Teunissen-Cremers Syndrome: A Clinical, Surgical, and Genetic Report


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Objective: To describe clinical and radiologic features, results of ear surgery, and genetic analysis in three families with Teunissen-Cremers syndrome.

Design: Case series.

Setting: Tertiary referral center.

Background: The NOG gene encodes the protein noggin, which has antagonist action in osteogenesis. Malformation of bones and joints may result from defects in noggin. Teunissen-Cremers syndrome is caused by mutations in the NOG gene. Two mutations in this gene were reported previously. The proximal symphalangism-hearing impairment syndrome, also caused by mutations in the NOG gene, is characterized by proximal symphalangism, conductive hearing loss, and occasionally synostoses.

Methods: We examined nine affected members of three Dutch families. Reconstructive middle ear surgery was performed in five patients (nine ears), and we sequenced the NOG gene in these families.

Results: Affected members had conductive hearing impairment, hyperopia, and broad thumbs and first toes with brachytelephalangia. Surgery manifested stapes ankylosis with additional incudal fixation frequently in the fossa incudis. Air-bone gaps decreased to less than 10 dB in six ears. Genetic analysis revealed three new mutations in the NOG gene.

Conclusion: The Teunissen-Cremers syndrome is an entity in its clinical presentation, distinct from other syndromes with proximal symphalangism and hearing impairment. So far, in five families with Teunissen-Cremers syndrome, four truncating mutations and one amino acid substitution were found in the NOG gene. The majority of other mutations found in this gene are missense mutations, which might result in some residual protein activity. Reconstructive middle ear surgery is an option for treatment.

Key Words: Autosomal dominant—Genetic conductive hearing impairment—Congenital incus fixation—Congenital stapes ankylosis—Hyperopia—NOG mutations—Teunissen-Cremers syndrome.


In 1990, Teunissen and Cremers presented five affected male members of a Dutch family with hearing loss caused by congenital stapes ankylosis, severe hyperopia (farsightedness), as well as broad thumbs and first toes with brachytelephalangia (short distal phalanges) (1). Proximal symphalangism (ankylosis of a proximal interphalangeal joint) of the fifth digit was seen in one individual and therefore considered only to be an associated feature. This remarkable combination of features was also found in three other families (2–4).

Mutation analysis in the families reported by Milunsky et al. (3) and by Brown et al. (4) revealed pathologic mutations in the noggin (NOG) gene. The NOG gene encodes the protein noggin, which acts as an antagonist to bone morphogenic proteins (BMPs) in osteogenesis (5). Studies in mice have shown that functional defects of noggin can result in malformation of bones and joint cavities (6). Besides the typical features as seen in the Teunissen-Cremers (TC) syndrome, other symptoms can be caused by mutations in the NOG gene (e.g., syndactyly, facial abnormalities, tarsal or carpal bone coalition, and proximal symphalangism). A minor feature in the TC syndrome, proximal symphalangism is known to be the most prominent feature in the proximal symphalangism–hearing impairment (SYM1) syndrome. Proximal symphalangism is also prominent in the atypical variant of the proximal symphalangism–hearing impairment syndrome (SYNS1) and in the tarsal-carpal coalition syndrome (TCC) (7–9). Hearing loss caused by stapes ankylosis, and fusion of carpal or tarsal bones, which can cause a duck-like gait, are frequently reported in SYM1 (8,10). Mutation analysis in families with typical and atypical variants of the SYM1 syndrome have already revealed 11 pathologic mutations in the NOG gene (17q21-22) (11–13). Genetic defects in the NOG gene...
also turned out to be the cause of the TCC syndrome, an autosomal dominant disorder, which is characterized by extensive fusion of carpal and tarsal bones (14). Symphalangism, short first metacarpals causing brachydyactyly and fusion of humeroradial fusion, is also seen in this syndrome. The TCC syndrome as well as the SYM1 and SYNS1 syndromes display an interfamilial and intrafamilial variation in expression of symptoms. Therefore, the lines between these syndromes seem to be rather thin. Fibrodysplasia ossificans progressiva, another connective tissue disorder, is characterized by congenital malformation of the first toes and by progressive heterotopic ossification of the tendons, ligaments, fasciae, and skeletal muscles. Whether the fibrodysplasia ossificans progressiva syndrome is caused by a mutation in the NOG gene remains a subject of dispute (15–17).

In this report, the clinical findings and results of ear surgery in nine affected members of three families with the TC syndrome are described. Recently, we performed additional ophthalmologic examinations and radiologic examinations of the orbits in seven affected members of these families. The first family (Family A) was already reported (1). The other two families (Families B and C) are newly diagnosed with the TC syndrome.

The clinical features that were seen in the families with the TC syndrome described in this article and in the families described in three other reports (2–4) are compared with those of associated syndromes to display distinctive features. Furthermore, we report three new mutations in the NOG gene that were detected in the presented families. We compare the NOG mutations found in the TC syndrome with those reported in related clinical entities, looking at the nature and position of the mutations and the possible effect on the noggin protein.

PATIENTS AND METHODS

Clinical examination

Family A

We reexamined Family A. Additional clinical, audiometric, ophthalmologic, and radiologic examinations were performed in three of five affected members. One person (II:1) had already died and another person (III:1) did not want to participate. Pure-tone audiometry was performed in a sound-treated room with an Interacoustic Clinical Audiometer AC 40 (Interacoustics A/S, Assens, Denmark), calibrated to ISO 389 according to the ISO 8253-1 standard (18). Air conduction thresholds were measured in decibels hearing level. Bone-conduction thresholds were also measured to exclude conductive or mixed hearing impairment. For audiometric analysis of reconstructive ear surgery, preoperative impairment in bone conduction was considered equal to postoperative impairment in bone conduction.

The patients had ocular examinations, including assessment of best-corrected visual acuity, subjective and objective (1% tropicamide [Thea Pharma NV, Ukkel, Belgium]) measurement of refraction, orthoptic examination of binocular functions, slit lamp biomicroscopy, ophthalmoscopy, measurement of intraocular pressure, and ultrasound axial length measurement of the eyes. Additional radiographs were obtained of hands and feet.

To detect any possible bony deformities of the skull and facial bones, an orthopantomogram and lateral and anteroposterior head films were obtained. The head films were taken using a cephalostat (CraneX Tome Cephalostat, 70 kV, 10 mA, Soredex, Helsinki, Finland) with the lips in rest position and the teeth in occlusion. The focus-film distance was 5.04 m, and an intensifying screen (Kodak TMAP, Eastman Kodak, Rochester, NY, U.S.A.) was used. The magnification factor was 1.098. The radiographs were traced and analyzed by one observer (A. K.-I.). To describe the orbital area, the following cephalometric points and planes were determined on the anteroposterior head film:

Lo: the intersection of the lateral wall of the orbit with the greater wing of the sphenoid.
Or: the lower most contour of the bony orbit.
Frankfort horizontal: line through the left and right Or.
Midsagittal plane: a perpendicular plane from the neck of the crista galli to the Frankfort horizontal line.
Lo-Horiz: the horizontal distance from Lo to the midsagittal plane.
Lo-Vert: the vertical distance from Lo to the Frankfort horizontal plane.

As no age-related norms for the orbital area are available for the Dutch population, cephalometric values were compared with age-related norms from the atlas of Basyouni and Nanda (19) for individuals from northern and western European ancestry in the Denver area (U.S.A.).

Families B and C

In both families, only the mother and one daughter displayed both a hearing impairment and hyperopia and underwent clinical, otoscopic, and audiometric examinations. Pure-tone audiometry was performed under the conditions as stated above. The ISO standard for presbyacusis was used to identify persons with thresholds above the 95th percentile of presbyacusis. Only when a hearing threshold larger than the 95th percentile was found was the individual considered to be affected (20). For speech recognition, standard monosyllabic Dutch word lists were presented at either ear (21). Ipsilateral and contralateral stapedial reflexes were examined. Ophthalmologic examinations, radiographs, and cephalometric analyses were performed in the affected individuals of Families B and C, as described for Family A. Computed tomographic (CT) scans of the petrous bones were retrieved.

Genetic analysis

DNA from lymphocytes was isolated as described (22). For amplification of the coding region of the NOG gene, the following primers were used: forward primer, 5'-TGTGTC-GCTTTCCTCCGC-3'; and reverse primer, 5'-AGATCAAGTGTCCTCGGTG-3'. Conditions for amplification are available on request. For sequencing, the above-mentioned primers were used in addition to the primers 5'-TACGACCCAGGCT-TCATGG-3' and 5'-CCTTTGATCTCGCTCGGCAT-3'. Sequencing was performed with the ABI PRISM Big Dye Terminator Cycle Sequencing V2.0 Kit and the reactions were analyzed with the ABI PRISM 3700 DNA analyzer (Applied Biosystems, Foster City, CA, U.S.A.).

RESULTS

Family case histories

The clinical findings of the affected family members are presented in Table 1.
Family A

Family A consists of 22 persons in four consecutive generations (1). Five individuals in three consecutive generations were affected (Cases A II:2, A III:1, A III:5, A IV:4, and A IV:5). The facial appearances of a father (Case A III:5) and his two sons (Cases A IV:4 and A IV:5) are shown in Figure 1. One other person, who did not want to participate in the study, was only known to have syndactyly (Case A III:4). Clinical description of the five affected persons has already been given by Teunissen and Cremers (1). Reconstructive ear surgery, performed in Cases A III:5, A IV:4, and A IV:5, was also described (Table 2) (1). In 1990, after publication of the report, the contralateral ear was operated on in Cases A IV:4 and A IV:5.

At the age of 59, Case A III:5 was reexamined. Medical and otologic histories only revealed a lumbar hernia nucleus pulposus at age 58. Clinical examination manifested a large, overhanging tip of the nose, but no hemicylindrical shape or hypoplasia of the alae of the nose was seen. His eyes seemed rather small. His cervical spine did not seem impaired clinically, although an impairment on the thoracic or lumbar level could not be excluded. The range of motion in the wrists was full. Dorsal extension of the fingers of the left hand was impaired. Bilaterally, the distal phalanx of the thumb was extremely broad, without brachytelephalangia (Fig. 2). He had a slight degree of clinodactyly in the second digit of the left hand. The feet showed broad distal phalanges of all toes, without brachytelephalangia. Syndactyly was found between the second and third toes bilaterally. Symphalangism was found in neither the hands nor the feet. Radiologic examination at age 44 showed fusion of vertebrae C6 and C7 and conspicuous short and broad metatarsal bones of the first toes. Additional radiologic examination at age 59 manifested a possible subtalar synostosis in both feet. Synostoses were found in neither hands nor feet.

In Case A IV:4, preoperative otoscopy manifested normal tympanic membranes and well-aerated middle ear clefts at 19 years of age. Cortical mastoidectomy with epitympanotomy and posterior tympanotomy on the right ear were performed, which manifested stapes ankylosis with fixation of the short process of the incus in the fossa incudis. Stapedotomy was followed by interposition of a polytetrafluoroethylene (Teflon) wire piston (Fisch type; Richards Co, Memphis, TN, U.S.A.; shaft length, 5.5 mm; diameter, 0.4 mm). Preoperative hearing impairment of 43 dB (mean value at 0.5, 1, and 2 kHz) at the right ear was reduced to 17 dB (mean value at 0.5, 1, and 2 kHz), with a residual air-bone gap of 20 dB at 0.5 kHz, 20 dB at 1 kHz, and 20 dB at 2.0 kHz (mean value of 20 dB at 0.5, 1, and 2 kHz; follow-up, 157 mo) (Fig. 3 and Table 2). Except for bilateral stapedotomy, medical and otologic histories at age 33 were normal. Clinical examination showed small eyes compared with other facial structures. He displayed hypoplasia of the alae of the nose, with a low insertion of the columella but no hemicylindrical shape of the nose. Lateroflexion of the cervical spine was moderately impaired, mainly to the left side. The distal phalanges of the thumbs and first toes were broad without brachytelephalangia (Figs. 2 and 4). Symphalangism was seen in the proximal interphalangeal joints of the fifth fingers, second toes, and fourth right toe and in the distal interphalangeal joint of the right second toe. Syndactyly was noticed between the second and third digits of both feet and hands (Fig. 4). The fifth fingers showed clinodactyly. Radiologic examination of the cervical spinal vertebrae at age 18 did not show any anomalies. At age 33, radiologic examination showed ankylosis of the fifth fingers bilaterally. Synostoses were found in neither hands nor feet.

At age 13, preoperative otoscopy manifested normal tympanic membranes and well-aerated middle ear clefts in Case A IV:5. Cortical mastoidectomy with epitympanotomy and posterior tympanotomy at the left ear was performed, which manifested a congenital stapes ankylosis with congenital fixation of the short process in the fossa incudis. The short process of the incus was mobilized and stapedotomy was performed with fixation of

**TABLE 1. Clinical findings in the affected members of the three presented families**

<table>
<thead>
<tr>
<th>Case</th>
<th>A II:2</th>
<th>A III:1</th>
<th>A III:5</th>
<th>A IV:4</th>
<th>A IV:5</th>
<th>B I:1</th>
<th>B II:1</th>
<th>C I:1</th>
<th>C II:1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hearing loss</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>40–50</td>
<td>60</td>
<td>35–45</td>
<td>35–65</td>
<td>20–30</td>
<td>30–40</td>
</tr>
<tr>
<td>Stapes ankylosis</td>
<td>Noo</td>
<td>Noo</td>
<td>+</td>
<td>+</td>
<td>Noo</td>
<td>+</td>
<td>Noo</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fixed short process</td>
<td>Noo</td>
<td>Noo</td>
<td>–</td>
<td>+</td>
<td>Noo</td>
<td>–</td>
<td>Noo</td>
<td>–</td>
<td>Possibly</td>
</tr>
<tr>
<td>Broad thumbs/first toes</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Brachytelephalangia</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fused cervical vertebrae on radiography</td>
<td>C6-C7</td>
<td>–</td>
<td>C6-C7</td>
<td>–</td>
<td>–</td>
<td>C4-T2</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Symphalangism</td>
<td>–</td>
<td>–</td>
<td>Fifth fingers</td>
<td>–</td>
<td>Fifth fingers</td>
<td>b,c</td>
<td>Fifth fingers</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Additional findings

- Broad second fingers.
- Limitation of the elbow joint.
- Possible limitation in hip or knee joint.
- Synostoses of distal interphalangeal joints of third to fifth toes.
- Additional bone nucleus proximally of styloid process.
- Ossification disorder in radiohumeral joint.
- Noo, not operated on.
FIG. 1. Facial appearance of father (Case A III:5, 44 years old) and both sons (Case A IV:4, 19 years old; Case A IV:5, 13 years old) in Family A (first row, Case A III:5 [left] and Case A IV:4 [right]; second row, IV:5); the mother (Case B I:1, 42 years old) and daughter (Case B II:1, 10 years old) in Family B (third row, Case B I:1 [left] and Case B II:1 [right]); and the mother (Case C I:1, 42 years old) and daughter (Case C II:1, 13 years old) in Family C (fourth row, Case C I:1 [left] and Case C II:1 [right]).
RESULTS OF RECONSTRUCTIVE EAR SURGERY

<table>
<thead>
<tr>
<th>Air-bone gap (dB)</th>
<th>Ears operation on (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>4</td>
</tr>
<tr>
<td>10–20</td>
<td>4</td>
</tr>
<tr>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
</tr>
</tbody>
</table>

*a n = 9 ears; five new reconstructive ear surgeries; details on reconstructive ear surgeries in four ears were previously published by Teunissen and Cremers (1990).

Postoperative mean values of air-bone gaps at 0.5, 1, and 2 kHz.

In this family, only 2 of 20 members of four generations are affected; a mother (Case B I:1) and her daughter (Case B II:1). The 9-year-old daughter (Fig. 1) presented with bilateral congenital hearing impairment. During pregnancy, her mother had oligohydramnios. The daughter was born by cesarean section, because of a breech position, at 33 weeks’ gestation. She had congenital hypoplasia of the sternocleidomastoideus muscle at the right side, with a tendency to torticollis. She had a history of otitis media with effusion, for which she had been treated with tympanostomy tube insertions at the age of 5.

At otoscopy, the right ear canal showed extreme upward sloping. A slight degree of myringosclerosis of the tympanic membrane and well-aerated middle ear clefts were noted. Using the microscope, a clearly visible incudostapedial joint was seen, shining through the left tympanic membrane. Pure-tone audiometry showed a mainly conductive hearing impairment of 62 dB (mean value at 0.5, 1, and 2 kHz) at the left ear and 45 dB (mean value at 0.5, 1, and 2 kHz) at the right ear (Fig. 6). At the right ear, there was a “notch” at 2 kHz in the perceptive threshold. Speech recognition showed a phoneme score of 100%. CT scan of the temporal bones showed no anomalies. During an exploratory tympanotomy of the right ear, stapes ankylosis was seen. In addition, a severe fixation of the malleoincudal joint was found that resolved “spontaneously” by manipulation.

Only a slight immobility of the malleoincudal joint remained, which was considered acceptable. A Teflon platinum piston (Fisch type; Richards; shaft length, 4.75 mm; diameter, 0.4 mm) was fixated to the long process of the incus. Preoperative hearing impairment of 58 dB (mean value at 0.5, 1, and 2 kHz) at the left ear was reduced to 15 dB (mean value at 0.5, 1, and 2 kHz), with a residual air-bone gap of 20 dB at 0.5 kHz, 15 dB at 1 kHz, and 0 dB at 2 kHz (mean value of 12 dB at 0.5, 1, and 2 kHz; follow-up, 157 mo) (Fig. 5 and Table 2). Medical and otologic histories at age 33 were normal, except for bilateral stapedotomy. Clinical examination showed small eyes compared with other facial structures. The shape of the nose was considered normal. Spinal and elbow ranges of motion were full. The distal phalanges of the thumbs were broad and short (Fig. 2). The second and third digits on the right and second to fourth digits on the left were short and slightly broad. Only slight synostoses were found between the third and fourth fingers on the left and bilaterally between the second and third digits of hands and feet. Bilaterally, the forefoot was remarkably broad. Radiologic examination at age 11 showed short first metacarpal bones and short distal phalanges of the first to fourth fingers. Shortness of distal phalanges of the hands is still noticed at age 26. No other anomalies were seen in hands or feet.

Cephalometric analysis was performed at the age of 59 years 11 months for Case A III:5, at 33 years for Case A IV:5 (Table 3). Generally, the cephalometric values were within normal limits. Case A III:5 had a remarkably long styloid process extending beyond the gonial angle of the mandible.

FAMILY B

In this family, only 2 of 20 members of four generations are affected; a mother (Case B I:1) and her daughter (Case B II:1). The 9-year-old daughter (Fig. 1) presented with bilateral congenital hearing impairment. During pregnancy, her mother had oligohydramnios. The daughter was born by cesarean section, because of a breech position, at 33 weeks’ gestation. She had congenital hypertrophy of the sternocleidomastoideus muscle at the right side, with a tendency to torticollis. She had a history of otitis media with effusion, for which she had been treated with tympanostomy tube insertions at the age of 5.

At otoscopy, the right ear canal showed extreme upward sloping. A slight degree of myringosclerosis of the tympanic membrane and well-aerated middle ear clefts were noted. Using the microscope, a clearly visible incudostapedial joint was seen, shining through the left tympanic membrane. Pure-tone audiometry showed a mainly conductive hearing impairment of 62 dB (mean value at 0.5, 1, and 2 kHz) at the right ear and 45 dB (mean value at 0.5, 1, and 2 kHz) at the left ear (Fig. 6). At the right ear, there was a “notch” at 2 kHz in the perceptive threshold. Speech recognition showed a phoneme score of 100%. CT scan of the temporal bones showed no anomalies. During an exploratory tympanotomy of the right ear, stapes ankylosis was seen. In addition, a severe fixation of the malleoincudal joint was found that resolved “spontaneously” by manipulation.

Only a slight immobility of the malleoincudal joint remained, which was considered acceptable. A Teflon platinum piston (Fisch type; Richards; shaft length, 4.75 mm; diameter, 0.4 mm) was fixated to the long process of the incus. The hearing threshold was reduced to 18 dB (mean value at 0.5, 1, and 2 kHz), with a residual air-bone gap of 20 dB at 0.5 kHz, 15 dB at 1 kHz, and 20 dB at 2 kHz (mean value of 18 dB at 0.5, 1, and 2 kHz; follow-up, 9 mo) (Fig. 6 and Table 2).

During clinical examination, we still observed a torticollis at the right side. No hypoplasia of the alae of the nose was seen. She had broad and short distal phalanges of the thumbs (Fig. 2) and proximal symphalangism of the fifth digit of both hands. Only slight impairment in flexion of the distal interphalangeal joint of the thumbs was noticed. Furthermore, she had a slight degree of synostoses between the second and third fingers bilaterally and brachydactyly of the fifth fingers. Syndactylies was more prominent between the second and third toes bilaterally. Spinal range of motion was full.

Radiologic investigation manifested synostosis of the proximal phalanges and middle phalanges of the fifth fingers. The proximal phalanx of the first toe of the left foot was short. The intervertebral disk was narrow between C5 and C6. No bone or joint abnormalities were seen in the elbow joint.

The mother (Case B I:1) was 42 years of age (Fig. 1) and presented with congenital conductive hearing impairment of the right ear. Bilaterally, the ear canal showed an extreme upward sloping. The anterior external canal impaired the sight at one-third of the anterior tympanic membrane. The part of the tympanic membrane that could be examined was normal, and middle ear clefts were well-aerated. Using the microscope, a clearly visible incudostapedial joint was seen, shining through the tympanic membrane. Pure-tone audiometry manifested a pure conductive hearing impairment of 40 dB (mean value at 0.5, 1, and 2 kHz) in the right ear. Hearing impairment of 7 dB (mean value at 0.5, 1, and 2 kHz) in the left ear was not significant. Speech recognition showed a phoneme score of 100%. Contralateral stapedial reflexes could not be elicited. Clinical examination of the mother manifested incomplete range of motion of the neck. No hypoplasia of the nasal alae was seen. Bilaterally, the distal phalanges of the first two digits were broad and short (Fig. 2). All fingers were
rather short, especially the fifth digits. The first toes were broad and short. There was syndactyly between the second and third toes bilaterally. No symphalangism was detected.

Radiologic investigation confirmed short distal phalanges of both hands and feet without any symphalangism. Synostoses of the talocalcaneal joints could not be confirmed or excluded. Evident fusion of vertebrae from C4 to T2 were noticed. No bone or joint abnormalities were present in the elbow joint.
The mother (Case B I:1) was 42.9 years of age and the daughter (Case B II:1) was 11.5 years of age at the time of cephalometric examination (Table 3). Generally, the cephalometric values were within normal limits. Case B I:1 had a long styloid process extending to the gonial angle of the mandible. According to the mother, her 45-year-old sister had short fifth fingers and a short fourth digit of the right foot.

**Family C**

In this family, 2 of 22 family members from five consecutive generations are affected: a mother (Case C I:1) and her daughter (Case C II:1) (Fig. 1). The 10-year-old daughter was referred for congenital hearing impairment. Medical history revealed birth by cesarean section because of a breech position and a long stature, for which she was referred to a pediatrician. She had a history of otitis media with effusion, for which she had been treated with tympanostomy tube insertions. Otoscopy showed normal tympanic membranes and well-aerated middle ear clefts. Pure-tone audiometry revealed a symmetrical, nonprogressive, mainly conductive hearing impairment of 38 dB (mean value at 0.5, 1, and 2 kHz) at the right ear and 40 dB (mean value at 0.5, 1, and 2 kHz) at the left ear, and a notch in the perceptive hearing threshold at 2 kHz bilaterally (Fig. 7). Speech recognition was not affected (phoneme score, 100%). Contralateral stapedial reflexes could not be elicited. A CT scan of the temporal bones showed no anomalies. Exploratory tympanotomy was performed at the left ear at the age of 11. Congenital stapes ankylosis with a possible bony fixation of the short process of the incus in the fossa incudis was found. Mobility of the malleoincudal joint was somewhat less in the medial direction but was sufficient in the lateral direction. A regular stapedotomy was performed with fixation of a Teflon platinum piston (Fisch type; Richards; shaft length, 5.0 mm; diameter, 0.4 mm) to the long process of the incus, which reduced the hearing threshold to 22 dB (mean value at 0.5, 1, and 2 kHz), with a residual air-bone gap of 25 dB at 0.5 kHz, 15 dB at 1 kHz, and 5 dB at 2 kHz (mean value of 15 dB at 0.5, 1, and 2 kHz; follow-up, 32 mo) (Fig. 7 and Table 2). Fifteen months later, an exploratory tympanotomy at the right ear revealed fixation of the stapes in the oval win-

**FIG. 4.** Feet of Case A IV:4 showing broad and short distal phalanges of the first toes with additional synostoses.

**FIG. 5.** Preoperative and postoperative audiograms of Case A IV:5. Preoperative (above) and postoperative audiograms (below) 157 months after stapedotomy at the right ear in Case A IV:5. O, air conduction OD (= bone conduction OD, X = air conduction OS) = bone conduction OS.
dow and a diminished mobility of malleus and incus. By removing the posterior half of the footplate, a successful stapedectomy was performed. The anterior half of the footplate was removed. The incus, which was fixated in both the epitympanum and in the fossa incudis, was mobilized and removed. The head of the malleus was removed and the handle of the malleus was only superiorly separated from the tympanic membrane. A Teflon platinum piston (Fisch type; Richards; shaft length, 5.75 mm; diameter, 0.4 mm) was interposed onto the handle of the malleus (23). Thus, malleovestibulopexy was performed. Hearing threshold was reduced to 25 dB (mean value at 0.5, 1, 2 kHz), with a residual air-bone gap of 20 dB at 0.5 kHz, 0 dB at 1 kHz, and 5 dB at 2 kHz (mean value of 8 dB at 0.5, 1, and 2 kHz; follow-up, 16 mo) (Fig. 7 and Table 2).

Clinical examination showed a long stature (1.84 m; \( p > 97 \)). The eyes seem to be rather small, compared with other facial structures. No abnormalities were seen in the shape of the nose. Spinal range of motion was full. Distal phalanges of the thumbs were broad and short (Fig. 2). There was only a slight degree of syndactyly between the second and third digits of the left hand and also between the third and fourth digits bilaterally. Proximal symphalangism of the fifth digits was seen in both hands (Fig. 8). The basis of the first toes had a conspicuous proximal insertion. There was brachytelephalangia of the left first toe, and both first toes were broad. Bilaterally, the third and second toes were long, with short and broad distal phalanges of the second and third toes. There was syndactyly between the second and third toes in both feet, but no symphalangism. Orthopedic exami-

#### TABLE 3. Cephalometric findings in seven affected members of the three presented families

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex</th>
<th>Age (yr, mo)</th>
<th>Right</th>
<th>Left</th>
<th>Right</th>
<th>Left</th>
<th>Additional cephalometric findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>A III:5</td>
<td>M</td>
<td>59, 11</td>
<td>47.4</td>
<td>50.1</td>
<td>36.9</td>
<td>40.1 (±1 SD)</td>
<td>Long styloid process</td>
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<tr>
<td>A IV:4</td>
<td>M</td>
<td>33, 0</td>
<td>46.5</td>
<td>46.5</td>
<td>37.3</td>
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</tr>
<tr>
<td>A IV:5</td>
<td>M</td>
<td>26, 8</td>
<td>43.7 (−1 SD)</td>
<td>45.9</td>
<td>38.0</td>
<td>38.2</td>
<td></td>
</tr>
<tr>
<td>B I:1</td>
<td>F</td>
<td>42, 9</td>
<td>47.3</td>
<td>49.2 (+1 SD)</td>
<td>38.2</td>
<td>37.3</td>
<td>Long styloid process</td>
</tr>
<tr>
<td>B II:1</td>
<td>F</td>
<td>11, 5</td>
<td>41.9 (−1 SD)</td>
<td>42.8</td>
<td>31.9</td>
<td>34.6</td>
<td></td>
</tr>
<tr>
<td>C I:1</td>
<td>F</td>
<td>42, 2</td>
<td>44.6 (−1 SD)</td>
<td>44.6 (−1 SD)</td>
<td>33.6 (−1 SD)</td>
<td>33.7 (−2 SD)</td>
<td></td>
</tr>
<tr>
<td>C II:1</td>
<td>F</td>
<td>13, 8</td>
<td>46.0</td>
<td>45.8</td>
<td>34.1</td>
<td>34.0</td>
<td>Broad spinal process C2 articulating with vertebra C1</td>
</tr>
</tbody>
</table>

*Lo*, the intersection of the lateral wall of the orbit with the greater wing of the sphenoid; *Lo-Horiz*, the horizontal distance from Lo to the midsaggital plane; *Lo-Vert*, the vertical distance from Lo to the FH plane.

SD, standard deviation.

\^Cervical vertebrae C1–C4 are visible on the head films.

FIG. 6. Preoperative and postoperative audiograms of Case B II:1. Preoperative (above) and postoperative audiograms (below) 9 months after stapedotomy at the right ear in Case B II:1. O = air conduction OD, [ = bone conduction OD, X = air conduction OS, ] = bone conduction OS.

FIG. 7. Preoperative and postoperative audiograms of Case C II:1. Preoperative (above) and postoperative audiograms (below) of Case C II:1 at 21 months (left ear) and 6 months (right ear) after stapedotomy. O = air conduction OD, [ = bone conduction OD, X = air conduction OS, ] = bone conduction OS.

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nation of the right and left elbow joints manifested limitations in flexion (110/130 degrees) and slight limitations in pronation (70/80 degrees) and supination (80/90 degrees), which did not cause impairment in the patient’s daily life (Fig. 8).

Radiologic examination manifested broad and short distal phalanges of the thumbs. The shaft of the metacarpal bone was broad in both thumbs. The metacarpal bones of the second to fourth fingers were long compared with the surrounding bones. The middle phalanges of the fifth fingers were absent. In the right hand, there was fusion of the hamatum and capitatum bones. In the fifth finger, the proximal phalanx was long and the middle phalanx was absent bilaterally. In both feet, the metatarsal bone and the proximal phalanx of the great toe were short and broad. Compared with the surrounding bones, the metatarsal bones of the second to fifth toes were rather long. The basis of the medial cuneiform bones were broad in both feet. Unilaterally, a slight disorder in the ossification of the radiohumeral joint was revealed. The radial head was not totally congruent. Radiologic images of the cervical spine manifested vertebral bodies in which the height was greater than the transverse diameter, which is unusual. The laminae and the facet joints were rather broad. The spinolaminar line could not be distinguished. Possibly, the C1 vertebra articulated with the posterior side of the spinal process of C2. Generally, the cervical spinal processes were conspicuously broad. Schmorl nodes were noticed in upper and lower thoracic vertebral endplates and irregularities were seen in lumbar vertebrae.

The mother (C I:1), 38 years of age, also had congenital hearing impairment. Except for an appendectomy and a cesarean section, her medical and otologic histories were normal. Otoscopy showed normal tympanic membranes and well- aerated middle ear clefts. Pure-tone audiometry manifested a symmetrical, nonprogressive, mainly conductive hearing impairment of 37 dB (mean value at 0.5, 1, and 2 kHz) at the right ear and 32 dB (mean value at 0.5, 1, 2 kHz) and a notch in the perceptive hearing threshold at 2 kHz bilaterally. Speech recognition was not affected (phoneme score, 100%), Contralateral stapedial reflexes could not be elicited. An exploratory tympanotomy was not performed.

FIG. 8. Proximal symphalangism of fifth digit and elbow impairment in Case C II:1. Proximal symphalangism of the fifth digit (left) and slight impairment of flexion in right elbow joint (right) in Case C II:1 (left elbow joint not shown).
At clinical examination, the eyes seemed to be rather small, compared with the face. No abnormalities were seen in the shape of the nose. In contrast to movements of the cervical spine, the lumbar spinal range of motion was moderately impaired. Flexion of the elbow joints was only slightly impaired. Both hands showed broad and short distal phalanges of the thumbs (Fig. 2); short distal phalanges of the second, fourth, and fifth digits; a slight impairment of flexion in the distal interphalangeal joint of the right fifth digit; and a slight degree of syndactyly between the second and third digits of both hands. Both feet showed a slightly proximal insertion of the basis of the first toes. The first toes were broad. The distal phalanx of the second toe was slightly broad in both feet. Syndactyly was found between the second and third digits of both feet. No symphalangism was seen. Extreme exorotation of the hip joints during flexion in the knee joints when sitting on the floor was also limited.

Radiologic examination revealed conspicuous brachytelephalangia of the thumbs and fifth fingers. Hypoplasia of the middle phalanges and distal phalanges of the second, third, and fourth fingers was seen. Metacarpal bones of the second and third fingers were rather long. An additional bone nucleus proximal to the styloid process of the ulna was seen at the right site. No carpal or tarsal synostoses were noted. The metatarsal bone and the proximal phalanx of the first toes were short and broad. In addition, the distal phalanx of the first toes was also broad. Neither symphalangism nor syndactyly was noted in both hands and feet. Radiographs of the cervical spinal vertebrae showed a narrow intervertebral space between C5 and C6. The spinal processes and laminae seemed to be broad. The spinolaminar line seemed to be in the same line as the posterior sides of the laminae. On the lumbar level of the spine, a convex scoliosis of approximately 5 degrees was noticed. Schmorl nodes were present at the level of the body of the L4 vertebra at the level of the epiphysis. The transverse diameter of the L5 vertebra was small. The bodies of the other lumbar vertebrae also showed variation in transverse diameter. The elbow joints were considered normal. A CT scan of middle and inner ear structures showed no anomalies.

The mother (Case C I:1) was 42 years 2 months of age and the daughter (Case C II:1) was 13 years 8 months of age at the time of cephalometric examination (Table 3). For Case C I:1, all measurements related to the bony orbit were 1 or 2 standard deviations below the norm values. For Case C II:1, the cephalometric values were within normal limits. The head film confirmed the finding that the C1 vertebra probably articulates with the posterior side of the spinal process of C2. Generally, the cervical spinal processes were broad.

Measurement of ocular refraction of the seven patients (14 eyes) revealed a bilateral hyperopia in all patients (mean, +8 diopters; range, +3.5–+14.75 diopters). Ultrasonic axial length measurements showed short eyes (mean, 19.4 mm; range, 17.7–20.7 mm). Orthoptic examination showed strabismus in all seven patients (five with esotropia and two with exotropia), with unilateral amblyopia in four of them. The rest of the ocular examination showed no unusual findings (Table 4).

In Table 5, the features of the presented families are compared with features of families with the TC syndrome (2–4) and literature reports of the SYM1 syndrome (10,13,24–32), the SYNS1 syndrome (33–51), and the TCC syndrome (9,52,53). Occasionally, variety in expression of symptoms made it difficult to assign a report to a certain syndrome. Concerning the reports of the SYM1 syndrome, we mainly included those reports that were referred to as such by Gorlin et al. (54).

### Genetic analysis

Mutation analysis by sequencing the protein-coding region of the NOG gene revealed mutations in the affected members of all three families. In Family A, an insertion of two nucleotides, guanosines, was detected between nucleotides 130 and 131 of the protein-coding region (c130–131insGG). For the analysis of the segre-
TABLE 5. Features of presented families compared with features in reported families with Teunissen-Cremers and other syndromes

<table>
<thead>
<tr>
<th>Clinical features (%)</th>
<th>Family A (n = 5)</th>
<th>Family B (n = 2)</th>
<th>Family C (n = 2)</th>
<th>TC (n = 19)</th>
<th>PS (n = 55)</th>
<th>APS (n = 134)</th>
<th>TCC (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conductive hearing loss</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>74</td>
<td>42</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td>Hyperopia</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>89</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Broad thumbs</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>63-68</td>
<td>2</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Short thumbs</td>
<td>60</td>
<td>100</td>
<td>100</td>
<td>68-89</td>
<td>0</td>
<td>10</td>
<td>8-42</td>
</tr>
<tr>
<td>Broad first toes</td>
<td>100</td>
<td>50</td>
<td>100</td>
<td>74-79</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Short first toes</td>
<td>40</td>
<td>50</td>
<td>50</td>
<td>47-74</td>
<td>0</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Carpometacarpal fusions</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>24</td>
<td>17</td>
<td>54</td>
</tr>
<tr>
<td>Tarsometacarpal fusions</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>35</td>
<td>35-45</td>
<td>100</td>
</tr>
<tr>
<td>Shortness first metacarpal</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Symphalangism</td>
<td>20</td>
<td>50</td>
<td>50</td>
<td>5</td>
<td>80</td>
<td>87</td>
<td>42</td>
</tr>
<tr>
<td>Syndactyly</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>53</td>
<td>24</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Strabismus</td>
<td>60-100</td>
<td>50</td>
<td>100</td>
<td>11</td>
<td>9</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Hemicylindric nose/hypoplasia alae of nose</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>74</td>
<td>2</td>
<td>24</td>
<td>0</td>
</tr>
<tr>
<td>Fusion vertebrae</td>
<td>40</td>
<td>50</td>
<td>0</td>
<td>11</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Elbow joint involvement</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>21-42a</td>
<td>0</td>
<td>13</td>
<td>38</td>
</tr>
<tr>
<td>Clindactyly</td>
<td>40</td>
<td>0</td>
<td>0</td>
<td>11</td>
<td>4</td>
<td>13</td>
<td>42</td>
</tr>
<tr>
<td>Aplasia/hypoplasia distal phalanges</td>
<td>100</td>
<td>50</td>
<td>0</td>
<td>11</td>
<td>11</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Aplasia/hypoplasia mesophalanges</td>
<td>0</td>
<td>0</td>
<td>50</td>
<td>0</td>
<td>9</td>
<td>33-40</td>
<td>0</td>
</tr>
<tr>
<td>Aplasia/hypoplasia proximal phalanges</td>
<td>0</td>
<td>50</td>
<td>100</td>
<td>0</td>
<td>0</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

*Prevalence of clinical features is expressed in percentage (including n < 100 cases).
*Brown et al. described elbow function of only four of eight affected individuals.
*Bloom reports some vertebral anomalies, but no synostoses.
TC, Teunissen-Cremers syndrome; PS, proximal symphalangism-hearing loss syndrome; APS, atypical variants of PS; TCC, tarsal-carpal coalition syndrome.

The mutation of this mutation in the family, samples were available from the Cases A III:5, A III:6, A IV:4, and A IV:5 (1). The mutation was not found in the unaffected mother (Case A III:6) but was inherited from their affected father (Case A III:5) by the affected children (Cases A IV:4 and IV:5). The mutation can be predicted to cause a frameshift mutation in the mRNA in codon 44 (V44fs) and a premature stop codon after the codons for 18 aberrant amino acids.

The transition of nucleotide 608 of the coding sequence of a thymidine (T) to a cytidine (C) was found in both the affected mother and daughter of Family B. At the protein level, the mutation can be predicted to cause the substitution of proline for leucine, Leu203Pro, which is a nonconservative amino acid change. The mutation was not present in 50 control individuals and therefore can be regarded as causative for the syndrome.

In Family C, a deletion of a cytidine at position 561 was found in both the affected mother and daughter. This mutation can be predicted to cause a frameshift in the coding sequence at the codon for amino acid 187, proline (187fs), and the incorporation of 76 aberrant amino acids. All three mutations were not described before.

**DISCUSSION**

Literature review of syndromes with symphalangism or synostoses shows a great diversity in expression of symptoms (Table 5). Several families have been reported in which their members showed conductive hearing impairment, hyperopia, and broad thumbs and first toes with brachytelephalangia (1–4). Except for conductive hearing loss, these features are rarely seen in associated syndromes (Table 5). The assignment of the clinical features of a family to a certain syndrome might be somewhat artificial, because the clinical presentation of the reviewed cases showed both interfamilial and intrafamilial variation (Table 5). Furthermore, data were not completely available occasionally. Taking this into account, we consider the TC syndrome to be a distinct clinical entity, because the combination of features (conductive hearing impairment, high hyperopia, and broad thumbs and first toes with brachytelephalangia) is unique and the intrafamilial prevalence of affected persons is rather high.

High hyperopia, with associated strabismus since childhood, was found in all of our patients. The hyperopia was caused by a short axial length of the eye (<21 mm in adults). High hyperopia is a well-known risk factor for development of strabismus. Remarkably, strabismus has been reported in only two cases (11%) of other families with the TC syndrome, although the prevalence of hyperopia is high (approximately 90%). In one of these cases, the strabismus was not explicitly mentioned but could be seen in a photograph (2). Except for a few cases of strabismus in families with the SYM1 syndrome (approximately 10%), strabismus and hyperopia had an extremely low prevalence in the associated syndromes.

Even though the distribution of other symptoms in the syndromes mentioned above varies to some extent (i.e., syndactyly, elbow involvement, nasal features), there is overlap in the symptoms. Regarding the fact that these various syndromes are caused by mutations in the same gene (NOG), similarity in defects at the protein level might be assumed.

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The secreted polypeptide noggin (encoded by the NOG gene) binds and inactivates BMPs. BMPs are members of the transforming growth factor-β superfamily of signaling proteins. Noggin shows a high affinity for BMP-4 (5,55). Groppa et al. (55) described the three-dimensional structure of the noggin–BMP-7 complex. Noggin binding effectively masks the binding epitopes of BMP-7, thereby blocking the cell-surface receptors (Type I and Type II) of BMP.

During embryogenesis, noggin participates in the control of several processes, such as establishment of the dorsoventral axis and neural induction, and also in the ongoing process of neurogenesis (56). Noggin is also involved in formation of joints in the developing skeletal system (6). In mice, complete loss of noggin protein leads to multiple malformations, including joint fusion, whereas heterozygous noggin null mutants are normal. In contrast, various skeletal abnormalities are found in humans with heterozygous NOG mutation (6.57). This difference in effects of only one functional NOG gene copy in mice and humans suggests a species-specific dosage dependence for the noggin protein.

So far, 17 different mutations in the NOG gene have been found, including the mutations presented in this report (4,11–14). Only five NOG mutations are known to cause a syndrome with stapes ankylosis, broad thumbs and first toes, and hyperopia (4). Four of these are truncating mutations. The truncating mutation in Family A leads to a frameshift shortly after the part of the mRNA encoding the signaling sequence, which is cleaved off, and thus very early in the excreted part of the protein. Therefore, it can be assumed that the function of the noggin protein is completely abolished and that no stable aberrant protein is synthesized. The mutation in Family C can be predicted to cause a frameshift in codon 187, which is between the two finger structures of the protein. From here, the amino acid sequence is abnormal. The second finger structure, which is missing from the truncated protein, contacts BMP and masks the Type II receptor-binding site of BMP (55). In addition to this, the structure of the protein might well be drastically disturbed, leading to a completely inactive protein. In Family B, a nucleotide change leads to the replacement of leucine 203 by a proline. The leucine at this position is conserved in all noggin proteins known so far from different species. Proline is known to have a fixed structural angle and therefore the mutation can be predicted to lead to a structural change of the noggin protein. Leucine 203 is located in finger 2 of the protein, which plays a role in masking the Type II receptor-binding site of BMP (55).

Why do different mutations in the NOG gene lead to different phenotypes? With the present knowledge, this question is difficult to answer. Four of the five known mutations in TC syndrome are truncating mutations and only 2 of 12 mutations in 14 SYM1, SYNS1, and TCC families. This suggests that truncating mutations might be more prone to cause TC syndrome than amino acid substitutions in the protein. Analysis of mutant noggin proteins have shown that amino acid substitutions lead to reduced or undetectable secretion of the protein but do not interfere with the dimerization and secretion of the wild-type protein (57). Therefore, it has been suggested that a reduced amount of the secreted noggin protein, and not the presence of an aberrant protein, leads to disease and that the lowest amount of secreted protein leads to the most severe phenotype (57). At least the c130-131insGG mutation found in one of the present families with TC syndrome can be predicted to lead to a drastically reduced amount of secreted noggin protein. Whether the other truncating mutations in TC syndrome have the same effects as the missense mutations studied by Marcelino et al. (57) remains to be determined, but this seems likely. Possibly, some symptoms that are seen in the TC syndrome, but that are absent in associated syndromes, might only be generated by a stronger reduction of the amount of functional noggin protein. Assuming that the amount of functional noggin is lowest in the TC syndrome, we cannot explain why symptoms that occur in associated syndromes are not seen in the TC syndrome.

That other genetic factors and/or environmental factors play a role in the phenotypic outcome of a specific mutation can be concluded from intra- and interfamilial variation. For example, the Pro35Arg mutation is found both in a family with the SYM1 syndrome and a family with TCC syndrome (11,14). The tissue-specific dosage-dependent function of noggin during joint formation, suggested by Gong et al. (11) and Marcelino et al. (57), contributes to the variation in the effects of different mutations. In five of the presented affected persons, the eyes seemed to be rather small at clinical examination. The bony measurements on the anteroposterior radiograph confirmed this finding in only one individual. In addition, the axial length of the eye was shorter in all individuals examined. Unfortunately, it is not possible to measure the axial length of the bony orbit on conventional cephalometric radiographs. In the literature, we could not find any specific data on the effect of noggin on development of the orbital bones.

**CONCLUSION**

Reconstructive ear surgery resulted in normal hearing with a closed or almost closed air-bone gap in four of five ears in Family A (1). The daughter in Family B, who had reconstructive ear surgery, did not need a hearing aid anymore in the ear that was operated on. A hearing aid or an exploratory tympanotomy of the right ear was also offered to the mother. However, because the hearing loss caused only mild impairment in her daily life, she did not consider either of these options. In Family C, the daughter was operated on bilaterally. In both ears, the air-bone gap was almost closed. In the past, good results could also be achieved by reconstructive surgery of stapes ankylosis in the SYM1 syndrome (58). In addition to stapes ankylosis, the ear surgery manifested fixation of the short process of the incus in the fossa incudis. This was found in four ears, and a possible fixation of this
process was suspected in one ear. These fixations could be resolved during the operation. This suprastapedial anomaly, which is very uncommon, was also reported in the literature regarding proximal symphalangism (29,32,58). One of the hazards in surgery of stapes ankylosis is a recurrent bony closure of the footplate after stapedotomy (59). Therefore, partial platinectomy might be considered to prevent reclosure of the oval window (58). Hearing aids also remain a good option for treatment.

Acknowledgments: The authors thank the families for their participation and J. Bodegom, Ph.D., for contributing to the cephalometric analysis.

REFERENCES