Novel and Recurrent KIF21A Mutations in Congenital Fibrosis of the Extraocular Muscles Type 1 and 3

Shasha Lu, MD, PhD; Chen Zhao, MD, PhD; Kanxing Zhao, MD, PhD; Ningdong Li, MD, PhD; Catharina Larsson, MD, PhD

Objective: To characterize the disease-causing mutations and associated clinical phenotypes in 5 Chinese families with congenital fibrosis of the extraocular muscles (CFEOM).

Methods: Ophthalmic investigations included visual acuity, levator function, documentation of compensatory head position, ocular motility, and slitlamp and fundus examinations. The kinesin family member 21A gene (KIF21A) was sequenced for mutation detection. Genotyping and linkage analysis were performed for the KIF21A/FEOM1 and FEOM3 loci.

Results: Four families were clinically classified as having CFEOM type 1 (CFEOM1) with full expression of severe ptosis and ophthalmoplegia. One family had CFEOM type 3 (CFEOM3) with typically varying expression of phenotypes between individuals. Recurrent heterozygous KIF21A mutations were identified in 2 CFEOM1 families (2860C>T) and the CFEOM3 family (2861G>A). In another CFEOM1 family, a novel missense mutation (84C>G, C28W) was revealed.

Conclusions: The novel KIF21A mutation 84C>G demonstrated in a CFEOM1 family affects the kinesin motor domain, supporting that mutations may also occur outside the commonly involved coiled-coil domain. The 2861G>A mutation found in a CFEOM3 family has been previously reported in CFEOM1, further supporting that different phenotypes can arise from identical mutations.

Clinical Relevance: Clinical and genetic characterization are complementary tools for diagnostic, prognostic, and treatment purposes in CFEOM.

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CONGENITAL FIBROSIS OF the extraocular muscles (CFEOM) is a group of developmental disorders in which defective innervation by the oculomotor and/or trochlear nerves impairs the extraocular muscles, leading to ophthalmoplegia and ptosis.1,2 Autosomal dominant CFEOM occurs in 2 clinical forms with varying expressivity.2 In CFEOM1 (OMIM #135700), which is the most common, all affected family members are born with bilateral severe ptosis and ophthalmoplegia characterized by the chin-up position of the head and restricted vertical and horizontal ocular motility.3 By contrast, the members of a CFEOM3 (OMIM %600638) family demonstrate variable expressivity of CFEOM, and at least 1 affected individual should lack or have only unilateral ophthalmoplegia or ptosis or have 1 or both eyes fixed above the midline or the ability to raise 1 or both eyes above the midline.4,5 The majority of CFEOM kindreds are caused by mutations in the kinesin family member 21A gene (KIF21A) at the FEOM1 locus in the chromosomal region 12q12.5,6,7 KIF21A mutations have also been reported in CFEOM3 families6,10; however, most CFEOM3 families are assigned to the FEOM3 locus on 16qter,11 where the causative gene remains to be identified. CFEOM type 2 is a recessive form of the disease involving the PHOX2A gene at the FEOM2 locus in 11q13.12,13

Herein, we have further investigated the phenotype-genotype relationship in CFEOM by characterizing the clinical phenotypes and KIF21A genotypes in 5 affected kindreds.

Methods

Clinical Evaluations and Sample Collections

The 5 studied CFEOM families (families 1, 2, 3, 4, and 5) (Figure 1 and Figure 2) reside...
in various regions of China and were clinically investigated in Tianjin Eye Hospital. None of the patients had been treated surgically at the time of examination. Each participating individual underwent a detailed ophthalmic investigation to evaluate corrected visual acuity, palpebral fissure size, levator function, compensatory head position, and ocular motility including ab-
errant eye movements, together with examinations by slit-lamp and direct funduscopy (Table 1). Genomic DNA was isolated from peripheral leukocytes by standard methods and used for sequencing and genotyping analysis. The samples were collected with informed consent from the participating individuals or their parents after explanation of the nature and pos-

Figure 2. A, Pedigree of family 5 with congenital fibrosis of the extraocular muscles type 1 (CFEOM1) and haplotypes of the FEOM1/KIF21A region. The genotypes represent the microsatellite loci D12S1648, D12S59, D12S1029, and D12S1048 and the affected haplotype is indicated by a box. Individuals participating in the study are indicated by an asterisk to the left. Arrow indicates the proband. B, Sequencing chromatograms showing the novel mutation 84C>G in exon 2 of KIF21A. C, Confirmation of the presence or absence of the 84C>G mutation in affected and unaffected family members using Bcl cleavage. bp Indicates base pair. D, Location of KIF21A mutations on the genomic (top) and protein (below) levels. Mutations identified in this study are boxed. The novel C28W and the known M356T mutations affect the kinesin motor domain (green) while the other mutations affect amino acids in the coiled-coil region (yellow).
sible consequence of the study and with local ethics approval according to the tenets of the Declaration of Helsinki.

**MUTATION ANALYSIS OF KIF21A**

The 38 exons and flanking exon-intron boundaries of the KIF21A gene were sequenced using primers and conditions detailed elsewhere (data not shown). The polymerase chain reaction amplicons were sequenced in both directions and analyzed in an automated ABI 3730 Genetic Analyzer system (Applied Biosystems, Foster City, California) using methods previously described.14 Initially, exons 8, 20, and 21, with reported mutations,6,9,10,15-19 were sequenced in the probands of the 5 families. Subsequently, all 38 exons of KIF21A were sequenced in families 4 and 5 using previously described methods.14 Possible linkage to the FEOM1 locus was analyzed by markers D12S1029, D12S1048, and FEOM1, under the assumption of an autosomal dominant trait with recombination frequencies in males and females. Pedigrees were formed using the LINKAGE software package of SimWalk2 (Version 3.35; E. Sobel, University of California, Los Angeles), under the assumption of an autosomal dominant trait with 99% penetrance and a disease-allele frequency of 0.00001. Each marker was assumed to have equally frequent alleles, with equal 292-base pair (bp) fragment and the mutated allele, in 2 fragments of approximately 88 bp and approximately 204 bp.

**LINKAGE ANALYSES**

Genotyping of microsatellite markers was carried out in families 4 and 5 using previously described methods.14 Possible linkage to the FEOM1 locus was analyzed by markers D12S1029, D12S1048, and FEOM1, under the assumption of an autosomal dominant trait with 99% penetrance and a disease-allele frequency of 0.00001. Each marker was assumed to have equally frequent alleles, with equal recombination frequencies in males and females. Pedigrees were drawn and haplotypes were generated using Cyrillic software (version 2.1; CyrillicSoftware, Oxfordshire, England) and confirmed by inspection.

**Table 1. Results From Ophthalmic Investigations in Affected Members of 5 CFEDM Kindreds**

<table>
<thead>
<tr>
<th>Pedigree Member</th>
<th>Sex</th>
<th>Age (y)</th>
<th>Visual Acuity</th>
<th>Phtosis/Levorator Function</th>
<th>Ocular Motility</th>
<th>Compensatory Head Position</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II:1</td>
<td>M</td>
<td>70</td>
<td>0.2 0.2</td>
<td>Severe/3 mm Severe/3 mm</td>
<td>Hypo Fixed</td>
<td>Limited Yes</td>
</tr>
<tr>
<td>II:2</td>
<td>F</td>
<td>67</td>
<td>0.1 0.2</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo Fixed</td>
<td>Fixed Yes</td>
</tr>
<tr>
<td>II:3</td>
<td>M</td>
<td>65</td>
<td>0.9 0.8</td>
<td>No/12 mm No/12 mm</td>
<td>Hypo Limited</td>
<td>Normal No</td>
</tr>
<tr>
<td>II:4</td>
<td>M</td>
<td>45</td>
<td>0.3 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo Fixed</td>
<td>Limited Yes</td>
</tr>
<tr>
<td>III:3</td>
<td>F</td>
<td>41</td>
<td>0.4 0.5</td>
<td>Severe/3 mm Mild/7 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:5</td>
<td>F</td>
<td>40</td>
<td>0.1 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo Fixed</td>
<td>Limited Yes</td>
</tr>
<tr>
<td>III:7</td>
<td>M</td>
<td>26</td>
<td>0.7 0.3</td>
<td>Mild/8 mm Severe/4 mm</td>
<td>Hypo Limited</td>
<td>Limited No</td>
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<tr>
<td>III:8</td>
<td>F</td>
<td>38</td>
<td>0.1 0.1</td>
<td>Severe/0 mm Severe/1 mm</td>
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<td>Limited Yes</td>
</tr>
<tr>
<td>IV:1</td>
<td>M</td>
<td>17</td>
<td>0.1 0.3</td>
<td>Severe/3 mm Mild/7 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited No</td>
</tr>
<tr>
<td><strong>Family 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II:1</td>
<td>M</td>
<td>60</td>
<td>0.3 0.2</td>
<td>Severe/2 mm Severe/2 mm</td>
<td>Hypo with exo</td>
<td>Limited Limited Yes</td>
</tr>
<tr>
<td>III:1</td>
<td>M</td>
<td>33</td>
<td>0.4 0.3</td>
<td>Severe/2 mm Severe/3 mm</td>
<td>Hypo with exo</td>
<td>Limited Limited Yes</td>
</tr>
<tr>
<td>III:2</td>
<td>M</td>
<td>29</td>
<td>0.4 0.5</td>
<td>Severe/1 mm Severe/3 mm</td>
<td>Hypo with exo</td>
<td>Limited Limited Yes</td>
</tr>
<tr>
<td><strong>Family 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I:2</td>
<td>F</td>
<td>68</td>
<td>0.05 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>II:1</td>
<td>F</td>
<td>42</td>
<td>0.1 0.3</td>
<td>Severe/1 mm Severe/2 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>II:2</td>
<td>F</td>
<td>39</td>
<td>0.2 0.2</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Fixed Yes</td>
</tr>
<tr>
<td>II:4</td>
<td>M</td>
<td>34</td>
<td>0.2 0.3</td>
<td>Severe/0 mm Severe/1 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:1</td>
<td>M</td>
<td>19</td>
<td>0.1 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:4</td>
<td>M</td>
<td>11</td>
<td>0.2 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Fixed Yes</td>
</tr>
<tr>
<td><strong>Family 4</strong></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>II:1</td>
<td>M</td>
<td>67</td>
<td>0.1 0.1</td>
<td>FC Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:2</td>
<td>M</td>
<td>41</td>
<td>0.2 0.3</td>
<td>Severe/1 mm Severe/2 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:3</td>
<td>F</td>
<td>38</td>
<td>0.1 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Limited Limited Yes</td>
</tr>
<tr>
<td>IV:1</td>
<td>M</td>
<td>20</td>
<td>0.2 0.2</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Fixed Yes</td>
</tr>
<tr>
<td>IV:2</td>
<td>M</td>
<td>16</td>
<td>0.4 0.1</td>
<td>Severe/3 mm Severe/1 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td><strong>Family 5</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II:1</td>
<td>M</td>
<td>73</td>
<td>0.1 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>II:2</td>
<td>M</td>
<td>69</td>
<td>0.05 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:1</td>
<td>M</td>
<td>50</td>
<td>0.1 0.2</td>
<td>Severe/0 mm Severe/1 mm</td>
<td>Hypo with exo</td>
<td>Fixed Limited Yes</td>
</tr>
<tr>
<td>III:3</td>
<td>F</td>
<td>41</td>
<td>0.2 0.2</td>
<td>Severe/2 mm Severe/4 mm</td>
<td>Hypo with exo</td>
<td>Limited Limited Yes</td>
</tr>
<tr>
<td>III:4</td>
<td>M</td>
<td>44</td>
<td>0.1 0.1</td>
<td>Severe/0 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Fixed Fixed Yes</td>
</tr>
<tr>
<td>IV:1</td>
<td>M</td>
<td>19</td>
<td>0.2 0.1</td>
<td>Severe/1 mm Severe/0 mm</td>
<td>Hypo with exo</td>
<td>Limited Limited Yes</td>
</tr>
</tbody>
</table>

Abbreviations: CFEDM, congenital fibrosis of the extraocular muscles; CFEDM1, CFEDM type 1; CFEDM3, CFEDM type 3; FC, finger count within 30 cm; Hypo, hypotropia; Exo, exotropia.
CHARACTERIZATION OF CFEOM1 AND CFEOM3 PHENOTYPES

The 5 families studied were diagnosed with autosomal dominant CFEOM based on the inheritance patterns and clinical phenotypes (Figure 1 and Figure 2) (Table 1). Slitlamp and funduscopy examination results were normal in all the affected individuals. All affected members of families 2 through 5 presented similar phenotypes with bilateral severe ptosis, compensatory head position with typical chin-up appearance, hypotropia with or without exotropia, and severely impaired vertical and horizontal ocular motility (Table 1). All affected members had poor visual acuity, which might have resulted from deprived amblyopia secondary to congenital ptosis. In addition, patients II:1 and III:3 in family 4 had aberrant eye movements in the form of synergistic convergence when attempting upgaze. Based on these findings, families 2 through 5 were classified as having CFEOM1.

The members of family 1 showed variable involvement and severity of ophthalmoplegia and ptosis consistent with a diagnosis of CFEOM3 (Table 1). For example, individuals II:1, II:3, III:2, III:5, and III:8 presented a classical phenotype with bilateral severe ptosis, restricted upgaze, and compensatory head position. By contrast, individuals III:3, III:7, and IV:1, at least 1 eye had mild ptosis with residual upgaze or the ability to elevate above the midline. Similarly, individuals III:7 and IV:1 had varying ptosis without compensatory head position. Individual II:4, who is an obligate carrier, had only subtle symptoms in the form of mild limitation of vertical ocular motility without ptosis, strabismus, or compensatory head position (Table 1). The uneven visual acuity observed in this family is possibly due to variable severity of ptosis.

DETECTION OF RECURRENT KIF21A MUTATIONS IN CFEOM1 AND CFEOM3 FAMILIES

The initial screening of exons 8, 20, and 21 of the KIF21A gene identified 2 missense mutations in exon 21 in 3 of the 5 families. In families 2 and 3, the same heterozygous base substitution 2860C>T was observed (Figure 1). These substitutions are predicted to give a missense alteration from arginine to tryptophan (R954W). Family 1 with CFEOM3 harbored another heterozygous base substitution (2861G>A) (Figure 1) giving an amino acid shift from arginine to glutamine (R954Q). These 2 missense mutations were shown to cosegregate with the CFEOM phenotype in the respective families. To date, they are the 2 most commonly reported mutations, with 2860C>T having been reported in both CFEOM1 and CFEOM3 pedigrees and 2861G>A having been previously reported in CFEOM1 pedigrees.

RESULTS

IDENTIFICATION OF A NOVEL KIF21A MUTATION IN EXON 2

Families 4 and 5 were genotyped for markers at the KIF21A/FEOM1 and FEOM3 loci. Both families had positive logarithm of odds scores for markers at KIF21A/FEOM1 in agreement with a possible involvement of KIF21A (data not shown). FEOM3 was excluded in family 5 and gave inconclusive results in family 4. The ambiguity of linkage data in family 4 is likely because of the relatively limited number of family members.

Sequencing of all 38 exons of KIF21A in families 4 and 5 revealed a heterozygous base transition at nucleotide 84 in exon 2 (84C>G) (Figure 2) in the proband of family 5. This alteration is predicted to give an alteration of amino acid 28 from cysteine to tryptophan (C28W). Families 1 with CFEOM3 harbored another heterozygous base substitution (2861G>A) (Figure 1) giving an amino acid shift from arginine to glutamine (R954Q). These 2 missense mutations were shown to cosegregate with the CFEOM phenotype in the respective families. To date, they are the 2 most commonly reported mutations, with 2860C>T having been reported in both CFEOM1 and CFEOM3 pedigrees and 2861G>A having been previously reported in CFEOM1 pedigrees.

Table 2. Summary of the Clinical and Genetic Findings in the 5 Kindreds Studied

<table>
<thead>
<tr>
<th>Pedigree No.</th>
<th>Clinical Phenotype</th>
<th>Mode of Inheritance</th>
<th>Linkage to KIF21A Mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>CFEOM3</td>
<td>AD</td>
<td>ND</td>
</tr>
<tr>
<td>Family 2</td>
<td>CFEOM1</td>
<td>AD</td>
<td>ND</td>
</tr>
<tr>
<td>Family 3</td>
<td>CFEOM1</td>
<td>AD</td>
<td>ND</td>
</tr>
<tr>
<td>Family 4</td>
<td>CFEOM1</td>
<td>AD</td>
<td>Suggestive</td>
</tr>
<tr>
<td>Family 5</td>
<td>CFEOM1</td>
<td>AD</td>
<td>Suggestive</td>
</tr>
</tbody>
</table>

Abbreviations: AD, autosomal dominant; CFEOM, congenital fibrosis of the extraocular muscles; CFEOM1, CFEOM type 1; CFEOM3, CFEOM type 3; ND, not determined; wt, wild type.

Mutations were numbered according to complementary DNA sequence reference number AM177179.
In this study, we report a novel (84C>G) and 2 recurrent (2860C>T, 2861G>A) missense KIF21A mutations identified in 4 Chinese families with CFEOM1 and CFEOM3 phenotypes. In support of their pathogenic nature, the mutations were shown to cosegregate with the CFEOM phenotype in the respective families, and in addition, the novel mutation was absent in 150 normal controls. Our findings add to the knowledge about KIF21A mutation spectra and support the genetic heterogeneity of CFEOM1 and CFEOM3.

The KIF21A gene spans 150 kilobases of genomic DNA and consists of 38 exons encoding an amino acid 1674 protein, which is part of the kinesin superfamily involved in transportation of vesicles and organelles. Its N terminal kinesin motor domain interacts with microtubules and tends to be highly conserved, the coiled-coil domain is important for dimer formation, and the tail with 7 WD40 repeats is assumed to interact with the presently unidentified cargo based on functional study of another kinesin family member KIF21B. Despite the large size of KIF21A, only a small number of different mutations have been reported. Nine of the 11 published mutations were found in families with the CFEOM1 phenotype (1067T>C, 2830G>C, 2839A>G, 2840T>G, 2840T>C, 2861G>A, 2861G>T, 3022G>C, 3029T>C). The mutation 2861G>A was identified in a CFEOM3 kindred (2841G>A), and 1 has been associated with both CFEOM1 and CFEOM3 (2860C>T). Figure 2 illustrates the known KIF21A mutations, including those described herein. Intriguingly, 10 of the published mutations are clustered, resulting in substitutions of 5 amino acid residues in the coiled-coil region (944Glu, 947Met, 954Arg, 1008Ala, 1010Ile), and the 11th mutation, involving amino acid 356 at the α-helix 6 of the KIF21A motor domain, is close to the neck-linker region, which is located between the motor domain and the coiled-coil region. Because the C terminal of α-helix 6 is the base of the neck linker, it has been proposed that all these reported mutations could impair protein dimerization and thus interfere with the transportation of cargos from the oculomotor neurons to the synapse of the developing neuromuscular junction of the extraocular muscle. By contrast, the novel mutation reported herein, 84C>G, is located in exon 2, which encodes the beginning of the kinesin motor domain. This finding would further support a role for dysfunction of the kinesin motor domain in the etiology of CFEOM because the previous mutation 356M>T was close to the linker region and could have interfered with its function. Point mutations affecting motor domains of other kinesin family genes have been reported in spastic paraplegia (KIF5A) and Charcot-Marie-Tooth disease (KIF1Bβ) and have been shown to prevent stimulation of the motor adenosine triphosphatase by microtubule binding. Furthermore, specific point mutations in kinesin motor orthologs have been associated with loss of kinesin motor function. Whether the KIF21A mutation identified herein, 84C>G, could interfere with motor function through similar mechanisms remains to be determined.

Two recurrent mutations (2860C>T, 2861G>A) were identified in 3 of the 5 studied families. The mutation 2860C>T, found in families 2 and 3 with CFEOM1, represents the most frequent KIF21A mutation and is found in approximately 70% of all kindreds with a demonstrated mutation. The CFEOM3 family (family 1) segregated a 2861G>A mutation, which, to our knowledge, has not been previously reported. However, the same mutation has previously been described in families and isolated cases with CFEOM1. The present findings thus are supportive of previous findings that identical mutations can give rise to distinct phenotypes, suggesting that additional genetic factors determine the expressivity of CFEOM. Taken together with previous reports, 3 different KIF21A mutations have presently been associated with CFEOM3 families. These mutations are all predicted to give substitutions at amino acid 947 or amino acid 954, similar to CFEOM1.

In family 4, no KIF21A mutation was demonstrated implicating the involvement of a different disease gene in support of genetic heterogeneity for CFEOM1. Results from linkage analysis were consistent with a putative involvement of the FEOM1 as well as the FEOM3 loci. On precise identification of the still elusive disease gene at the FEOM3 locus, it will be worthwhile to screen for mutations in this strong candidate gene.

Taken together with the results of previously published studies, our present findings clearly support a genetic heterogeneity in CFEOM1 as well as CFEOM3. This underlines the need to base classification of CFEOM in clinical practice on both genetic findings and clinical presentations. Furthermore, the possibility of KIF21A mutations occurring outside the previously reported exons 8, 20, and 21 needs to be taken into account in genetic diagnostic procedures. Further analyses of the molecular effects of different KIF21A mutations are expected to provide insights into KIF21A functions and the possibility of genetic treatment.

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In the sixties, de Wecker, Stellwag, and others, believing that scleral section alone was sufficient to relieve the
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operation which for a short time provides an artificial channel of exit for the aqueous humor, and probably exercises only an indirect influence upon the restoration of the normal channels.

31:450, 459.