An Allele of Microtubule-Associated Protein 1A (Mtap1a) Reduces Photoreceptor Degeneration in Tulp1 and Tub Mutant Mice

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PURPOSE. To identify genes that modify photoreceptor cell loss in the retinas of homozygous Tulp1tm1Pjn and Tubtub mice, which exhibit juvenile retinitis pigmentosa.

METHODS. Modifier loci were identified by genetic quantitative trait locus analysis. F2 Tulp1tm1Pjn×/tm1Pjn mutant mice from a B6-Tulp1tm1Pjn×/tm1Pjn × AKR/J intercross were genotyped with a panel of single nucleotide polymorphism markers and phenotyped by histology for photoreceptor nuclei remaining at 9 weeks of age. Genotype and phenotype data were correlated and examined with Pseudomarker 2.02 using 128 imputations to map modifier loci. Thresholds for the 95%, 10%, and 1% significance levels were obtained from 100 permutations. A significant, protective candidate modifier was identified by bioinformatic analysis and confirmed by crossing transgenic mice bearing a protective allele of this gene with Tulp1- and Tub-deficient mice.

RESULTS. A significant, protective modifier locus on chromosome 2 and a suggestive locus on chromosome 13 that increases photoreceptor cell loss were identified in a B6-Tulp1tm1Pjn×/tm1Pjn × AKR/J intercross. The chromosome 2 locus mapped near Mtap1a, which encodes a protein associated with microtubule-based intracellular transport and synapse function. The protective Mtap1a129P2/Ckatlnd allele was shown to reduce photoreceptor loss in both Tulp1tm1Pjn×/tm1Pjn and Tubtub mice.

CONCLUSIONS. It was demonstrated that the gene Mtap1a, which modifies hearing loss in Tubtub mice, also modifies retinal degeneration in Tubtub mice and Tulp1tm1Pjn×/tm1Pjn mice. These results suggest that functionally nonredundant members of the TULP family (TUB and TULP1) share a common functional interaction with MTAP1A.

Retinal degenerative diseases are highly variable in onset, severity, and rate of progression. Retinitis pigmentosa (RP), with an incidence of roughly 1:4000 in the United States, is a prominent example of this variability.1 RP consists of a heterogeneous group of retinal dystrophies characterized by rod and cone photoreceptor cell degeneration, usually through apoptotic cell death. Clinical features of the disease include night blindness, which is often accompanied by a gradual loss of peripheral visual field and eventual loss of central vision. Variation in the clinical presentation of the disease is partly explained by the existence of >48 RP genes, each with multiple alleles that may cause substantial differences in disease phenotype (Retinal Information Network, http://www.sph.uth.tmc.edu/Retnet/). However, variation has been documented even among family members of similar age with identical RP mutations, suggesting contributions from other genetic or environmental factors.7–12 Modifier genes, which influence the phenotypic expression of genes in monogenic and multigenic traits, are a potential source of variation in such cases.13 Identifying modifier genes in RP may help to explain variation in disease presentation and therapeutic response, improve understanding of functional pathways that underlie the RP phenotype, and reveal important targets for clinical intervention.

Our interest in RP gene modifiers arose from studying two members of the tubby-like protein (TULP)4 gene family that are associated with retinal degeneration. The TULP gene family consists of four members: Tub, Tubp, Tulp2, and Tulp3. Homozygous mutations of Tub (Tubtm1b) and Tulp1 in mice cause increased apoptotic photoreceptor cell death and early-onset retinal degeneration; Tub mutants also exhibit cochlear degeneration and late-onset obesity.14–17 In humans, a disruption in Tulp1 has been identified as the causative factor of RP type 14, a rare, autosomal recessive form of RP that is genetically heterogeneous.20–25 Indeed, 23 pathogenic TULP1 mutations were identified from the literature in a recent study of human patients with RP or Leber congenital amaurosis.24 Much evidence suggests that TUB and TULP1 function in vesicular transport in neurons, because disruption of either Tub or Tulp1 leads to abnormal accumulation of vesicles in the photoreceptor matrix at the level of the inner segments,27,28 and deficiency of Tulp1 results in structural and functional defects at the photoreceptor synapse.27,28 These defects are thought to be responsible for the observed photoreceptor cell apoptosis. However, other studies point to a role of the TULP family14 in insulin signaling,29 transcriptional regulation,30,31 and phagocytosis.32,33 Thus, it remains to be determined which of the proposed functions of TUB and TULP1 are of greatest relevance in the healthy and diseased retina.

To gain insight into how disruptions in TULP family members lead to retinal degeneration, we previously performed a quantitative trait locus (QTL) analysis by outcrossing B6.Cg-Tubtm1b mutant mice to strain AKR/J, and assessed the progression of photoreceptor degeneration in F2 progeny.34 In homozygous tub F2 mice, a suggestive protective locus (P = 0.05) from AKR/J was identified on chromosome 2. Likewise, here, in a similar cross with Tulp1tm1Pjn×/tm1Pjn mutant mice, a

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significant locus ($P < 0.01$) from AKR/J is identified in the same region on chromosome 2. In both studies, the photoreceptor protective locus on chromosome 2 overlaps the mott1 (modifier of tubby hearing1) locus, which our laboratory had previously identified as Mtap1a.55,36

Crossing the Tulp1tm1Pjn/tm1Pjn and Tubtub/tub mutant mice to transgenic mice carrying a 129P2/OlaHsd Mtap1a+ allele resulted in a significant protective effect ($P < 0.0005$ and $P < 0.04$, respectively) against photoreceptor loss in the F2 generation in transgene-positive (tg+) Tulp1tm1Pjn/tm1Pjn and B6.Cg-Tubtm1Pjn/tb mutant mice. These results indicate that, although Tulp1 and Tub are not functionally redundant, they both exhibit a genetic interaction with Mtap1a. Because MTAP1A is implicated in cytoskeletal processes at the neuronal synapse,37 these findings further support the hypothesis that TULP family members are involved in synapse maintenance36 or architecture.28,38

**METHODS**

**Experimental Animals**

All mice were treated in accordance with the Animal Care and Use Committees at each of the contributing institutions and in compliance with the Association for Research in Vision and Ophthalmology (ARVO) statement for ethical care and use of animals.

**Mouse Production and Mapping**

Mutant mice from an intercross of homozygous B6.129 × 1-Tulp1tm1Pjn/P AKR/J were genotyped by PCR to identify Tulp1tm1Pjn homozygotes (designated as Tulp1tm1Pjn/tm1Pjn mice elsewhere in this study). The eyes from 9-week-old F2 Tulp1tm1Pjn/tm1Pjn × intercross mice were processed for histologic observation and scored for the loss of photoreceptor nuclei (1, mild; 2, moderate; 3, severe). Mice were genotyped (KBiosciences, Beverly, MA) with a panel of single nucleotide polymorphism (SNP) markers spaced at approximate 20-cM intervals. The genotype and phenotype data were analyzed with Pseudomarker 2.0239 using 128 imputations. One hundred permutations were performed to determine thresholds for the 63%, 10%, 5%, and 1% significance levels.

To confirm the chromosome 2 QTL, additional F2 Tulp1tm1Pjn/tm1Pjn mutant mice were collected, and follow-up genotyping on these mice combined with the initial cohort was performed in a fashion similar to that described by Danciger and colleagues.40 Briefly, DNA was genotyped with simple sequence length polymorphic (SSLP) markers at 10-cM intervals in chromosomal regions, demonstrating possible QTL loci, and analyzed using Pseudomarker 2.02 as described earlier.

**Microscopy**

Whole eyes were enucleated, fixed in 37.5% methanol, 12.5% glacial acetic acid in phosphate buffered saline, embedded in paraffin, and sectioned at 6-μm intervals. The sections were mounted on commercial slides (SuperFrost Plus; Fisher Scientific, Pittsburgh, PA) and stained with hematoxylin and eosin. Sections were analyzed by brightfield illumination on a light microscope (Leitz DMRO; Leica Microsystems, Buffalo Grove, IL) and images were collected with a commercial software package (FireCam software; Leica Microsystems). Brightness and contrast of images were optimized with a digital imaging package (Photoshop 7.0; Adobe Systems, San Jose, CA).

**Quantification of Retinal Degeneration**

To quantify the degree of retinal degeneration, we followed a previously published protocol.35 The section in which the optic nerve was at its greatest width was selected from serial sections, and carefully photographed. For a quantitative measure of retinal degeneration the number of rows of nuclei contained within the outer nuclear layer (ONL) were counted at three points within a 200-μm square near the optic nerve head and the values were averaged. Because the thickness of the inner nuclear layer (INL) is not affected by the Tulp1 mutation,54 INL thickness was measured to identify oblique sections, which were subsequently removed from the data set.

**RESULTS**

**QTL Analysis of Genetic Modifiers of Tulp1tm1Pjn/tm1Pjn Retinal Degeneration**

To detect genetic modifiers of Tulp1tm1Pjn/tm1Pjn retinal degeneration, we first conducted pilot studies of F2 Tulp1tm1Pjn/tm1Pjn mutant mice from a B6-Tulp1tm1Pjn/tm1Pjn × AKR/J intercross to identify an age at which the greatest range of ONL phenotypes could be detected. The ONL phenotype of the oldest mice examined, 21 weeks of age, consisted of only one or two rows of photoreceptor nuclei and exhibited little variation (data not shown). Thus, 9-week-old mice were selected for QTL analysis. A total of 72 age-matched F2 Tulp1tm1Pjn/tm1Pjn mutant mice from a B6-Tulp1tm1Pjn/tm1Pjn × AKR/J intercross were identified by PCR genotyping and the eyes processed for histologic analysis. Although the retinas of wild-type and heterozygous mice were arranged in orderly layers (Fig. 1A) with a prominent INL and ONL, the retinas of Tulp1tm1Pjn/tm1Pjn × AKR/J mutant mice were abnormal, with a marked reduction in the number of nuclei in the ONL, indicating photoreceptor cell loss (Figs. 1B–F, arrows). Strikingly, the number of ONL nuclei among these animals varied considerably. This variation in ONL nuclei was specific for homozygous Tulp1tm1Pjn/tm1Pjn mice and was not observed in randomly sampled retinas from heterozygous or wild-type littermates (data not shown).

Photoreceptor cell loss in each mutant mouse was scored by assigning a value based on the distribution of photoreceptor nuclei remaining (1, mild; 2, moderate; 3, severe loss) and the animals were genotyped with SNP markers. Although QTL analysis identified no statistically significant modifier loci with the first cohort of 72 animals, peaks on chromosomes 1, 2, 6, 12, and 13 nearly reached the significance level for suggestive loci ($P < 0.63$; $n = 72$; Fig. 2A). Therefore, 44 additional mutant mice were collected, and SSLP markers were tested at 10-cM intervals across chromosomes 1, 2, 6, 12, and 13 in all samples combined ($n = 116$ mice). Analysis of the combined data indicated a significant modifier locus on chromosome 2 ($P < 0.01$) and a suggestive locus on chromosome 13 ($P < 0.63$) (Fig. 2B). The locus on chromosome 2 slowed the rate of photoreceptor cell degeneration (Fig. 2C), whereas the locus on chromosome 13 enhanced the rate of photoreceptor cell loss (Fig. 2D).

**Identification of Candidate Modifier Genes on Chromosome 2**

The region contained under the highest peak on chromosome 2 comprised an interval of approximately 45 Mb (115 to 160 Mb). We expected modifier genes within this interval to show nonsynonymous coding sequence differences between the strain backgrounds that were intercrossed, C57BL/6J and AKR/J. Since this interval contained too many genes to analyze individually, candidate quantitative trait genes (QTGs) were identified by a “virtual” approach using bioinformatic tools as described.40 Searching the critical interval with the PosMed virtual positional cloning database (http://omicspace.riken.jp/PosMed/) and the keyword “retina” produced a list of 161 genes known to be expressed or function in the retina. To further narrow the list of candidate genes, each gene from the PosMed list was evaluated as to whether mutant alleles were associated with an abnormal eye phenotype using the MGI Phenotypes database (http://www.informatics.jax.org/phenotypes).
An Allele of Mtap1a Modifies Retinal Degeneration in Tulp1tm1Pjn/tm1Pjn Mutant Mice

Our laboratory has previously reported a modifier of Tub hearing (motb1) on chromosome 2 in strains AKR/J, CAST/Ei, and 129P2/OlaHsd. Subsequent fine mapping and sequencing identified multiple polymorphisms in the microtubule-associated protein 1A (Mtap1a) gene. A C57BL/6J mouse carrying a transgenic Mtap1a

\[ Mtap1a^{motb1+} \]

allele from the 129P2/OlaHsd strain (Mtap1a transgene) was mated to Tub

\[ Tub^tub/tub \]

mice and, subsequently, the Mtap1a transgene was found to rescue hearing loss in Tub

\[ Tub^tub/tub \]

mice. To test whether the Mtap1a transgene also attenuates photoreceptor cell loss in Tulp1tm1Pjn/tm1Pjn mice, Tulp1tm1Pjn tm1Pjn mutant mice were mated to Mtap1a transgene positive mice, and the F1s were intercrossed to generate F2 progeny. Retinas of F2

\[ Tulp1tm1Pjn/tm1Pjn \]

mice with the Mtap1a transgene (tg+) and without the Mtap1a transgene (tg−) were compared histologically at 9 weeks of age (Figs. 3A, 3B). The number of ONL nuclei remaining in the central retina of Tulp1tm1Pjn/tm1Pjn mutant mice with and without the Mtap1a transgene were counted. The average number of photoreceptor nuclei remaining in mutant retinas lacking the Mtap1a transgene averaged 112 ± 7.5 (Fig. 3A), whereas the number of photoreceptor nuclei remaining in the mutant retinas carrying the Mtap1a transgene averaged 177 ± 12.2 (Fig. 3B). The degree of photoreceptor cell loss was significantly decreased in mutant mice carrying the Mtap1a transgene (P < 0.0005, Student’s t-test, n = 6 each) (Fig. 3C).

Mtap1a Modifies Retinal Degeneration in Tub

\[ Tub^tub/tub \]

Mutant Mice

Mtap1a maps to a region located at 121 Mb on mouse chromosome 2, near the peak location (D2Mit17, 122 Mb) of a suggestive QTL for retinal degeneration in an intercross of B6.Cg-tub/tub × AKR/J mice (Fig. 4A). Due to the ability of the 129P2/OlaHsd Mtap1a

\[ Mtap1a^{motb1+} \]

transgene to slow the rate of photoreceptor loss in Tub

\[ Tub^tub/tub \]

mutant mice, we investigated whether the same allele of Mtap1a was capable of modifying retinal degeneration in homozygous Tub

\[ Tub^tub/tub \]

mutant mice as well. Mtap1a transgenic mice were intercrossed with B6.Cg-tub/tub mice and the retinas of the F2 generation were examined. Retinas of B6.Cg-tub/tub mice with and without the Mtap1a transgene were compared histologically at 22 weeks of age. The later time point was selected because retinal degeneration in B6.Cg-tub/tub is slower than that in Tulp1tm1Pjn/tm1Pjn mutant mice. The numbers of ONL nuclei remaining in the central retina of B6.Cg-tub/tub mice with and without the Mtap1a transgene were counted. The average number of photoreceptor nuclei remaining in
mutant retinas lacking the Mtap1a transgene averaged $76 \pm 18.2$ (Fig. 4B), whereas the number of photoreceptor nuclei remaining in mutant retinas carrying the Mtap1a transgene averaged $126 \pm 14.4$ (Fig. 4C). Statistical analysis indicated the degree of photoreceptor cell loss was markedly decreased in the mutant B6.Cg-tub/tub mice carrying the Mtap1a transgene ($P < 0.04$, Student’s $t$-test, $n = 5$ each) (Fig. 4D).

**DISCUSSION**

This study has identified a significant locus on AKR/J chromosome 2 that modifies the progression of retinal degeneration in Tulp1tm1Pjn/tm1Pjn mice. Mating of Tulp1tm1Pjn/tm1Pjn mice to mice carrying an Mtap1a transgene derived from the 129P2/OlaHsd strain indicated that the protective gene within the chromosome 2 locus was Mtap1a. We demonstrated a similar protective effect of the 129P2/OlaHsd Mtap1a$m^{oth1-r}$ allele on photoreceptor loss in Tub$tub/tub$ mice. Our results indicate that Mtap1a is a genetic modifier of both Tulp1 and Tub raise the possibility that two members of the TULP protein family (TULP1 and TUB) share a common functional interaction with MTA1A. This interaction may be a characteristic feature of sensory neurons because the protective allele of Mtap1a modulates the Tub$tub/tub$ mutant phenotype in both the ear and retina.

We combined QTL analysis and bioinformatic techniques to identify candidate genetic modifiers. Although QTL analysis is a powerful tool for identifying large chromosomal regions that influence a given phenotype, the identification of individual genes within the QTL that specifically influence the phenotype of interest is rare. This is inherent to this type of analysis because, as the region of interest becomes smaller, the number of crossovers observed within the region become correspondingly infrequent. Moreover, the imperfect phenotype–genotype correspondence of a QTL dictates that quantitative statistical analysis must be performed to define the most likely candidate regions. The expense to generate, house, and genotype enough mice to obtain sufficient crossovers to delineate the critical region required to narrow the candidate gene pool to a single or a few genes is often prohibitive. Even well-designed studies using large numbers of mice with closely spaced genotypes can fail to minimize the critical region to a manageable number of candidate genes. For this reason, we chose to filter our results through the PosMed database as reported by Danciger and colleagues, and to further filter the results through reports of phenotypic relevance of these genes to retinal development, degeneration, and function and by the pres-
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TABLE 1. Candidate QTGs Identified on AKR/J Chromosome 2

<table>
<thead>
<tr>
<th>Gene*</th>
<th>Position</th>
<th>GO Molecular Function‡</th>
<th>Mutant Eye Phenotype‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meta2</td>
<td>115 Mb</td>
<td>Sequence-specific DNA binding transcription factor activity (GO:0003700)</td>
<td>Developmental eye defects</td>
</tr>
<tr>
<td>Tyro3</td>
<td>119 Mb</td>
<td>Transmembrane receptor protein tyrosine kinase activity (GO:0004714)</td>
<td>Vision/eye; retinal degeneration</td>
</tr>
<tr>
<td>Mtap1a5</td>
<td>121 Mb</td>
<td>Actin binding (GO:0003779)</td>
<td>Possible modifier of tub/tub retinal degeneration</td>
</tr>
<tr>
<td>Nphp1</td>
<td>127 Mb</td>
<td>Protein binding (GO:0005515)</td>
<td>Vision/eye; retinal degeneration</td>
</tr>
<tr>
<td>Mertk</td>
<td>128 Mb</td>
<td>Transmembrane receptor protein tyrosine kinase activity (GO:0004714)</td>
<td>Vision/eye; retinal degeneration</td>
</tr>
<tr>
<td>Bel211</td>
<td>128 Mb</td>
<td>Microtubule binding (GO:0008017)</td>
<td>Increased retinal thickness</td>
</tr>
<tr>
<td>Pamk2</td>
<td>131 Mb</td>
<td>Pantetheine kinase activity (GO:0004594)</td>
<td>Vision/eye; retinal degeneration</td>
</tr>
<tr>
<td>Plocb4</td>
<td>135 Mb</td>
<td>Mitogen-activated protein kinase binding (GO:0051019)</td>
<td>Vision/eye; reduced visual processing</td>
</tr>
<tr>
<td>Jag1</td>
<td>136 Mb</td>
<td>Notch binding (GO:0005112)</td>
<td>Vision/eye; developmental eye defects</td>
</tr>
<tr>
<td>Mkks</td>
<td>136 Mb</td>
<td>ATP binding (GO:0005524)</td>
<td>Vision/eye; retinal degeneration</td>
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<tr>
<td>Bfsp1</td>
<td>143 Mb</td>
<td>Structural constituent of eye lens (GO:0005212)</td>
<td>Vision/eye; cataract</td>
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<td>Vst1</td>
<td>150 Mb</td>
<td>Sequence-specific DNA binding transcription factor activity (GO:0003700)</td>
<td>Vision/eye; impaired retinal electrophysiology</td>
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<td>E2f1</td>
<td>154 Mb</td>
<td>Sequence-specific DNA binding transcription factor activity (GO:0003700)</td>
<td>Vision/eye; defects</td>
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<tr>
<td>Gss</td>
<td>155 Mb</td>
<td>Glutathione synthase activity (GO:0004363)</td>
<td>Seasonal sensitivity to light</td>
</tr>
<tr>
<td>Src</td>
<td>157 Mb</td>
<td>Nonmembrane spanning protein tyrosine kinase activity (GO:0004715)</td>
<td>Vision/eye; Glaucoma</td>
</tr>
<tr>
<td>Rbl1</td>
<td>157 Mb</td>
<td>Transcription factor binding (GO:0008134)</td>
<td>Vision/eye; retinoblastoma</td>
</tr>
</tbody>
</table>

* Candidate genes within the modifier locus were identified from PosMed, MGI Phenotypes, and PubMed databases as described in the text. ‡ When multiple gene ontology (GO) molecular functions were found, a single informative molecular function was chosen, with the corresponding GO term accession number given in parentheses. ‡ The existence of mutant alleles affecting vision or the eye (Vision/eye) was determined with MGI Phenotypes. Other evidence for an ocular phenotype was obtained from PubMed listings. § Nonsynonymous coding difference between strains.

ence of nonsynonymous coding SNPs. The filtering process allowed us to test a subset of biologically relevant genes with known retinal associations within the critical interval for sequence changes. The success of this combined QTL and bioinformatics approach is expected to improve as genetic tools such as the Collaborative Cross and Diversity Outbred mice become available for high-resolution genetic mapping, and as the annotations and quality of bioinformatics search engines increase.

Although the modifier locus on chromosome 13 identified in our study did not reach statistical significance, the data raise the possibility of an intriguing modifier gene that enhances the loss of photoreceptor cells. By filtering genes with the same PosMed and bioinformatic criteria we used for chromosome 2 and by screening the results for nonsynonymous coding changes between C57BL/6j and AKR/J (data not shown), we have tentatively identified Lyst as a potential candidate gene in the critical interval of chromosome 13. LYST is a widely expressed protein involved in vesicular trafficking, particularly in the biogenesis of lysosomes and related organelles. Lyst mutations in beige and gray mice exhibit lysosomal abnormalities within the retinal pigment epithelium, and LYST mutations in humans cause Chediak-Higashi syndrome, a systemic disease with ocular manifestations that include a progressive visual loss consistent with retinal degeneration. A spontaneous mouse mutant of the Lyst gene is available (Lystsh+/−), which might be used to test for modifier effects on Tulp1 and Tub photoreceptor degeneration.

Our finding that Mtap1a is a genetic modifier of both Tulp1 and Tub supports the hypothesis that TUB and TULP1 function in synaptic maintenance or architecture, possibly reflecting their role in vesicular trafficking throughout the photoreceptor cell. MTAP1A (also known as MAP1A) is predominantly found at the synapses of adult neurons, where it associates with both filamentous-actin and microtubules, presumably integrating these two components of the cytoskeleton. We previously showed that MTAP1A interacts with DLG4 (previously known as PSD95), a PDZ-domain protein that organizes transmembrane signaling proteins and the cytoskeleton at postsynaptic membranes. In the mouse retina, DLG4 local-
izes to the presynaptic terminal of rod and cone photoreceptor cells.50 Interestingly, TULP1 has also been shown to interact with dynamin-1, a neuron-specific GTPase that has roles in endocytosis, vesicle formation, vesicular movement at the trans-Golgi network, and plasma membrane and vesicle recycling at neuronal synapses.51 Tub- and Tulp1-deficient mice mislocalize rhodopsin into extracellular vesicles and alter the cellular distribution of arrestin and transducin, consistent with a trafficking defect.25,26 Tulp1 mice also show striking defects in the normal distribution of photoreceptor synaptic proteins.27,28 Together with our observations, these findings suggest a working model in which MTAP1, TUB, and TULP1 in conjunction with components of the cytoskeleton are necessary for maintaining the architecture of the photoreceptor synapse and/or vesicular trafficking at the synapse and inner segment.

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