  |          | 100 (50.3)      |
|          | G/G    | 28 (25.9)   |          | 19 (22.4)  |          | 36 (18.1)       |
| rs2141388| T/T    | 39 (36.1)   | 0.100    | 29 (34.1)  | 0.470    | 61 (30.7)       |
|          | T/C    | 42 (38.9)   |          | 37 (43.5)  |          | 106 (53.3)      |
|          | C/C    | 27 (25.0)   |          | 19 (22.4)  |          | 32 (16.1)       |
| rs6970064| G/G    | 74 (68.5)   | 0.0315   | 58 (68.2)  | 0.0345   | 151 (75.9)      |
|          | G/A    | 29 (26.9)   |          | 23 (27.1)  |          | 47 (23.6)       |
|          | A/A    | 5 (4.6)     |          | 4 (4.7)    |          | 1 (0.5)         |

XFS; Exfoliation Syndrome, XFG; Exfoliation Glaucoma. Data presented are number of patients, unless otherwise indicated. The significance of the association was determined by a contingency table analysis using the $\chi^2$ test.

**Table 3. Haplotype analysis with rs1404699 and rs7803992 in patients with exfoliation syndrome and in controls in Japanese.**

| Haplotype | Overall | XFS | Control | p-value |
|-----------|---------|-----|---------|---------|
| C-A       | 0.5966  | 0.5217 | 0.637 | 0.003   |
| T-G       | 0.2464  | 0.3273 | 0.2024 | 0.003   |
| T-A       | 0.0972  | 0.0847 | 0.1041 | 0.489   |
| C-G       | 0.0597  | 0.0662 | 0.0564 | 0.708   |

XFS; Exfoliation Syndrome. The significance of the association was determined by a contingency table analysis using the $\chi^2$ test.

from our Japanese cohorts. We found that two SNPs in CNTNAP2 were strongly associated with XFS. In an earlier study [26], the frequencies of rs2107856 and rs2141388 SNPs in CNTNAP2 were confirmed in an independent German cohort but not in the Italian cohort. Although neither the rs2107856 or rs2141388 SNPs was significant in our study, rs1404699 and nearby rs7803992 were statistically significant between the XFS group and the control group. Thus, it is possible that CNTNAP2 could be associated with XFS. Like other susceptible variants of a complex disease, the OR in the earlier study was modest at about 1.4. In our study, the highest OR was 1.86 for rs7803992. This difference can be explained by racial differences and heterogeneities. Because the number of XFG patients was small, it seemed that the statistical power was weak.

**No association between CNTNAP2 and LOXL1 in Japanese:** Because a strong association of variants in LOXL1 in XFS has been reported [10], we compared the allele frequencies at CNTNAP2 locus based on the presence of the identified Japanese LOXL1 common risk haplotype T-G. We found no significant association to allele T of the rs1404699 and rs7803992 SNPs of CNTNAP2 in carriers of LOXL1 the risk T-G haplotype (Table 4), and also in non-risk haplotypes. These findings suggest that there is no association between
CNTNAP2 and LOXL1 in the Japanese. This would then mean that a LOXL1-independent mechanism is involved in CNTNAP2 function.

In a molecular genetic study, the most promising loci at 18q12.1–21.33 and 2q, 17p, and 19q have been proposed to be the susceptible loci in a Finnish population in an autosomal dominant mode of inheritance [31]. In a microarray study, 23 genes with different expression patterns in the anterior segment tissues of eyes with XFS have recently been reported [32]. This strongly suggests that an unidentified gene or environmental factors independent of the LOXL1 gene strongly influence the phenotypic expression of the XFS.

**CNTNAP2 function and molecular genetics:** CNTNAP2 is a single-pass transmembrane protein with multiple protein-interaction motifs typical of the neurexins, e.g., epidermal growth factor repeats, laminin globular domains, and F5/8-type C domain, and a putative PDZ-binding site. Poliak et al. [33] reported that CNTNAP2 is necessary to maintain the potassium channels at the juxtaparanodal region in myelinated axons. The SNPs we selected were located in introns 9, 10, and 11 (Figure 1), while several SNPs related to autism were located in intron 2 [34] and intron 13 [35]. The cortical dysplasia-focal epilepsy syndrome is caused by a single nucleotide deletion in Exon 22. Therefore, it seems that our SNPs have nearly no correlation with neuropsychiatric disorders. The rs1404699 and rs7803992 SNPs are located in intron 9 of the CNTNAP2 gene. Exon 9, nearby to intron 9, codes for the laminin globular domain, which contains proteins that play a wide variety of roles in cell adhesion, signaling, migration, assembly, and differentiation of cells. We suggest that alterations in membrane stabilization may contribute to the abnormal exfoliation matrix processes, which are associated with cell-surface irregularities, basement membrane destruction and degenerative alterations.

**Conclusions:** Identification of XFS-associated SNPs that will allow early detection of an increase in the IOP, or even before an elevation of IOP, would be desirable. Our findings showed that variants of CNTNAP2 rs1404699 and rs7803992 are significantly associated with XFS in the Japanese population. More studies of the functions and genotype-phenotype correlation of CNTNAP2 are required to determine the pathophysiology of XFS. In addition, further studies searching for secondary genetic and environmental factors that contribute to XFS is required to gain better understanding of the complex etiology of XFS.

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**REFERENCES**

1. Tarkkanen A, Kivela T, John G. Lindberg and the discovery of exfoliation syndrome. Acta Ophthalmol Scand 2002; 80:151-4. [PMID: 11952480]
2. Schlötzer-Schrehardt U, Naumann GO. Ocular and systemic pseudoexfoliation syndrome. Am J Ophthalmol 2006; 141:921-37. [PMID: 16678509]
3. Forsman E, Cantor RM, Lu A, Eriksson A, Fellman J, Jarvela I, Forsius H. Exfoliation syndrome: prevalence and inheritance in a subisolate of the Finnish population. Acta Ophthalmol Scand 2007; 85:500-7. [PMID: 17655611]
4. Forsius H. Prevalence of pseudoexfoliation of the lens in Finns, Lapps, Icelanders, Eskimos, and Russians. Trans Ophthalmol Soc U K 1979; 99:296-8. [PMID: 298430]
5. Forsius H. Exfoliation syndrome in various ethnic populations. Acta Ophthalmol Suppl 1988; 184:71-85. [PMID: 2853925]
6. Ringvold A. Epidemiology of glaucoma in northern Europe. Eur J Ophthalmol 1996; 6:26-9. [PMID: 8744847]
7. Mitchell P, Wang JI, Hourihan F. The relationship between glaucoma and pseudoexfoliation: the Blue Mountains Eye Study. Arch Ophthalmol 1999; 117:1319-24. [PMID: 10532440]
8. Shiose Y, Kitazawa Y, Tsukahara S, Akamatsu T, Mizokami K, Futa R, Katsushima H, Kosaki H. Epidemiology of glaucoma in Japan–a nationwide glaucoma survey. Jpn J Ophthalmol 1991; 35:133-55. [PMID: 1779484]
9. Iwase A, Suzuki Y, Araie M, Yamamoto T, Abe H, Shirato S, Kuwayama Y, Mishima HK, Shimizu H, Tomita G, Inoue Y, Kitazawa Y. The prevalence of primary open-angle glaucoma in Japanese: the Tajimi Study. Ophthalmology 2004; 111:1641-8. [PMID: 15350316]
10. Thorleifsson G, Magnusson KP, Sulem P, Walters GB, Guðbjartsson DF, Stefansson H, Jonsson T, Jonasdottir A, Stefandsottir G, Masson G, Hardarson GA, Petursson H, Arnarsson A, Motallebipour M, Wallerman O, Wadelius C, Gulcher JR, Thorsteinsdottir U, Kong A, Jonasson F,
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Stefansson K. Common sequence variants in the LOXL1 gene confer susceptibility to exfoliation glaucoma. Science 2007; 317:1397-400. [PMID: 17690259]

11. Fingert JH, Alward WL, Kwon YH, Wang K, Streb LM, Sheffield VC, Stone EM. LOXL1 mutations are associated with exfoliation syndrome in patients from the midwestern United States. Am J Ophthalmol 2007; 144:974-5. [PMID: 18036875]

12. Challá P, Schmidt S, Liu Y, Qin X, Vann RR, Gonzalez P, Allingham RR, Hauser MA. Analysis of LOXL1 polymorphisms in a United States population with pseudoexfoliation glaucoma. Mol Vis 2008; 14:146-9. [PMID: 18334928]

13. Fan BJ, Pasquale L, Grosskreutz CL, Rhee D, Chen T, Challa P, Schmidt S, Liu Y, Qin X, Vann RR, Gonzalez P, Allingham RR, Hauser MA. Analysis of LOXL1 polymorphisms in a United States population with pseudoexfoliation glaucoma. Mol Vis 2008; 14:1395-1401 [http://www.molvis.org/molvis/v18/a145] © 2012 Molecular Vision

14. Hewitt AW, Sharma S, Burdon KP, Wang JJ, Baird PN, Dimasi DP, Mackey DA, Mitchell P, Craig JE. Ancestral LOXL1 variants are associated with pseudoexfoliation in Caucasian Australians but with markedly lower penetrance than in Nordic people. Hum Mol Genet 2008; 17:710-6. [PMID: 18037624]

15. Hayashi H, Gotoh N, Ueda Y, Nakanishi H, Yoshimura N. Lysyl Oxidase-like 1 Polymorphisms and Exfoliation Syndrome in the Japanese Population. Am J Ophthalmol 2008; 145:582-5. [PMID: 18201684]

16. Fuse N, Miyazawa A, Nakazawa T, Mengekage M, Otomo T, Nishida K. Evaluation of LOXL1 polymorphisms in eyes with exfoliation glaucoma in Japanese. Mol Vis 2008; 14:1338-43. [PMID: 18648524]

17. Mabuchi F, Sakurada Y, Kashiwagi K, Yamagata Z, Iijima H, Tsukahara S. Lysyl oxidase-like 1 gene polymorphisms in Japanese patients with primary open angle glaucoma and exfoliation syndrome. Mol Vis 2008; 14:1303-8. [PMID: 18636115]

18. Mori K, Imai K, Matsuda A, Ikeda Y, Naruse S, Hitora-Takeshita H, Nakano M, Taniguchi T, Omi N, Tashiro K, Kinoshita S. LOXL1 genetic polymorphisms are associated with exfoliation glaucoma in the Japanese population. Mol Vis 2008; 14:1037-40. [PMID: 18552979]

19. Ozaki M, Lee KY, Vithana EN, Yong VH, Thalamuthu A, Mizoguchi T, Venkatraman A, Aung T. Association of LOXL1 gene polymorphisms with pseudoexfoliation in the Japanese. Invest Ophthalmol Vis Sci 2008; 49:3976-80. [PMID: 18450598]

20. Tanito M, Minami M, Akahori M, Kaidzu S, Takai Y, Ohira A, Iwata T. LOXL1 variants in elderly Japanese patients with exfoliation syndrome/glaucoma, primary open-angle glaucoma, normal tension glaucoma, and cataract. Mol Vis 2008; 14:1898-905. [PMID: 18958304]

21. Chen L, Jia L, Wang N, Tang G, Zhang C, Fan S, Liu W, Meng H, Zeng W, Liu N, Wang H, Jia H. Evaluation of LOXL1 polymorphisms in exfoliation syndrome in a Chinese population. Mol Vis 2009; 15:2349-57. [PMID: 19936304]

22. Lemmelä S, Forsman E, Onkamo P, Nurmi H, Laivuori H, Kivela T, Puska P, Heger M, Eriksson A, Forsius H, Jarvela I. Association of LOXL1 gene with Finnish exfoliation syndrome patients. J Hum Genet 2009; 54:289-97. [PMID: 19343041]

23. Williams SE, Whigham BT, Liu Y, Carmichael TR, Qin X, Schmidt S, Ramsay M, Hauser MA, Allingham RR. Major LOXL1 risk allele is reversed in exfoliation glaucoma in a black South African population. Mol Vis 2010; 16:705-12. [PMID: 20431720]

24. Thomassin L, Werneck CC, Broekelmann TJ, Gleyzal C, Hornstra IK, Mecham RP, Sommer P. The Pro-regions of lysyl oxidase and lysyl oxidase-like 1 are required for deposition onto elastic fibers. J Biol Chem 2005; 280:42848-55. [PMID: 16251195]

25. Liu X, Zhao Y, Gao J, Pawlyk B, Starcher B, Spencer JA, Yanagisawa H, Zuo J, Li T. Elastic fiber homeostasis requires lysyl oxidase-like 1 protein. Nat Genet 2004; 36:178-82. [PMID: 14745449]

26. Crumbiegel M, Pasutto F, Schlotzer-SchreHar J, Ubee C, Zenkel M, Mardin CY, Weisschu N, Paoli D, Gramer E, Becker C, Ekici AB, Weber BH, Nurnberg P, Kruse FE, Reis A. Genome-wide association study with DNA pooling identifies variants at CNTNAP2 associated with pseudoexfoliation syndrome. Eur J Hum Genet 2011; 19:186-93. [PMID: 20808326]

27. Poliak S, Gollan L, Martinez R, Custer A, Einheber S, Salzer JL, Trimmer JS, Shragar P, Peles E. Caspr2, a new member of the neurexin superfamily, is localized at the juxtaparanodes of myelinated axons and associates with K+ channels. Neuron 1999; 24:1037-47. [PMID: 10624965]

28. Einheber S, Sanazari G, Ching W, Scherer S, Milner TA, Peles E, Salzer JL. The axonal membrane protein Caspr, a homologue of neurexin IV, is a component of the septate-like paranodal junctions that assemble during myelination. J Cell Biol 1997; 139:1495-506. [PMID: 9396755]

29. Strauss KA, Puffenberger EG, Huertlfel MJ, Gottlieb S, Dobrin SE, Parod JM, Stephan DA, Morton DH. Recessive symptomatic focal epilepsy and mutant contactin-associated protein-like 2. N Engl J Med 2006; 354:1370-7. [PMID: 16571880]

30. Zweier C, de Jong JK, Zweier M, Orrico A, Ousager LB, Collins AL, Blijisma EM, Oortveld MA, Ekici AB, Reis A, Schenck A, Rauch A. CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. Am J Hum Genet 2009; 85:655-66. [PMID: 19896112]

31. Lemmelä S, Forsman E, Sistonen P, Eriksson A, Forsius H, Jarvela I. Genome-wide scan of exfoliation syndrome. Invest Ophthalmol Vis Sci 2007; 48:4136-42. [PMID: 17724198]

32. Zenkel M, Poschi E, von der Mark K, Hofmann-Rummelt C, Naumann GO, Kruse FE, Schlotzer-SchreHar U. Differential gene expression in pseudoexfoliation syndrome. Invest Ophthalmol Vis Sci 2005; 46:3742-52. [PMID: 16186358]

33. Poliak S, Salomon D, Elhanany H, Sabanay H, Kiernan B, Zenkel M, Mardin CY, Weisschu N, Paoli D, Gramer E, Becker C, Ekici AB, Weber BH, Nurnberg P, Kruse FE, Reis A. Genome-wide association study with DNA pooling identifies variants at CNTNAP2 associated with pseudoexfoliation syndrome. Eur J Hum Genet 2011; 19:186-93. [PMID: 20808326]

34. Arking DE, Cutler DJ, Brune CW, Teslovich TM, West K, Collins AL, Blijisma EM, Oortveld MA, Ekici AB, Reis A, Schenck A, Rauch A. CNTNAP2 and NRXN1 are mutated in autosomal-recessive Pitt-Hopkins-like mental retardation and determine the level of a common synaptic protein in Drosophila. Am J Hum Genet 2009; 85:655-66. [PMID: 19896112]
common genetic variant in the neurexin superfamily member CNTNAP2 increases familial risk of autism. Am J Hum Genet 2008; 82:160-4. [PMID: 18179894]
35. Alarcón M, Abrahams BS, Stone JL, Duvall JA, Perederiy JV, Bomar JM, Sebat J, Wigler M, Martin CL, Ledbetter DH, Nelson SF, Cantor RM, Geschwind DH. Linkage, association, and gene-expression analyses identify CNTNAP2 as an autism-susceptibility gene. Am J Hum Genet 2008; 82:150-9. [PMID: 18179893]