Genetics of Craniosynostosis

Maximilian Muenke, M.D.
Chief, Medical Genetics Branch
Director, NIH Medical Genetics and
Genomic Medicine Residency and Fellowship Programs
National Human Genome Research Institute
National Institutes of Health, Bethesda, Maryland, U.S.A.
Email: muenke@nih.gov
Disclosures

NIH
US DHHS
Disclosures

NIH
US DHHS

Founding Editor-in-Chief
MGGM
Wiley & Sons

Incoming Editor-in-Chief
AJMG Part A
Wiley & Sons
Genetics and genomic medicine around the world

Atlas of Human Malformation Syndromes in Diverse Populations

www.genome.gov/atlas
Browse by Atlas Condition

Aneuploidies
- Trisomy 21 (Down syndrome)
- Trisomy 18 (Edwards syndrome)
- Trisomy 13
- Klinefelter syndrome
- Turner syndrome

Microdeletion Syndromes
- 22q11.2 Deletion syndrome (DiGeorge syndrome and Velocardiofacial syndrome)
- Williams syndrome
- 1p36 deletion syndrome
- 5p deletion syndrome
- 4p deletion syndrome (Wolf-Hirschhorn syndrome)

Single Gene Disorders
- Aarskog syndrome
- Alagille syndrome
- Angelman syndrome
- Antley-Bixler syndrome
INVITED COMMENTARY

Mentors without Borders

Maximilian Muenke

Medical Genetics Branch, National Human Genome Research Institute, National Institutes of Health, Bethesda, Maryland 20814

Correspondence
Maximilian Muenke, National Human Genome Research Institute, National Institutes of Health, 35 Convent Drive, 35/18-203, Bethesda, MD 20814. Tel: +1 301 402 8167; Fax: +1 301 496 7184; E-mail: muenke@nih.gov

doi: 10.1002/mgg3.246

There is a special place in hell for women who do not help other women. — Madeleine Albright

In order to be a mentor, and an effective one, one must care. You must care. You don’t have to know how many square miles are in Idaho, you don’t need to know what is the chemical makeup of chemistry, or of blood or water. Know what you know and care about the person, care about what you know and care about the person you’re sharing with. — Maya Angelou

Colleagues are a wonderful thing — but mentors, that’s where the real work gets done. — Junot Diaz

Mentors Without Borders/Doctors Without Borders

The name Mentors without Borders (Fig. 1) is inspired by the original Médecins Sans Frontières (MSF) or Doctors without Borders. French physicians founded MSF in 1971 in the aftermath of the Nigerian Civil War (1967–1970) that led to the blockade and starvation of those who lived in the newly independent Biafra. MSF is an international, nongovernmental organization that delivers “emergency aid to people affected by armed conflict, healthcare exclusion and natural or man-made disasters” (www.msf.org).

Many other professions have used the “... without Borders” name, including: Accountants, Acupuncturists, etc.
Holoprosencephaly  Craniosynostosis Syndromes
Craniosynostosis Syndromes
Sporadic Pfeiffer Syndrome
Abnormal Head Shapes

- Unicoronal Synostosis
- Lambdoid Synostosis
Positional Deformity vs. Unilateral Lambdoid Synostosis
Positional Deformity vs. Unilateral Lambdoid Synostosis
Craniosynostosis

• Premature fusion of one or several sutures of the skull

• Prevalence: 1 in 2,100 to 1 in 3,000 at birth
Isolated Nonsyndromic Craniosynostosis

Sagittal synostosis: 50-60%
Coronal synostosis: 20-30%
Metopic and lambdoidal synostosis less common

Etiology: mostly sporadic, but familial instances are known
Syndromic Craniosynostosis

Craniosynostosis with associated anomalies
(mostly limb defects)
Over 200 syndromes with craniosynostosis
Hand and Foot Findings in Patients with Craniosynostosis Syndromes

Pfeiffer Syndrome  Saethre-Chotzen Syndrome   Muenke Syndrome
Syndromic Craniosynostosis

Apert Syndrome 1906
Crouzon Syndrome 1912
Pfeiffer Syndrome 1964
Saethre-Chotzen Syndrome 1931; 1932
Syndromic Craniosynostosis

Apert Syndrome 1906
Crouzon Syndrome 1912
Pfeiffer Syndrome 1964

Saethre-Chotzen Syndrome 1931; 1932
Craniofrontonasal Syndrome 1979
Syndromic Craniosynostosis

Apert Syndrome 1906
Crouzon Syndrome 1912
Pfeiffer Syndrome 1964
Muenke Syndrome 1996
Saethre-Chotzen Syndrome 1931; 1932
Craniofrontonasal Syndrome 1979
## Syndromic Craniosynostosis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apert Syndrome</td>
<td>FGFR2</td>
</tr>
<tr>
<td>Crouzon Syndrome</td>
<td>FGFR2</td>
</tr>
<tr>
<td>Pfeiffer Syndrome</td>
<td>FGFR1; FGFR2</td>
</tr>
<tr>
<td>Muenke Syndrome</td>
<td>FGFR3</td>
</tr>
<tr>
<td>Saethre-Chotzen Syndrome</td>
<td>TWIST1</td>
</tr>
<tr>
<td>Craniofrontonasal Syndrome</td>
<td>EFNB1</td>
</tr>
</tbody>
</table>
Apert Syndrome
Pfeiffer Syndrome
Crouzon Syndrome
Muenke Syndrome
Saethre-Chotzen Syndrome
Craniofrontonasal Syndrome (CFNS)

Craniofacial findings:
- Coronal synostosis (brachycephaly/plagiocephaly)
- Facial asymmetry (with unicoronal synostosis)
- Hypertelorism with down-slanting palpebral fissures & broad nasal root
- Grooved nasal tip
- Cleft lip+/- palate (occasionally)

Other findings:
- Various skeletal anomalies

Inheritance: X-Linked
## Syndromic Craniosynostosis

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apert Syndrome</td>
<td>$FGFR2$</td>
</tr>
<tr>
<td>Crouzon Syndrome</td>
<td>$FGFR2$</td>
</tr>
<tr>
<td>Pfeiffer Syndrome</td>
<td>$FGFR1; FGFR2$</td>
</tr>
<tr>
<td>Muenke Syndrome</td>
<td>$FGFR3$</td>
</tr>
<tr>
<td>Saethre-Chotzen Syndrome</td>
<td>$TWIST1$</td>
</tr>
<tr>
<td>Craniofrontonasal Syndrome</td>
<td>$EFNB1$</td>
</tr>
</tbody>
</table>
Sporadic Pfeiffer Syndrome
A common mutation in the fibroblast growth factor receptor 1 gene in Pfeiffer syndrome

Maximilian Muenke¹², Ute Schell¹, Andreas Hehr¹, Nathaniel H. Robin¹, H. Wolfgang Losken³, Albert Schinzel⁴, Louise J. Pulley⁵, Paul Rutland⁶, William Reardon⁵, Sue Malcolm⁵ & Robin M. Winter⁵

Nature Genetics volume 8  November 1994

Mutations in FGFR1 and FGFR2 cause familial and sporadic Pfeiffer syndrome

Ute Schell¹, Andreas Hehr¹, George J. Feldman¹, Nathaniel H. Robin¹, Elaine H. Zackai¹, Christine de Die-Smulders⁴, David H. Viskochil⁵, Janet M. Stewart⁶, Gerhard Wolff⁷, Hiroyuki Ohashi⁸, R. Arlen Price²³, M. Michael Cohen, Jr.⁹, and Maximilian Muenke¹²,*
Identical mutations in three different fibroblast growth factor receptor genes in autosomal dominant craniosynostosis syndromes

Gary A. Bellus, Karin Gaudenz, Elaine H. Zackai, Lorne A. Clarke, Jinny Szabo, Clair A. Francomano & Maximilian Muenke

allowing rapid screening of DNA from all available family members. The disease phenotype cosegregated with the mutant allele in both families (Fig. 2b). In contrast, the mutation was not detected in over 120 normal chromosomes. We next screened DNA from 65 unrelated individuals with craniosynostosis with or without limb involvement and were able to identify an additional eight samples with this mutation. On clinical examination, five families segregated non-syndromic craniosynostosis, the remaining three had some clinical findings that were con-
nature genetics volume 14 october 1996

A Unique Point Mutation in the Fibroblast Growth Factor Receptor 3 Gene (FGFR3) Defines a New Craniosynostosis Syndrome


1. Ligand-dependent gain-of-function mutations act by increasing ligand-binding affinity and by overriding ligand-binding specificity of affected receptors.

2. Exclusive paternal origin, if de novo.

Fibroblast Growth Factor Receptors:

- FGFR1 p.P252R
- FGFR2 p.P253R
- FGFR3 p.P250R

Molecular Diagram:

- **FGFR1**
  - GAG CGG TCC
  - CCT Pro CAC

- **FGFR2**
  - GAG CGA TCG
  - CCT Pro Ser

- **FGFR3**
  - GAG CGC TCC
  - CCT Pro
Fibroblast Growth Factor Receptors

1. Ligand-dependent gain-of-function mutations act by increasing ligand-binding affinity and by overriding ligand-binding specificity of affected receptors

2. Exclusive paternal origin, if de novo
Muenke Syndrome

- Defined by FGFR3 mutation: p.Pro250Arg
- Most common craniosynostosis syndrome
- Muenke syndrome comprises 25% of molecularly defined craniosynostosis
- An estimated 8% of craniosynostosis patients have Muenke syndrome
- Incidence: 1 in 30,000
Muenke Syndrome
A Multicenter Natural History Study

Preliminary findings in 106 FGFR3 mutation-positive individuals

• Inheritance in 54%

• Craniosynostosis in 84%
  – Bicoronal in 48% (equal in males and females)
  – Unicoronal in 31%

• Skeletal anomalies (other than skull) in 75%

• Hearing loss in 72%
Muenke Syndrome
A Multicenter Natural History Study

Preliminary findings in 106 FGFR3 mutation-positive individuals

- Developmental delay (mainly speech) in 66%
- Intellectual disability in 42%
  - ADHD in 24%
  - Seizures in 21%
Muenke Syndrome: An International Multicenter Natural History Study

Paul Kruszka, Yonit A. Addissie, Colin M. P. Yarnell, Donald W. Hadley, Maria J. Guillen Sacoto, Petra Platte, Yvonne Paelecke, Hartmut Collmann, Nicole Snow, Tilmann Schweitzer, Simeon A. Boyadjiev, Christos Aravidis, Samantha E. Hall, John B. Mulliken, Tony Roscioli, and Maximilian Muenke

1Medical Genetics Branch, National Human Genome Research Institute, The National Institutes of Health, Bethesda, Maryland
2Department of Biological Psychology, Clinical Psychology and Psychotherapy, University of Würzburg, Germany
3Section of Pediatric Neurosurgery, Department of Neurosurgery, University of Würzburg, Germany
4Sydney Children’s Hospital, University of New South Wales, Sydney, Australia
5Kinghorn Centre for Clinical Genomics, The Garvan Institute, Darlinghurst, Sydney, Australia
6Department of Pediatrics, Section of Genetics, University of California Davis, Sacramento, California
7Department of Clinical Genetics, Akademiska University Hospital, Uppsala, Sweden
8Department of Plastic and Oral Surgery, Boston Children’s Hospital, Boston, Massachusetts

Manuscript Received: 19 September 2015; Manuscript Accepted: 9 December 2015

Muenke syndrome is an autosomal dominant disorder characterized by coronal suture craniosynostosis, hearing loss, developmental delay, carpal, and calcaneal fusions, and behavioral differences. Reduced penetrance and variable expressivity contribute to the wide spectrum of clinical findings. Muenke syndrome constitutes the most common syndromic form of craniosynostosis, with an incidence of 1 in 30,000 births and is defined by the presence of the p.Pro250Arg mutation in FGFR3. Participants were recruited from international craniofacial surgery and genetic clinics. Affected individuals, parents, and their siblings, if available, were enrolled in the study if they had a p.Pro250Arg mutation in FGFR3. One hundred and six patients from 71 families participated in this study. In 51 informative probands, 33 cases (64.7%) were inherited.

How to Cite this Article:
Craniosynostosis

Hearing loss (by report)

Behavioral Phenotype

"Behavioral" Phenotype
Craniosynostosis

Hearing loss (by report)

FGFR3 p.P250R mutation positive

Behavioral Phenotype (by report)
Craniosynostosis
Hearing loss (by report)
FGFR3 p.P250R mutation positive
Behavioral Phenotype (by report)

“Behavioral” Phenotype
Behavioral Rating Inventory of Executive Function (BRIEF) $T$ scores: Affected siblings ($FGFR3+$) vs. unaffected ($FGFR3-$) shown as box and whisker plots. Higher $T$ scores indicate lower skill levels.
Adaptive Behavior Assessment System (ABAS-II) scores:
Affected siblings (FGFR3+) vs. unaffected (FGFR3-) shown as box and whisker plots. Lower composite scores indicate lower skill levels.
Executive Function and Adaptive Behavior in Muenke Syndrome

Colin M. P. Yarnell, BA1,*, Yonit A. Addissie, BA1,*, Donald W. Hadley, MS1, Maria J. Guillen Sacoto, MD1, Nneamaka B. Agochukwu, MD1, Rachel A. Hart, BS1, Edythe A. Wiggs, PhD1, Petra Platte, PhD2, Yvonne Paelecke, PhD2, Hartmut Collmann, MD3, Tilmann Schweitzer, MD4, Paul Kruszka, MD, MPH1, and Maximilian Muenke, MD1

Objective To investigate executive function and adaptive behavior in individuals with Muenke syndrome using validated instruments with a normative population and unaffected siblings as controls.

Study design Participants in this cross-sectional study included individuals with Muenke syndrome (P250R mutation in FGFR3) and their mutation-negative siblings. Participants completed validated assessments of executive functioning (Behavior Rating Inventory of Executive Function [BRIEF]) and adaptive behavior skills (Adaptive Behavior Assessment System, Second Edition [ABAS-II]).

Results Forty-four with a positive FGFR3 mutation, median age 9 years, range 7 months to 52 years were enrolled. In addition, 10 unaffected siblings served as controls (5 males, 5 females; median age, 13 years; range, 3–18 years). For the General Executive Composite scale of the BRIEF, 32.1% of the cohort had scores greater than +1.5 SD, signifying potential clinical significance. For the General Adaptive Composite of the ABAS-II, 28.2% of affected individuals scored in the 3rd-8th percentile of the normative population, and 56.4% were below the average category (<25th percentile). Multiple regression analysis did not identify craniosynostosis as a predictor of BRIEF (P = .70) or ABAS-II scores (P = .70). In the sibling pair analysis, affected siblings performed significantly poorer on the BRIEF General Executive Composite and the ABAS-II General Adaptive Composite.

Conclusion Individuals with Muenke syndrome are at an increased risk for developing adaptive and executive function behavioral changes compared with a normative population and unaffected siblings. (J Pediatr 2015;167:428-34).
Genetics of Craniosynostosis

Maximilian Muenke, M.D.
Chief, Medical Genetics Branch
Director, NIH Medical Genetics and Genomic Medicine Residency and Fellowship Programs
National Human Genome Research Institute
National Institutes of Health, Bethesda, Maryland, U.S.A.
Email: muenke@nih.gov