Apert syndrome Prevalence in Michigan, 1992-2013

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Background Information

Apert syndrome (AS) is a genetic disorder that affects the body's growth and development in many ways. AS impacts the growth of the bones of the head and face. The skull is made of bony plates. They are held together in babies and children by tissues called cranial sutures. The skull bones fuse together by the time a person is full grown. Early fusion prevents the skull from growing normally. It affects the shape of the head and face. Babies and children with AS have early fusion of cranial sutures. This is known as craniosynostosis or craniostenosis. Craniosynostosis may be isolated or may be part of a craniofacial syndrome.[1] Early fusion of the skull bones and other factors affect the development of the brain.

AS can disrupt intellectual development. Cognitive abilities in people with AS range from normal to mild or moderate intellectual disability.[2] Babies with AS are also born with fusion of the fingers and toes. This is called syndactyly. The extent and severity ranges from skin webbing to fused bones. Some have extra fingers or toes. This is called polydactyly. Babies may have breathing problems that need medical treatment. Other signs and symptoms of AS can include hearing loss, feeding problems, unusually heavy sweating (hyperhidrosis), oily skin with severe acne, fusion of spinal bones in the neck (cervical vertebrae), and recurrent ear infections that may be associated with an opening in the roof of the mouth (a cleft palate).[2]

Occurrence

The estimated incidence of AS in newborns is 15 to 16 in 1,000,000 (or 0.15 to 0.16 in 10,000).[3] The condition affects people of all racial and ethnic backgrounds. AS is associated with severe craniosynostosis. It accounts for 4-5% of all craniosynostosis cases in different populations.[3]

Causes

AS is caused by certain changes (called mutations) in the fibroblast growth factor receptor 2 (*FGFR2*) gene. This gene makes a protein called fibroblast growth factor receptor 2. Normal FGFR2 protein helps cells receive growth signals. A mutation in the FGFR2 gene alters the protein and causes prolonged signaling, which can cause the fusion of bones in the skull, hands, and feet.[2]

- **Craniosynostosis** (from cranio (skull), syn (together), ost (bone) and osis (condition of)) is a condition in which the bones of the skull close together too early.
- **Syndactyly** (from syn (together) and dactyly (digits)) is a condition where two or more digits (fingers and/or toes) are fused together.
- **Polydactyly** (from polys (many) and dactyly (digits)) is a condition of having extra fingers or toes.
- **Hyperhidrosis** (from hyper (excessive), hidrosis (perspiration/sweat)) is a condition of excessive sweating.

AS is almost always due to new mutations in *FGFR2*, occurring randomly, not inherited. Thus, people with AS usually have no history of the disorder in their family. Everyone has two copies of the *FGFR2* gene in every cell of the body. People with AS have one copy of altered *FGFR2* and one normal gene copy in each cell. Children of older unaffected dads are more likely to have genetic conditions like AS that are the result of a new mutation. This is a result of more spontaneous gene changes in sperm as men age.[2] If a parent has AS, each child has a 50/50 chance to inherit the condition (called autosomal dominant inheritance). Specific environmental factors for AS have not been identified.

Several different clinical craniosynostosis syndromes are caused by changes in the *FGFR2* gene including:

- Apert Syndrome
- Beare-Stevenson syndrome
- Crouzon syndrome
- Pfeiffer syndrome
- Jackson-Weiss syndrome, plus
- Non-syndromic craniosynostosis[2]

Nearly everyone with Apert syndrome has one of two mutations in the *FGFR2* gene:

◊ **Ser252Trp**— occurs in approximately 64-67% of affected individuals.

◊ **Pro253Arg**— occurs in approximately 32-33% of affected individuals.

◊ Unique mutations occur in about 1-3%.

Treatment

Babies have cranial surgery to improve brain and skull growth. Several surgeries are usually necessary during childhood and puberty because the skull bones continue to grow and fuse. Face and jaw surgery is common. Children may have multiple hand surgeries. Babies and young children with serious breathing trouble may need a tracheostomy. Children with a craniosynostosis syndrome often benefit from a multidisciplinary team approach.

Most craniofacial clinics from major pediatric medical centers will use this approach. The team of specialists usually includes plastic surgeons, neurosurgeons, otolaryngologists, and dentists as well as audiologists, speech pathologists, developmental pediatricians, social workers, and medical geneticists. The team can usually identify and address physical and developmental problems as well as psychosocial and other issues.[4]

Michigan Birth Defects Registry Reporting

The Michigan Birth Defects Registry (MBDR) is a confidential system for tracking many serious conditions that affect health, growth and development from birth. MBDR is a part of the Michigan Department of Health and Human Services. Michigan law requires hospitals and medical labs to report certain health conditions to the MBDR. MBDR information is used to track the rate of birth defects, develop prevention plans, and help improve services. Craniosynostosis and craniosynostosis syndromes are reported to the MBDR. These conditions are very diverse and typically are not specified in the public data tables available online. They are added to the group total (see Diagnostic Grouping I: Congenital Anomalies of the Musculoskeletal System in the Birth Defects Diagnostic Code Group Summary. This can be viewed at: http://www.mdch.state.mi.us/pha/osr/BirthDefects/bdeftcausesum.asp).

The MBDR "other musculoskeletal defects" category contains several dozen musculoskeletal defects including acrocephalosyndactyly. AS is a type of acrocephalosyndactyly. These conditions are very rare.

◊ **Acrocephalosyndactyly** is the occurrence of craniosynostosis with syndactyly.

Other craniosynostosis syndromes and non-syndromic craniosynostosis, as well as other craniofacial anomalies, are also included in "anomalies of skull and face bones".

MBDR Apert Syndrome Cases

Acrocephalosyndactyly, or AS, is identified by a specific, distinct ICD-9-CM code (755.55). There are other craniosynostosis syndromes that are in the acrocephalosyndactyly family of disorders. It is possible that cases of other acrocephalosyndactyly syndromes (see page 2) have been reported to the MBDR using ICD9 755.55.

- In October 2015, the MBDR began collecting ICD-10-CM conditions.
- Apert Syndrome is identified by the ICD-10-CM code Q87.0.

On average, 2 to 4 babies are born with AS or another acrocephalosyndactyly each year in Michigan. Table 1 takes a closer look at these cases in the MBDR from 1992 to 2013. Typically, the prevalence of AS is reported as 1-2 per 100,000 live births.[3] As reported to the MBDR, the birth prevalence estimate in Michigan from 1992 to 2013 was 0.3 cases per 10,000 live births. That is about 3-4 per 100,000 live births affected. There is no difference observed in AS prevalence between males and females from 1992 to 2013 (Table 1). We also assessed how frequently AS and syndactyly were reported to the MBDR in the same child. Boys and girls that reported AS together with syndactyly were affected equally (Table 1). Due to the rarity of the conditions, the total numbers of cases found in the MBDR are also shown (Table 1).

Table 1: Prevalence rate of Apert syndrome (acrocephalosyndactyly): MBDR, 1992-2013

Congenital Anomaly (ICD-9-CM)	Prevalence [1,2]			
	Male	Female	Total	Number of Cases
Apert syndrome (Acrocephalosyndactyly) (755.55)	0.3	0.3	0.3	92
Apert syndrome with syndactyly (755.55 with 755.10, 755,11, 755.12, 755.13, 755.14)	0.1	0.1	0.1	31

[1]Prevalence rates are based on births to mothers living in Michigan at the time of delivery. Data are current through January 2015.

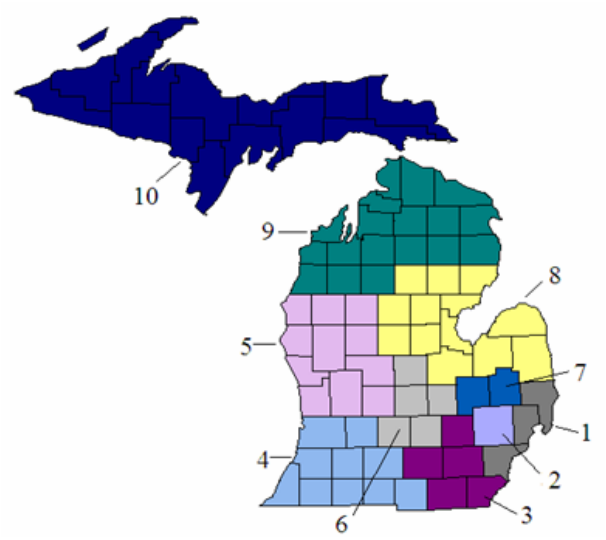
[2]Prevalence rate expressed as cases per 10,000 live births.

The number of cases and rate of AS from 1992 to 2013 were also analyzed by region of maternal residence, approximating pediatric specialty care service areas in Michigan (Table 2).

Region 1 — Macomb, Wayne and St. Clair counties reported the highest number of cases due to a much higher number of live births compared to the rest of the state. However, the prevalence rate of AS in Michigan was highest in Region 7 — Genesee and Lapeer counties with 0.6 cases per 10,000 live births (Table 2). There was no significant difference in AS rate by region.

Table 2: Number of Cases by Region of Maternal Residence, 1992-2013

Region	Apert Syndrome	
	Number	Rate
1	33	0.4
2	10	0.3
3	7	0.3
4	8	0.3
5	8	0.2
6	*	*
7	9	0.6
8	9	0.5
9	*	*
10	*	*
Total	92	0.3



*Data suppressed for fewer than 6 reported cases.

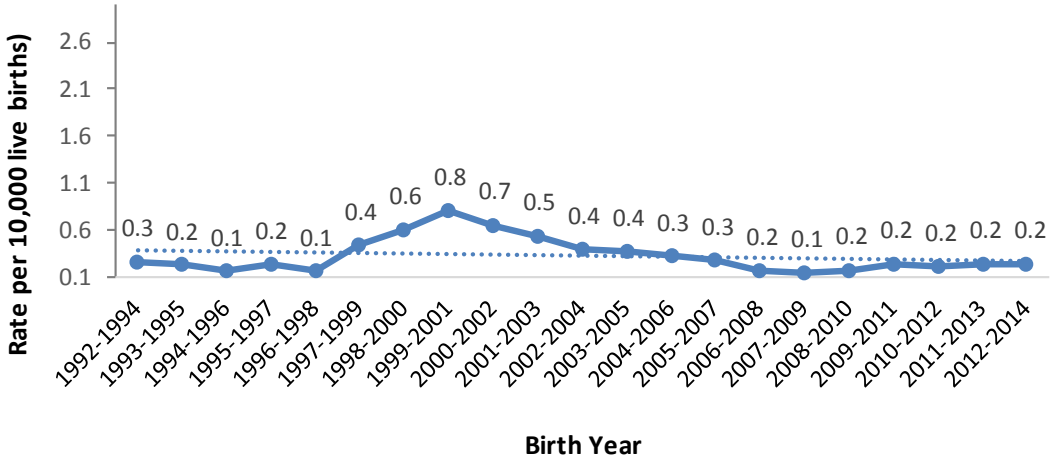
[1]Prevalence rates are based on births to mothers living in Michigan at the time of delivery. Data are current through January 2015.

[2]Prevalence rate expressed as cases per 10,000 live births.

Apert Syndrome Prevalence

The three year moving prevalence rates of AS were calculated to assess trends over time from 1992 to 2014. Rates were calculated for children reported to the MBDR at any age of diagnosis who were born in Michigan and whose mothers were residents of Michigan at the time of birth.

Figure 1: Three year moving prevalence rates of Apert syndrome: MBDR, 1992-2014

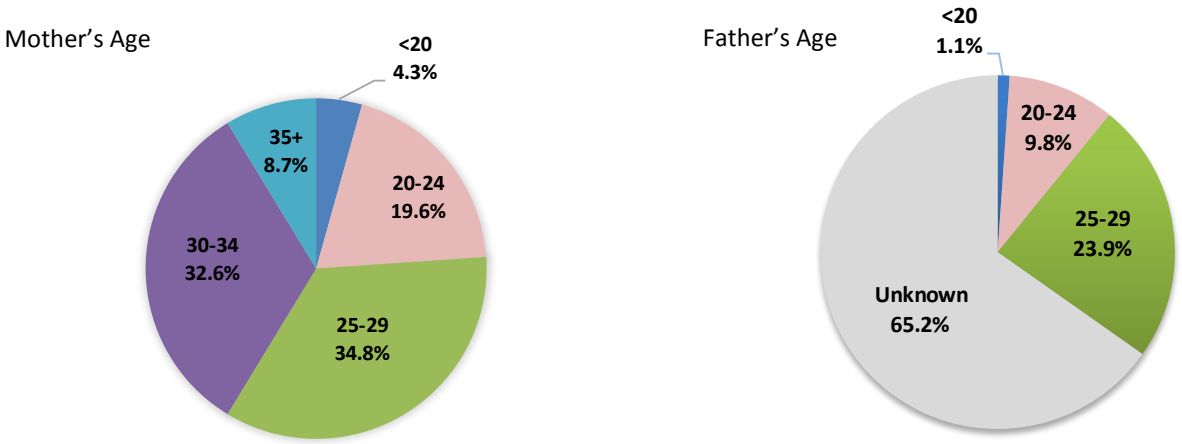


From 1992 to 2014, the overall rate of AS was 0.3 cases per 10,000 live births or 1 in 33,333 live births in Michigan. Overall, rates have decreased slightly over the years. Although the prevalence rate of AS increased from 0.3 cases per 10,000 live births in 1992 to 1994 to 0.8 cases per 10,000 live births in 1999 to 2001, the rate has decreased over the past 13 years with 0.2 cases per 10,000 live births in 2012 to 2014. No increase in the rate of AS was observed in 2014 compared to the previous few years. It is important to note that due to very few reported number of cases each year, rate estimates may fluctuate with just a few additional cases. This may explain the increased rate in 1999 to 2001.

Apert Syndrome by Maternal and Paternal Age

Most cases of AS are sporadic, resulting from new mutations with a potential paternal age effect.[2,5] The incidence of *FGFR2* mutations increases exponentially with father's age. This paternal age effect increases in fathers older than 40 years.[5] We assessed the distribution of AS reported to the MBDR by parental age. The assessment is limited by incomplete information on parental age, especially father's age.

Figure 2: Distribution of Apert syndrome by age of parents: MBDR, 1992-2013



Of 92 AS cases reported to the MBDR from 1992 to 2013, over 75% of affected children were born to mothers ages 25 and older with over a third (34.8%) born to mothers ages 25-29 and nearly a third (32.6%) born to mothers ages 30-34 (Figure 2). By paternal age, nearly a quarter of affected babies (23.9%) were born to fathers ages 25-29 while about 65% of cases had an unknown paternal age (Figure 2). It is not clear if the unknown age group were older fathers.

Public Health Implications

AS is a genetic disorder that causes abnormal growth of the skull bones and the bones of the hands and feet. Surgery may help. Studies have shown that most cases of AS are caused by new (not inherited), specific mutations in the *FGFR2* gene. Studies have not found specific environmental factors accounting for AS in humans.

Analysis of AS cases reported to the MBDR revealed that rates have remained relatively stable at about 0.2 cases per 10,000 live births since 2008. There is no observed increase in the incidence of AS in Michigan in 2014. In addition, no region of concern was identified.

Helpful resources for health professionals and families

Apert International, Inc: **www.apert-international.org**

Teeter's Page: **www.apert.org**

Craniofacial Foundation of America: **www.craniofacialfoundation.org**

Apert Syndrome Genetics Home Reference: **www.ghr.nlm.nih.gov/condition/apert-syndrome**

Chen, Harold. "Apert Syndrome." EMedicine: **www.emedicine.medscape.com/article/941723-overview**

Nathaniel H Robin et al, FGFR-Related Craniosynostosis Syndromes (GeneReviews®): **www.ncbi.nlm.nih.gov/books/NBK1455/**

References

1. Paritosh CK, Mahesh MT,1 Ramesh SL,1 and Shashank SP. Pictorial essay: The many faces of craniosynostosis.
2. Johnson D, Wilkie AOM. Practical Genetics. European Journal of Human Genetics. 2011; 19, 369-376.
3. Cohen MM Jr et al. Birth prevalence study of the Apert syndrome. American Journal of Medical Genetics. 1992; 42: 655–9.
4. Agochukwu NB, Solomon BD, Muenke M. Impact of genetics on the diagnosis and clinical management of syndromic craniosynostoses. Childs Nerv Syst. 2012; 28(9): 1447-63.
5. Yoon SR et al. The Ups and Downs of Mutation Frequencies during Aging Can Account for the Apert Syndrome Paternal Age Effect. PLOS Genetics, 2009; 5(7).

Appendix

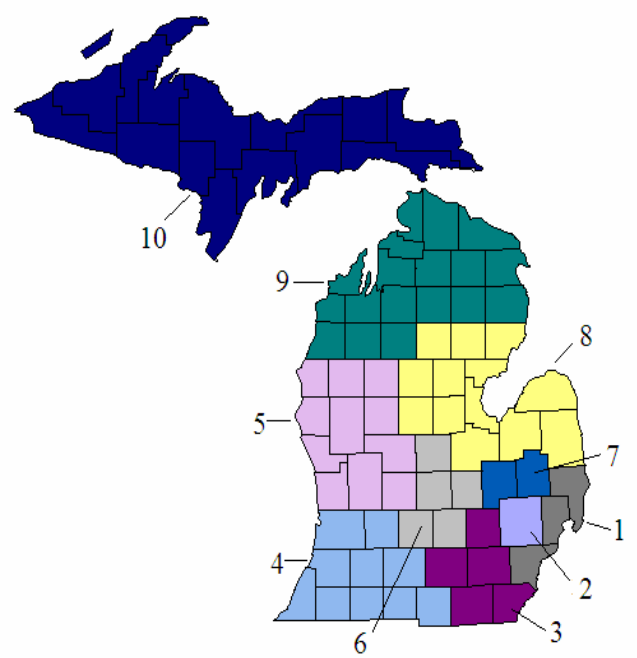


Figure 4: Geographic regions approximate pediatric specialty care service areas

Region 1
Macomb
St. Clair
Wayne

Region 2
Oakland

Region 3
Jackson
Lenawee
Livingston
Monroe
Washtenaw

Region 4
Allegan
Barry
Berrien
Branch
Calhoun
Cass
Hillsdale
Kalamazoo
St. Joseph
Van Buren

Region 5
Ionia
Kent
Lake
Mason
Mecosta
Montcalm
Muskegon
Newaygo
Oceana
Osceola
Ottawa

Region 6
Clinton
Eaton
Gratiot
Ingham
Shiawassee

Region 7
Genesee
Lapeer

Region 8
Arenac
Bay
Clare
Gladwin
Huron
Iosco
Isabella
Midland
Ogemaw
Roscommon
Saginaw
Sanilac
Tuscola

Region 9
Alcona
Alpena
Antrim
Benzie
Cheboygan
Charlevoix
Crawford
Emmet
Grand Traverse
Kalkaska
Leelanau
Manistee
Missaukee
Montmorency
Oscoda
Otsego
Presque Isle
Wexford

Region 10
Alger
Baraga
Chippewa
Delta
Dickinson
Gogebic
Houghton
Iron
Keweenaw
Luce
Mackinac
Marquette
Menominee
Ontonagon
Schoolcraft

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