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Muenke Syndrome (FGFR3-Related Craniosynostosis): Expansion of the Phenotype and Review of the Literature

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Muenke syndrome is an autosomal dominant disorder characterized by coronal suture craniosynostosis, hearing loss, developmental delay, carpal and tarsal fusions, and the presence of the Pro250Arg mutation in the *FGFR3* gene. Reduced penetrance and variable expressivity contribute to the wide spectrum of clinical findings in Muenke syndrome. To better define the clinical features of this syndrome, we initiated a study of the natural history of Muenke syndrome. To date, we have conducted a standardized evaluation of nine patients with a confirmed Pro250Arg mutation in *FGFR3*. We reviewed audiograms from an additional 13 patients with Muenke syndrome. A majority of the patients (95%) demonstrated a mild-to-moderate, low frequency sensorineural hearing loss. This pattern of hearing loss was not previously recognized as characteristic of Muenke syndrome. We also

report on feeding and swallowing difficulties in children with Muenke syndrome. Combining 312 reported cases of Muenke syndrome with data from the nine NIH patients, we found that females with the Pro250Arg mutation were significantly more likely to be reported with craniosynostosis than males ($P < 0.01$). Based on our findings, we propose that the clinical management should include audiometric and developmental assessment in addition to standard clinical care and appropriate genetic counseling. Published 2007 Wiley-Liss, Inc.†

Key words: craniosynostosis; Muenke syndrome; fibroblast growth factor receptor 3; coronal suture synostosis; hearing loss; developmental delay; speech delay

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INTRODUCTION

Muenke syndrome [OMIM#602849] is defined by the c.749 C > G mutation encoding a Pro250Arg substitution in the fibroblast growth factor receptor 3 (*FGFR3*) gene encoding the FGFR3 protein [Bellus et al., 1996; Muenke et al., 1997]. The classic presentation of the syndrome includes uni- or bilateral coronal suture craniosynostosis, broad toes, and carpal and tarsal fusions. However, the phenotype is quite variable and ranges from no detectable clinical manifestations to "isolated" craniosynostosis to more complex findings that overlap other classic craniosynostosis syndromes (e.g., Crouzon, Pfeiffer, or Saethre-Chotzen syndrome). Clinical diagnosis of Muenke syndrome in these cases may be difficult or impossible without molecular diagnostic testing. Subtle phenotypes such as macrocephaly or minor facial dysmorphisms alone have also been reported [Gripp et al., 1998; Sabatino et al., 2004]. Some individuals who are heterozygous for the *FGFR3* Pro250Arg mutation may be clinically and radiographically asymptomatic [Robin et al., 1998]. Sex-related expressivity of the mutation has been suggested, based on a more severe phenotype in females [Gripp et al., 1998; Lajeunie et al., 1999].

The c.749 C > G mutation responsible for Muenke syndrome is thought to be one of the most common transversions in humans. The mutation rate was estimated at 8×10^{-6} per haploid genome [Moloney et al., 1997]. Furthermore, there is convincing evidence for exclusive paternal origin of the mutation, as well as an association with advanced paternal age [Moloney et al., 1997].

Molecular confirmation of the Pro250Arg mutation is not only important for appropriate genetic counseling, but also for purposes of patient management. A study of craniosynostosis repair in individuals with uni- or bicoronal synostosis and a nonspecific phenotype found that those with Muenke syndrome were more likely to need reoperation because of increased intracranial pressure following surgery [Thomas et al., 2005]. A study of patients with bicoronal synostosis and a nonspecific phenotype found that those with Muenke syndrome had a poorer cosmetic outcome, however, the findings did not rise to the level of statistical significance [Arnaud et al., 2002].

Over 300 cases of Muenke syndrome have been reported in the current literature. We were intrigued by case reports documenting single anomalies associated with Muenke syndrome such as bilateral temporal lobe dysgenesis [Grosso et al., 2003] and Klippel-Feil anomaly with Sprengel shoulder [Lowry et al., 2001]. Because of incomplete documentation, it is not clear whether these findings are incidental to the Pro250Arg mutation. We were interested to learn more about the nature of the hearing loss and the

developmental delay/cognitive impairment reported in the syndrome. Additionally, there was very little information available on the ophthalmology and dental phenotype of individuals with Muenke syndrome. Therefore, we initiated a clinical protocol to thoroughly investigate a cohort of patients with Muenke syndrome. Here, we present the first results of a study of nine patients, along with a summary of the current literature.

METHODOLOGY

Patients

Nine patients from five separate families participated in clinical studies at the National Institute of Health. Of the five families, a family history of Muenke syndrome was present in two, and the remaining three were sporadic cases (Fig. 1) based on negative *FGFR3* genetic studies in the parents. All patients had uni- or bilateral coronal synostosis without other suture involvement. Five patients were children (age range 18–43 months), and all had undergone at least one coronal suture release surgery. Four patients were adults (age range 31–67 years) and none had a prior craniosynostosis repair.

Clinical Studies

Informed consent previously approved by the Institutional Review Board of the National Human Genome Research Institute at the National Institutes of Health (NIH) in Bethesda, Maryland was obtained from or on behalf of each patient prior to participation in the research studies. Patients with a confirmed Pro250Arg mutation in *FGFR3* underwent a 3–4 day series of outpatient evaluations. Evaluations included medical history, genetic, speech, otolaryngology, audiology, and dental examinations. Detailed anthropometric measurements were obtained and compared to standardized normative data [Hall et al., 1989; Jones 1997].

A comprehensive and age-appropriate audiometric and otolaryngologic evaluation was performed on all patients, including otoscopic examination, speech and pure-tone audiometry, middle ear assessment including tympanometry and middle ear muscle reflex testing, and otoacoustic emissions. For purposes of classification, normal hearing was defined as hearing thresholds less than or equal to 20 dB HL, a mild hearing loss was defined as hearing thresholds between 21 and 40 dB HL, a moderate hearing loss between 41 and 55 dB HL, a moderate-severe hearing loss between 56 and 70 dB HL, a severe hearing loss between 71 and 90 dB HL, and a profound hearing loss was defined as hearing thresholds greater than 91 dB HL. A conductive hearing loss was defined as hearing loss by air

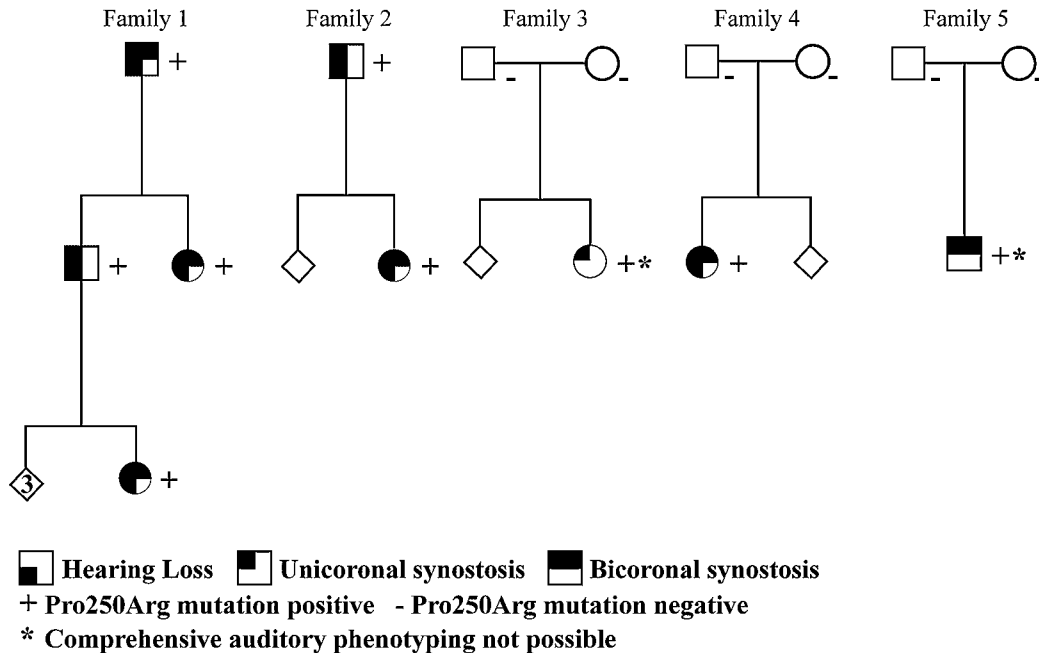


FIG. 1. Nine patients with Muenke syndrome evaluated at the NIH. Patient 1:II:1 has unilateral calcaneocuboid fusion and Patient 3:II:1 has a seizure disorder.

conduction, normal hearing by bone conduction and the simultaneous presence of air-bone gaps greater than 10 dB. A sensorineural hearing loss was defined as hearing loss by air and bone conduction with air-bone gaps of 10 dB or less, and a mixed hearing loss was defined as hearing loss by air and bone conduction with air-bone gaps greater than 10 dB.

A complete ophthalmology evaluation, including dilated funduscopic examination and fluorescein staining of the cornea was performed on all patients. Developmental testing with the Bayley Scales of Infant Development II, Second Edition (Bayley-II) or cognitive testing with the Wechsler Adult Intelligence Scale-III (WAIS-III) was performed as appropriate. Radiographs of the hands and feet were obtained for all nine patients. Skeletal surveys consisting of single views of the lateral feet, long bones, chest, pelvis, and anterior-posterior spine were obtained for six patients. To further define inner ear morphology, all adult patients had computed tomography scans of the skull and temporal bones, and magnetic resonance imaging of the brain and internal auditory canals.

Medical Record Review

Prior medical records for six NIH patients were reviewed. Pre-operative computed tomography scans of the skull were available for all five pediatric patients. These studies were reviewed to confirm suture involvement in craniosynostosis, and to look for temporal bone abnormalities. Magnetic reso-

nance images of the brain were available for patient 3:II:1 (Fig. 1) who had a partial seizure disorder.

Based on interesting preliminary audiology findings of patients seen at the NIH, audiograms of additional patients with Muenke syndrome were solicited from other clinical geneticists for inclusion in the study. Thirteen clinical audiograms stripped of personal identifiers were submitted. All studies were performed on individuals with mutation-confirmed Muenke syndrome. These individuals were personally examined (CK, DMM, EHZ, RBL, FSJ, MRPB) prior to inclusion.

Literature Review of Reported Cases of Muenke Syndrome

A Medline search was conducted to find previously reported cases of Muenke syndrome from 1996 to 2006. The key words and patient terms searched included “Muenke,” “coronal synostosis,” “FGFR3,” “P250R,” and “Pro250Arg”. References were also obtained from papers found through the literature search. Articles in languages other than English were translated. Cases were used from the following papers: [Golla et al., 1997; Muenke et al., 1997; Reardon et al., 1997; Graham et al., 1998; Gripp et al., 1998; Hollway et al., 1998; Passos-Bueno et al., 1998; Paznekas et al., 1998; Robin et al., 1998; Mulliken et al., 1999; Renier et al., 2000; Tsai et al., 2000; Cassileth et al., 2001; Dunne et al., 2001; Hughes et al., 2001; Lowry et al., 2001; Moko and de Chalain 2001; Mori et al., 2001; Roscioli et al., 2001; Chun et al., 2002; Grosso et al., 2003; Mulliken et al., 2004;

Sabatino et al., 2004; Thomas et al., 2005; van Aalst et al., 2005; Kress et al., 2006]. One family was described in detail [Ades et al., 1994] prior to definitive molecular testing [Muenke et al., 1997]. Only cases with a documented Pro250Arg mutation in *FGFR3* were included. Where a craniofacial clinic had published multiple papers on Muenke syndrome, it was assumed that the same patients were described in all papers, unless specifically stated otherwise. The skull phenotype (presence/absence and type of craniosynostosis), gender, and hearing phenotype (hearing loss present or absent) were tabulated. In the statistical analysis, cases with multiple suture involvement (pancraniosynostosis, bicoronal plus other sutures involved) were counted as cases of bilateral suture involvement, and cases with macrocephaly were counted as “no” craniosynostosis, unless expressly stated otherwise.

RESULTS

Literature Review

A total of 317 Muenke syndrome cases were ascertained from the literature. The skull phenotype was clearly documented in 312 cases. Combining those cases with the nine NIH patients, some form of craniosynostosis was present in 86%, macrocephaly was present in 3%, and a “normal” examination was present in 11% (Table I). Of the 276 cases with craniosynostosis, bicoronal synostosis was present in 55% with additional sutures involved in 4%. Unilateral synostosis was present in 26%. A single case of unilateral lambdoid suture synostosis without coronal synostosis was reported [Mulliken et al., 1999]. A single case of metopic suture synostosis without coronal synostosis was reported [van der Meulen et al., 2006]. The remaining cases were incompletely documented (Table II).

A total of 236 Muenke syndrome cases in the literature documented both the skull phenotype and the gender. Combining these cases with the nine NIH patients, we found that 60% of cases were female. Overall, 88% of females and 76% of males had some form of craniosynostosis. Approximately equal numbers of males were reported with unicoronal synostosis and bicoronal synostosis. While the proportion of individuals with craniosynostosis was slightly greater in females (88%) than males (76%), a greater proportion of females (58%) have

TABLE I. Skull Phenotype in Muenke Syndrome

Skull phenotype	Number (% of total)
Craniosynostosis	276 (86)
Macrocephaly	10 (3)
Not specified	35 (11)

Literature review (n = 312) and NIH subjects (n = 9).

TABLE II. Type of Craniosynostosis in Muenke Syndrome

Phenotype	Number (% of total)
Bicoronal synostosis	153 (55)
Unicoronal synostosis	71 (26)
Coronal synostosis, NOS	27 (10)
Coronal + lambdoid and/or sagittal	3 (<1)
Pancraniosynostosis	2 (<1)
Unilateral lambdoid synostosis only	1 (<1)
Metopic suture synostosis only	1 (<1)
Multiple synostosis, NOS	7 (3)
Craniosynostosis, NOS	11 (4)

Literature review (n = 267) and NIH subjects (n = 9). NOS, not otherwise specified.

bilateral craniosynostosis compared to males (37%). However, more than twice as many females were reported with bicoronal synostosis compared to those with unicoronal synostosis. Overall, females were significantly more likely than males to be reported with craniosynostosis (χ^2 value = 5.895, $P \leq 0.015$) with odds-ratio of 2.27 (95% CI = 1.16–4.43). Females were also significantly more likely to be reported with bicoronal synostosis than males (χ^2 value = 10.254, $P \leq 0.001$) with odds-ratio of 2.33 (95% CI = 1.39–3.93) (Table III).

The presence or absence of normal hearing was documented in 126 cases from the literature, including 51 cases with hearing loss. Of these cases, 65% had a sensorineural hearing loss. A conductive hearing loss was present in 8% and a mixed loss was present in 6%. The type of hearing loss was not specified in the remainder of cases (Table IV). Though the degree of hearing loss was not specified in the majority of cases, almost 1/4 of all cases have moderate hearing loss.

Craniofacial Findings

Six patients had bicoronal synostosis, and three patients had unicoronal synostosis. Although the pediatric patients tended to have a hypoplastic midface, this was not an obvious finding among the adult patients (Fig. 2). The two adult patients with

TABLE III. Gender Distribution in Muenke Syndrome

Phenotype	Males (%)	Females (%)
Cases from literature	95	141
Present cases	4	5
Total cases	99 (40)	146 (60)
Craniosynostosis present	75 (76)	128 (88)
Bilateral coronal suture	37 (37)	85 (58)
Unilateral coronal suture	29 (29)	29 (20)
CS not specified or other	9 (9)	14 (10)
Macrocephaly	7 (7)	3 (2)
Not specified	17 (17)	15 (10)

Literature review (n = 236) and NIH subjects (n = 9).

TABLE IV. Auditory Phenotype Previously Published Cases of Muenke Syndrome (n = 126)

No hearing loss	75 (60%)
Hearing loss	51 (40%)
Degree of hearing loss	
Mild	3 (6%)
Moderate	12 (24%)
Severe	0
Degree not specified	36 (71%)
Type of hearing loss	
Sensorineural	33 (65%)
Conductive	4 (8%)
Mixed	3 (6%)
Type not specified	11 (21%)

right uniconal synostosis had a moderate facial asymmetry, with the nasal root pointing toward the prematurely fused suture.

Audiology and Otolaryngology Findings

Three patients evaluated at the NIH reported a prior history of hearing loss. No patients used hearing aids. Eight patients reported a history of

recurrent otitis media. Two adult patients had myringotomy tubes inserted in the past for recurrent otitis media. No patients had myringotomy tubes in place at the time of evaluation. One patient reported difficulty equalizing ear pressure at high altitude, resulting in discomfort while flying and driving over mountain passes, suggestive of Eustachian tube dysfunction. Otoscopic examination of all patients showed normal tympanic membranes, however, examination of 3/5 pediatric patients revealed a middle ear effusion. Audiometric examination in all patients who were able to cooperate with complete testing revealed at least a mild hearing loss in the low-to-mid frequencies (250–2,000 Hz) (Table V).

Review of 11 audiograms performed outside the NIH also identified a mild-to-moderate low-to-mid frequency hearing loss in all individuals with Muenke syndrome. There was no difference between the averaged pure-tone hearing thresholds between NIH and non-NIH patients. A composite audiogram from 11 patients for whom complete audiometric data were obtained is shown in Figure 3 (composite audiogram).

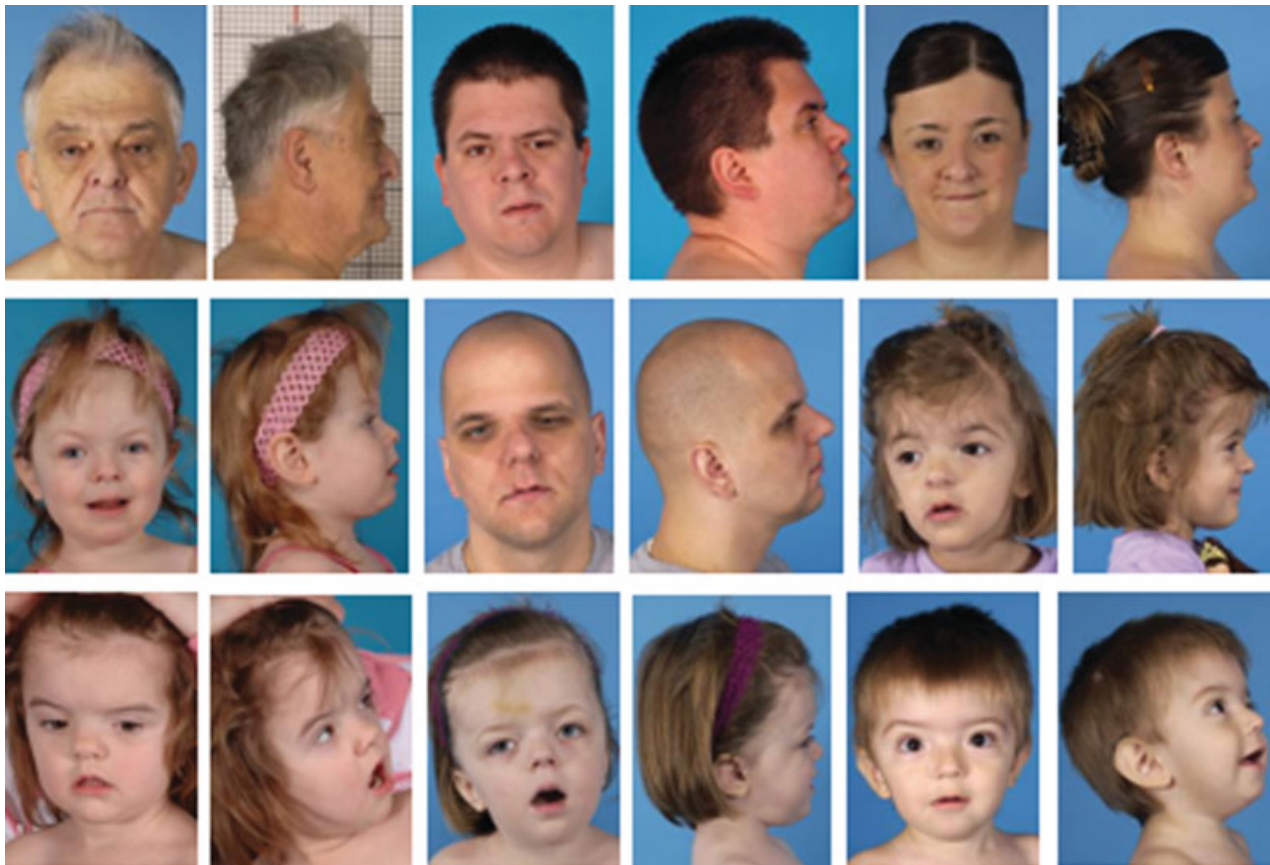


FIG. 2. Facial features of the nine patients with Muenke syndrome. From top left, first row: Patient 1:I:1, Patient 1:II:1, Patient 1:II:2. Second row: Patient 1:III:4, Patient 2:I:1, Patient 2:II:2. Third row: Patient 3:II:1, Patient 4:II:1, Patient 5:II:1.

TABLE V. Audiology Findings in NIH Subjects With Muenke Syndrome (n = 9)

Age of subject	Audiogram		Middle ear effusion
	Right	Left	
67 years	Mild-to-severe SNHL	Mild-to-moderately severe SNHL	No
35 years	Mild rising-to-normal SNHL	Mild rising-to-normal SNHL	No
30 years	Mild rising-to-normal SNHL	Mild rising-to-normal SNHL	No
28 years	Mild rising-to-normal SNHL	Mild rising-to-normal SNHL	No
3 years	Mild rising SNHL	Moderate rising mixed loss	No
3 years	Moderate rising mixed loss	Mild rising mixed loss	Bilateral
2 years	N/D	N/D	No
2 years	Mild Hearing loss	Mild Hearing loss	
	Conductive loss in at least one ear	L/T	Left
1 year	Borderline normal hearing	Borderline normal hearing	Right
	L/T	L/T	Right

SNHL, sensorineural hearing loss; N/D, no formal testing done (uncooperative patient); L/T, limited formal testing (uncooperative patient).

Oral Findings

No abnormalities were noted in the teeth morphology. Normal chronological dental eruption was observed in the pediatric patients. The following occlusal disharmonies were observed: (1) bilateral crossbites in Patients 1:I:1 and 1:II:2; (2) right-sided crossbites in Patients 1:II:1 and 2:I:1; (3) anterior openbite and left-sided crossbite in Patient 2:II:1; and (4) anterior openbite in Patient 5:II:1 (Fig. 1). All adult patients and 3/5 pediatric patients exhibited a high triangular palatal vault with a V-shaped maxillary

arch. Patients 1:I:1 and 1:II:2 had a bulging maxillary alveolar arch with a midline sagittal fibrotic palatal band (Fig. 1).

Ophthalmology Findings

The most common ocular complication was strabismus (4/9), which was accompanied by amblyopia in two of our cases. Orbital rotation appeared to result in bilateral “pseudo-inferior oblique overaction” in Patient 1:II:1 (Fig. 1), whose

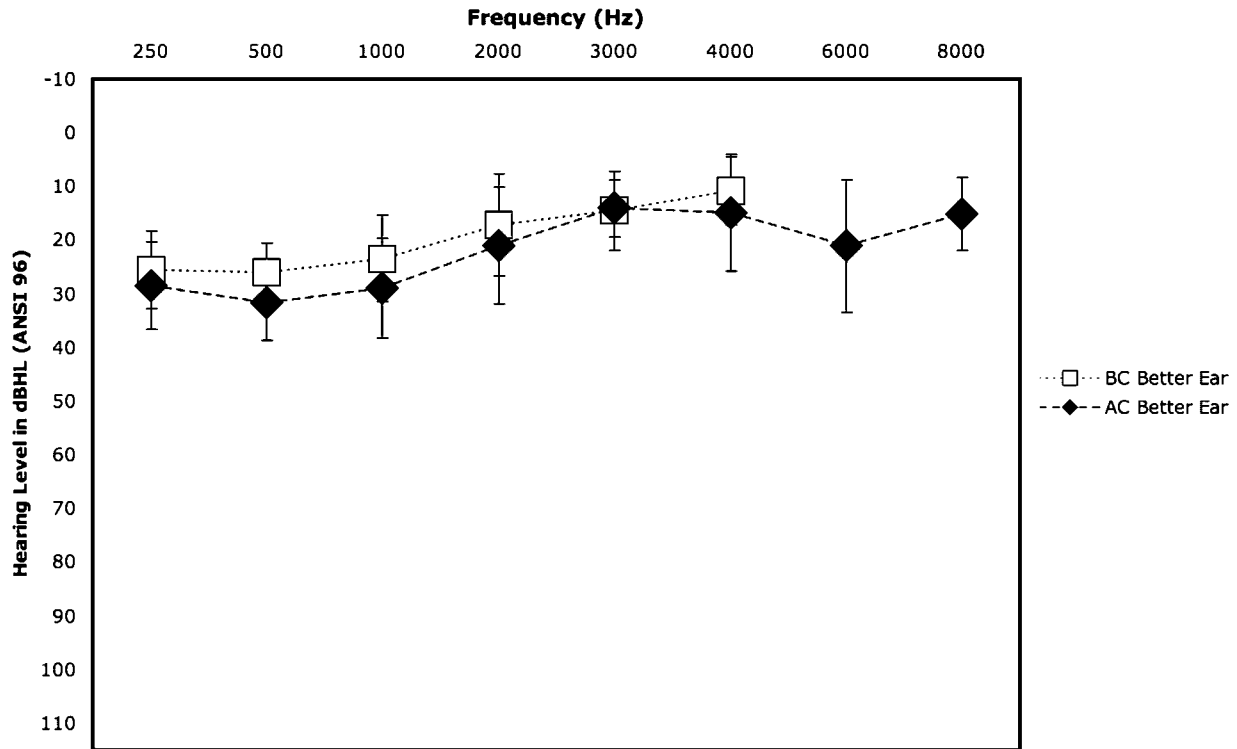


FIG. 3. Composite audiogram showing mean (±1 SD) hearing thresholds for air-conduction (AC) (250–8,000 Hz) and bone-conduction (BC) (250–8,000 Hz) for better hearing ear. Data represent averaged hearing thresholds on 18 patients from four facilities.



FIG. 4. Hands and feet of nine patients with Muenke syndrome. Normal thumbs and normal or slightly broad great toes. From top left to bottom left: Patient 1:1:1, Patient 1:II:1, Patient 1:II:2, Patient 1:III:4. From top right to bottom right: Patient 2:1:1, Patient 2:II:1, Patient 3:II:2, Patient 4:II:1, Patient 5:II:1.

craniosynostosis was unrepaired. Patient 5:II:1 (Fig. 1) had nasolacrimal duct obstruction and an incomplete blink response due to shallow orbits. We did not observe any significant corneal exposure or optic neuropathy in any patient.

Musculoskeletal Findings

Stature was normal in all patients. Total hand length and middle-finger length were within normal limits for all patients. Brachydactyly was not found in any patient. Likewise, no patients had broad thumbs. Toes varied from normal to slightly broad (Fig. 4). Patient 1:II:1 had persistent torticollis. Mild scoliosis was present in Patients 1:II:1 and 5:II:1 (Fig. 1).

Neurodevelopmental, Speech and Language Findings

Language delay was a presenting complaint in 4/5 of our pediatric patients. However, assessment with the Bayley-II showed general delays in all five patients. Total scores on the Bayley-II were in the low-average range. The mean mental index was 84 and motor index was 73. All five patients had either motor delay or general delay, with specific problems in visual/motor integration. Three of five had difficulty with balance; this was a presenting complaint in two patients. Behavioral concerns were reported in two of five patients. Misarticulations and articulatory imprecisions were noted in all pediatric patients. Swallowing difficulties and complaints from parents were noted in all children. These included

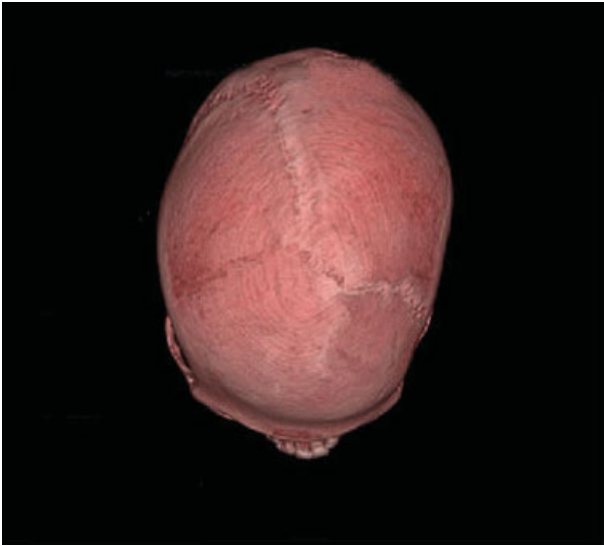


FIG. 5. Three-dimensional computed tomography scan of Patient 1:II:1, with obliteration of previously stenosed right coronal suture.

difficulties transitioning from puree to solid textures in 3/5 children; overstuffing of food in the oral cavity in 3/5 children; and difficulties with chewing solid texture food in 2/5 children. Cognitive testing in the adult patients showed normal intelligence quotients, with no obvious pattern of subtest deficit. Speech findings in the adult group did demonstrate misarticulations of the sibilant consonants and contextual articulatory imprecision in spontaneous speech samples.

Radiographic Findings

Three-dimensional computed tomography of the skull demonstrated obliteration of the prematurely fused sutures in the adult patients (Fig. 5). On review of available CT scans, no obvious inner ear malformation was apparent in any patient. No brain malformations were found on magnetic resonance imaging of the four adult patients and one pediatric patient. No cervical spine abnormalities were found. Left calcaneocuboid fusion was seen in Patient 1:I:1 (Fig. 1). A complete skeletal survey was obtained for five patients; hand and foot views were obtained for two pediatric patients. Shortening of middle phalanges of one or more fingers (5/7) and of the toes (2/7) were noted. Mild to moderate osteopenia was seen in three of the seven patients. In two adult patients, there was mild disc height loss on the cervical vertebrae C5–C6 (1:I:1) and mild central compression fractures of the thoracic vertebrae (1:II:1) (Fig. 1). Mild thoracolumbar (1:I:1) and lumbar scoliosis (5:II:1) were observed. Left calcaneocuboid fusion was seen in Patient 1:II:1. There were significant epiphyseal changes in patient (3:II:2 or 4:II:1) including irregular ossifications of bilateral

medial condylar epiphyses, coning of proximal phalangeal epiphyses, and supernumerary epiphyseal formation in the metatarsals. In the oldest patient 1:I:1, there is bilateral minimal uniform narrowing of the distal interphalangeal joints. No other obvious bony abnormalities were appreciated.

DISCUSSION

Our review of published cases of Muenke syndrome is consistent with previous reports noting that females with Muenke syndrome tend to be more severely affected than males [Gripp et al., 1998; Lajeunie et al., 1999; Cassileth et al., 2001]. We found that females with Muenke syndrome and craniosynostosis tended to be reported with bicoronal synostosis more often than unicoronal synostosis. In contrast, males with Muenke syndrome were reported about equally as often with bicoronal or unicoronal synostosis. It is possible that gender could influence whether or not an individual presents to a craniofacial clinic for repair: for cosmetic reasons, there may be more social pressure to repair synostosis in females, conversely, short hair in males is more likely to accent a skull deformity.

As most cases were obtained from craniofacial clinic populations, we expect a bias in the literature in favor of reporting cases with craniosynostosis. However, many authors also provided reasonable documentation of other family members besides the proband. Assuming that the literature is truly representative of the population of individuals with Muenke syndrome, craniosynostosis is approximately 87% penetrant in females and approximately 76% penetrant in males. The true penetrance of craniosynostosis may be less in an unselected population.

We report on a mild-to-moderate, low-to-mid frequency mostly sensorineural hearing loss in all individuals with Muenke syndrome who could be evaluated. This pattern was previously reported in single individuals [Dunne et al., 2001; Lowry et al., 2001] but was not recognized as characteristic of Muenke syndrome. In previous series, approximately one-third of patients with Muenke syndrome were reported to have hearing loss, typically described as sensorineural in nature [Muenke et al., 1997; Kress et al., 2006]. Our review of the literature found 126 cases with a documented auditory phenotype. This included 75 individuals said to have normal hearing, however, the method of ascertainment was almost never described. Because the audiograms we collected show a consistent pattern across age groups and between institutions, we suspect that many case reports of “normal” hearing were actually based on the individual’s self-report and/or normal brainstem auditory evoked response, which does not adequately evaluate low frequency hearing loss (see below).

There is evidence that this characteristic pattern of hearing loss is a direct result of the *FGFR3* Pro250Arg mutation, and not a secondary effect of craniosynostosis. Individuals with macrocephaly and hearing loss in the absence of craniosynostosis have been reported [Gripp et al., 1998]. We did not find any case definitively describing a *FGFR3* Pro250Arg mutation heterozygote with apparently isolated bilateral hearing loss (i.e., no craniosynostosis and no macrocephaly). Unilateral hearing loss was reported in an individual with the Pro250Arg mutation and normocephaly [Gripp et al., 1998]. Some supporting evidence is provided by a large family with 12 confirmed Pro250Arg mutation heterozygotes that was also segregating mild, bilateral sensorineural hearing loss [Hollway et al., 1998]. One relative had craniosynostosis as well as hearing loss, and 10 relatives had hearing loss without craniosynostosis (the presence or absence of macrocephaly was not documented). However, one relative without the mutation had unilateral hearing loss. The reporting authors suggested that the hearing loss in this case may have been secondary to an unrelated cause.

Hearing loss is common in the classic craniosynostosis syndromes, and may be conductive and/or sensorineural [Lee et al., 2002]. Conductive hearing loss may be caused by external auditory canal stenosis/atresia, middle ear disease, and/or ossicular malformations/fixation. Some patients with Muenke syndrome and conductive hearing loss have been described [Ades et al., 1994]. Skull base anomalies are present in both "classic" craniosynostosis syndromes and unicoronal synostosis [Goodrich, 2005]. One manifestation of skull base abnormalities in individuals with Muenke syndrome is a highly arched palate, seen in 4/7 patients evaluated at the NIH. A highly arched palate can cause functional interference with the tensor veli palatini, a muscle that assists in opening and closing the Eustachian tube. We note that recurrent otitis media was reported in 8/9 of the patients seen at NIH, and therefore we suspect that Eustachian tube dysfunction may cause frequent middle ear effusions and conductive hearing loss in some children with Muenke syndrome. The "characteristic" low-to-mid frequency sensorineural hearing loss in Muenke syndrome may be due to a developmental effect of the Pro250Arg mutation on the sensory epithelia of the cochlea. Studies in the inner ear of neonatal mice show the highest expression of *FGFR3* in the sensory and neural structures (specifically, the spiral ganglion and surrounding cartilage, spiral lamina and limbus, basilar membrane and organ of Corti) [Pickles, 2001]. *FGFR3* is required for the development of pillar cells in the organ of Corti [Mueller et al., 2002]. *Fgfr3* is up-regulated in the rat organ of Corti following acoustic overstimulation [Pirvola et al., 1995]. Therefore, *FGFR3* not only plays a role in the normal develop-

ment of the inner ear, but also probably contributes to the maintenance of inner ear homeostasis.

Low frequency sensorineural hearing loss is unusual. Autosomal dominant low frequency sensorineural hearing loss (LFSNHL) is a nonsyndromic disorder that was independently mapped to 4p16 in several large families [Lesperance et al., 1995; Van Camp et al., 1999; Young et al., 2001]. Named for the numeric code assigned to each family, DFNA6/14/38 was subsequently found to be caused by mutations in wolframín (WFS1) [Bespalova et al., 2001]. Both DFNA6 and Muenke syndrome may cause low-frequency hearing loss in the absence of other physical examination findings. However, the two disorders have a different etiology. Molecular investigation of the *FGFR3* gene in the original DFNA6 family did not reveal the Pro250Arg mutation [Bespalova et al., 1999]. The DNFA14 and DNFA38 families were also evaluated for syndromic features. Based on our literature review, craniosynostosis appears to have a relatively high penetrance in Muenke syndrome. It seems unlikely that the *FGFR3* Pro250Arg mutation would co-segregate in the large DNFA14 and DFNA38 families without any members manifesting craniosynostosis.

Because newborn hearing screens and many school-based hearing screens tend to focus on the mid and high frequencies, it is possible that the characteristic hearing loss seen in Muenke syndrome will not be detected on these screens. Therefore, we recommend that patients with Muenke syndrome should receive regular audiometric evaluations. This is important because the "characteristic" low-to-mid frequency Muenke syndrome hearing loss may be of consequence in environments with ambient noise, such as a classroom environment. Young school-aged children even with normal hearing have more difficulty understanding speech in the presence of real-life classroom noise [Jamieson et al., 2004]. Children with minimal degrees of sensorineural hearing loss have more difficulty with sentence recognition than their normal-hearing peers [Crandell, 1993]. Special accommodations such as sound field amplification (SFA) and preferential seating can improve speech perception in individuals with hearing loss [Lewis et al., 2004], and are indicated for hearing loss that could interfere with classroom learning. Therefore, children with "characteristic" Muenke syndrome hearing loss, even of a slight-to-mild degree, should receive regular audiometric evaluations, and should be considered for SFA or other special accommodations.

Another aim of our study was to thoroughly characterize a cohort of patients with Muenke syndrome in order to determine any ocular or dental findings. Ocular findings, primarily strabismus, may well be explained by the presence of the craniosynostosis and its effect on the bony structure of the orbits. We did not find any ocular anomalies that

TABLE VI. Suggested Clinical Management Following the Initial Diagnosis of Muenke Syndrome

Complete genetics and dysmorphology examination
Genetic counseling
Referral to craniofacial team
Referral to early intervention team (pediatric)/consider cognitive assessment (adult)
Audiology assessment
Dental/orthodontic assessment
Ophthalmology assessment

appeared to be directly due to the *FGFR3* Pro250Arg mutation. In children who have had craniosynostosis surgery, strabismus does not appear to be particularly prevalent. Based on our data, we recommend regular ophthalmologic follow-up for strabismus and corneal exposure.

Oral findings in nine patients consisted primarily of dental malocclusion and a highly arched palate. No abnormalities in dental morphology were seen. Routine oral examination and orthodontic evaluations, as needed, are suggested.

Despite reports of broad thumbs/toes in the Muenke syndrome literature, we did not appreciate these findings in our series of nine patients. In contrast we found shortening of the middle phalanges resulting in brachydactyly on skeletal radiographs. Additional bony changes in our series of patients included mild osteopenia, scoliosis and joint changes. None of these findings have been previously described, further studies in patients with Muenke syndrome will need to confirm these findings. On physical examination of all patients, dysmorphic features were essentially limited to the face and skull. Our finding underscores the importance of performing P250R mutation analysis in all individuals with apparently nongenetic uni- or bilateral coronal suture craniosynostosis.

Recently, cognitive outcome in craniosynostosis has been a topic of considerable interest [Becker et al., 2005; Kapp-Simon et al., 2005]. In previous series, approximately one-third of patients with Muenke syndrome had developmental delay or mental retardation, typically described as mild [Muenke et al., 1997; Kress et al., 2006]. Another study of patients with bicoronal synostosis and a nonspecific phenotype found that those with Muenke syndrome had a lower pre- and post-operative IQ, however, the findings did not rise to the level of statistical significance [Arnaud et al., 2002]. Although language delay tended to be the presenting complaint of the patients in our series, standardized evaluation revealed that all patients had some degree of general delay. These findings underscore the importance of referral of all individuals with Muenke syndrome to early intervention programs. We note that the Bayley-II scores of the pediatric patients we evaluated at the NIH were generally consistent with developmental delay,

in contrast, the adults had normal scores on the WAIS-III. It is unclear whether the developmental delays experienced by the pediatric patients will be significant in the long term. To answer this question, we plan to reassess these individuals in a long-term study, and to recruit more study participants.

Based on our findings, we propose a clinical management plan following the initial diagnosis of Muenke syndrome (Table VI). Audiometric and developmental assessment should be added to routine clinical management of craniosynostosis and appropriate genetic counseling for the *FGFR3* Pro250Arg mutation.

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REFERENCES

- Ades LC, Mulley JC, Senga IP, Morris LL, David DJ, Haan EA. 1994. Jackson-Weiss syndrome: Clinical and radiological findings in a large kindred and exclusion of the gene from 7p21 and 5qter. *Am J Med Genet* 51:121–130.
- Arnaud E, Meneses P, Lajeunie E, Thorne JA, Marchac D, Renier D. 2002. Postoperative mental and morphological outcome for nonsyndromic brachycephaly. *Plast Reconstr Surg* 110:6–12, discussion 13.
- Becker DB, Petersen JD, Kane AA, Craddock MM, Pilgram TK, Marsh JL. 2005. Speech, cognitive, and behavioral outcomes in nonsyndromic craniosynostosis. *Plast Reconstr Surg* 116:400–407.
- Bellus GA, Gaudenz K, Zackai EH, Clarke LA, Szabo J, Francomano CA, Muenke M. 1996. Identical mutations in three different fibroblast growth factor receptor genes in autosomal dominant craniosynostosis syndromes. *Nat Genet* 14:174–176.
- Bespalova IN, Burmeister M, Lesperance MM. 1999. No association between DFNA6 and Pro250Arg mutation in FGFR3. *Am J Med Genet* 88:451.
- Bespalova IN, Van Camp G, Bom SJ, Brown DJ, Cryns K, DeWan AT, Erson AE, Flothmann K, Kunst HP, Kurnool P, Sivakumar TA, Cremers CW, Leal SM, Burmeister M, Lesperance MM. 2001. Mutations in the Wolfram syndrome 1 gene (WFS1) are a common cause of low frequency sensorineural hearing loss. *Hum Mol Genet* 10:2501–2508.
- Cassileth LB, Bartlett SP, Glat PM, Gripp KW, Muenke M, Zackai EH, Whitaker LA. 2001. Clinical characteristics of patients with unicoronal synostosis and mutations of fibroblast growth factor receptor 3: A preliminary report. *Plast Reconstr Surg* 108:1849–1854.
- Chun K, Teebi AS, Jung JH, Kennedy S, Laframboise R, Meschino WS, Nakabayashi K, Scherer SW, Ray PN, Teshima I. 2002. Genetic analysis of patients with the Saethre-Chotzen phenotype. *Am J Med Genet* 110:136–143.

- Crandell CC. 1993. Speech recognition in noise by children with minimal degrees of sensorineural hearing loss. *Ear Hear* 14:210–216.
- Dunne AA, Bien S, Folz BJ, Werner JA. 2001. Standard variant venous dysplasia of the cerebellum in a patient suffering from Muenke's syndrome and tinnitus. *Auris Nasus Larynx* 28:249–252.
- Golla A, Lichner P, von Gernet S, Winterpacht A, Fairley J, Murken J, Schuffenhauer S. 1997. Phenotypic expression of the fibroblast growth factor receptor 3 (FGFR3) mutation P250R in a large craniosynostosis family. *J Med Genet* 34:683–684.
- Goodrich JT. 2005. Skull base growth in craniosynostosis. *Childs Nerv Syst* 21:871–879.
- Graham JM Jr, Braddock SR, Mortier GR, Lachman R, Van Dop C, Jabs EW. 1998. Syndrome of coronal craniosynostosis with brachydactyly and carpal/tarsal coalition due to Pro250Arg mutation in FGFR3 gene. *Am J Med Genet* 77:322–329.
- Gripp KW, McDonald-McGinn DM, Gaudenz K, Whitaker LA, Bartlett SP, Glat PM, Cassileth LB, Mayro R, Zackai EH, Muenke M. 1998. Identification of a genetic cause for isolated unilateral coronal synostosis: A unique mutation in the fibroblast growth factor receptor 3. *J Pediatr* 132:714–716.
- Grosso S, Farnetani MA, Berardi R, Bartalini G, Carpentieri M, Galluzzi P, Mostardini R, Morgese G, Balestri P. 2003. Medial temporal lobe dysgenesis in Muenke syndrome and hypochondroplasia. *Am J Med Genet Part A* 120A:88–91.
- Hall JG, Froster-Iskenius UG, Allanson JE. 1989. Handbook of normal physical measurements. Oxford: Oxford University Press.
- Hollway GE, Suthers GK, Battese KM, Turner AM, David DJ, Mulley JC. 1998. Deafness due to Pro250Arg mutation of FGFR3. *Lancet* 351:877–878.
- Hughes J, Nevin NC, Morrison PJ. 2001. Familial craniosynostosis due to Pro250Arg mutation in the fibroblast growth factor receptor 3 gene. *Ulster Med J* 70:47–50.
- Jamieson DG, Kranjc G, Yu K, Hodgetts WE. 2004. Speech intelligibility of young school-aged children in the presence of real-life classroom noise. *J Am Acad Audiol* 15:508–517.
- Jones KL, editor. 1997. Smith's recognizable patterns of human malformation, 5th edition. Philadelphia: W.B. Saunders Company.
- Kapp-Simon KA, Leroux B, Cunningham M, Speltz ML. 2005. Multisite study of infants with single-suture craniosynostosis: Preliminary report of presurgery development. *Cleft Palate Craniofac J* 42:377–384.
- Kress W, Schropp C, Lieb G, Petersen B, Busse-Ratzka M, Kunz J, Reinhart E, Schafer WD, Sold J, Hoppe F, Pahnke J, Trusen A, Sorensen N, Krauss J, Collmann H. 2006. Saethre-Chotzen syndrome caused by TWIST 1 gene mutations: Functional differentiation from Muenke coronal synostosis syndrome. *Eur J Hum Genet* 14:39–48.
- Lajeunie E, El Ghouzzi V, Le Merrer M, Munnich A, Bonaventure J, Renier D. 1999. Sex related expressivity of the phenotype in coronal craniosynostosis caused by the recurrent P250R FGFR3 mutation. *J Med Genet* 36:9–13.
- Lee S, Seto M, Sie K, Cunningham M. 2002. A child with Saethre-Chotzen syndrome, sensorineural hearing loss, and a TWIST mutation. *Cleft Palate Craniofac J* 39:110–114.
- Lesperance MM, Hall JW III, Bess FH, Fukushima K, Jain PK, Ploplis B, San Agustin TB, Skarka H, Smith RJ, Wills M, Wilcox ER. 1995. A gene for autosomal dominant nonsyndromic hereditary hearing impairment maps to 4p16.3. *Hum Mol Genet* 4:1967–1972.
- Lewis MS, Crandell CC, Valente M, Horn JE. 2004. Speech perception in noise: Directional microphones versus frequency modulation (FM) systems. *J Am Acad Audiol* 15:426–439.
- Lowry RB, Jabs EW, Graham GE, Gerritsen J, Fleming J. 2001. Syndrome of coronal craniosynostosis, Klippel-Feil anomaly, and Sprengel shoulder with and without Pro250Arg mutation in the FGFR3 gene. *Am J Med Genet* 104:112–119.
- Moko SB, de Chalmers TM. 2001. New Zealand Maori family with the pro250arg fibroblast growth factor receptor 3 mutation associated with craniosynostosis. *J Maxillofac Surg* 29:22–24.
- Moloney DM, Wall SA, Ashworth GJ, Oldridge M, Glass IA, Francomano CA, Muenke M, Wilkie AO. 1997. Prevalence of Pro250Arg mutation of fibroblast growth factor receptor 3 in coronal craniosynostosis. *Lancet* 349:1059–1062.
- Mori F, Kuwajima K, Yamanaka K, Kondou I. 2001. A case of bilateral coronal craniosynostosis with the P250R mutation in FGFR3 gene. *No To Hattatsu* 33:53–57.
- Mueller KL, Jacques BE, Kelley MW. 2002. Fibroblast growth factor signaling regulates pillar cell development in the organ of Corti. *J Neurosci* 22:9368–9377.
- Muenke M, Gripp KW, McDonald-McGinn DM, Gaudenz K, Whitaker LA, Bartlett SP, Markowitz RI, Robin NH, Nwokoro N, Mulvihill JJ, Losken HW, Mulliken JB, Guttmacher AE, Wilroy RS, Clarke LA, Hollway G, Ades LC, Haan EA, Mulley JC, Cohen MM, Bellus GA, Francomano CA, Moloney DM, Wall SA, Wilkie AO, Zackai EH. 1997. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) defines a new craniosynostosis syndrome. *Am J Hum Genet* 60:555–564.
- Mulliken JB, Steinberger D, Kunze S, Muller U. 1999. Molecular diagnosis of bilateral coronal synostosis. *Plast Reconstr Surg* 104:1603–1615.
- Mulliken JB, Gripp KW, Stolle CA, Steinberger D, Muller U. 2004. Molecular analysis of patients with synostotic frontal plagiocephaly (unilateral coronal synostosis). *Plast Reconstr Surg* 113:1899–1909.
- Passos-Bueno MR, Sertie AL, Richieri-Costa A, Alonso LG, Zatz M, Alonso N, Brunoni D, Ribeiro SF. 1998. Description of a new mutation and characterization of FGFR1, FGFR2, and FGFR3 mutations among Brazilian patients with syndromic craniosynostosis. *Am J Med Genet* 78:237–241.
- Paznekas WA, Cunningham ML, Howard TD, Korf BR, Lipson MH, Grix AW, Feingold M, Goldberg R, Borochowitz Z, Aleck K, Mulliken J, Yin M, Jabs EW. 1998. Genetic heterogeneity of Saethre-Chotzen syndrome, due to TWIST and FGFR mutations. *Am J Hum Genet* 62:1370–1380.
- Pickles JO. 2001. The expression of fibroblast growth factors and their receptors in the embryonic and neonatal mouse inner ear. *Hear Res* 155:54–62.
- Pirvola U, Cao Y, Oellig C, Suoqiang Z, Pettersson RF, Ylikoski J. 1995. The site of action of neuronal acidic fibroblast growth factor is the organ of Corti of the rat cochlea. *Proc Natl Acad Sci USA* 92:9269–9273.
- Reardon W, Wilkes D, Rutland P, Pulley LJ, Malcolm S, Dean JC, Evans RD, Jones BM, Hayward R, Hall CM, Nevin NC, Baraister M, Winter RM. 1997. Craniosynostosis associated with FGFR3 pro250arg mutation results in a range of clinical presentations including unisutural sporadic craniosynostosis. *J Med Genet* 34:632–636.
- Renier D, El-Ghouzzi V, Bonaventure J, Le Merrer M, Lajeunie E. 2000. Fibroblast growth factor receptor 3 mutation in non-syndromic coronal synostosis: Clinical spectrum, prevalence, and surgical outcome. *J Neurosurg* 92:631–636.
- Robin NH, Scott JA, Cohen AR, Goldstein JA. 1998. Nonpenetration in FGFR3-associated coronal synostosis syndrome. *Am J Med Genet* 80:296–297.
- Roscioli T, Flanagan S, Mortimore RJ, Kumar P, Weedon D, Masel J, Lewandowski R, Hyland V, Glass IA. 2001. Premature calvarial synostosis and epidermal hyperplasia (Beare-Stevenson syndrome-like anomalies) resulting from a P250R missense mutation in the gene encoding fibroblast growth factor receptor 3. *Am J Med Genet* 101:187–194.
- Sabatino G, Di Rocco F, Zampino G, Tamburrini G, Caldarelli M, Di Rocco C. 2004. Muenke syndrome. *Childs Nerv Syst* 20:297–301.

- Thomas GP, Wilkie AO, Richards PG, Wall SA. 2005. FGFR3 P250R mutation increases the risk of reoperation in apparent 'nonsyndromic' coronal craniosynostosis. *J Craniofac Surg* 16:347–352, discussion 353–354.
- Tsai FJ, Wu JY, Lee CC, Tsa CH. 2000. A unique point mutation in the fibroblast growth factor receptor 3 gene (FGFR3) causes non-syndromic craniosynostosis. *Acta Paediatr* 89:672–674.
- van Aalst JA, Schultz G, Eppley BL. 2005. Craniosynostosis anomalies in twins. *J Craniofac Surg* 16:696–699.
- Van Camp G, Kunst H, Flothmann K, McGuirt W, Wauters J, Marres H, Verstreken M, Bernalova IN, Burmeister M, Van de Heyning PH, Smith RJ, Willems PJ, Cremers CW, Lesperance MM. 1999. A gene for autosomal dominant hearing impairment (DFNA14) maps to a region on chromosome 4p16.3 that does not overlap the DFNA6 locus. *J Med Genet* 36:532–536.
- van der Meulen J, van den Ouweland A, Hoogeboom J. 2006. Trigenocephaly in Muenke syndrome. *Am J Med Genet Part A* 140A:2493–2494.
- Young TL, Ives E, Lynch E, Person R, Snook S, MacLaren L, Cater T, Griffin A, Fernandez B, Lee MK, et al. 2001. Non-syndromic progressive hearing loss DFNA38 is caused by heterozygous missense mutation in the Wolfram syndrome gene WFS1. *Hum Mol Genet* 10:2509–2514.