OPEN ACCESS
Scholars International Journal of Biochemistry
Abbreviated Key Title: Sch Int J Biochem
ISSN 2616-8650 (Print) |ISSN 2617-3476 (Online)
Scholars Middle East Publishers, Dubai, United Arab Emirates
Journal homepage: https://scholarsmepub.com/sijb/

Review Article

Carpenter Syndrome—A Genetic Disease

Dr. Anil Batta*

Professor & Head, Department of Medical Biochemistry Govt.Medical College, Amritsar, Punjab, India

DOI: 10.36348/sijb.2019.v02i12.005 | **Received:** 18.12.2019 | **Accepted:** 25.12.2019 | **Published:** 28.12.2019

***Corresponding author:** Dr. Anil Batta

Abstract

Carpenter syndrome is a condition characterized by the premature fusion of certain skull bones (craniosynostosis), abnormalities of the fingers and toes, and other developmental problems. Craniosynostosis prevents the skull from growing normally, frequently giving the head a pointed appearance (acrocephaly). Mutated genes cause Carpenter syndrome, and they are passed from parent to child during fetal development. These genes cause the coronal (from ear to ear) and sagittal (top of head, front to back) sutures to fuse together prematurely (craniosynostosis). Treatment of Carpenter syndrome depends on the symptoms the individual has and the severity of the condition. Surgery may be needed if a life-threatening heart defect is present. Surgery may also be used to correct craniosynostosis by separating the abnormally fused skull bones to allow for growth of the head. Craniosynostosis prevents the skull from growing normally, frequently giving the head a pointed appearance (acrocephaly). In severely affected individuals, the abnormal fusion of the skull bones results in a deformity called a cloverleaf skull. Craniosynostosis can cause differences between the two sides of the head and face (craniofacial asymmetry). Early fusion of the skull bones can affect the development of the brain and lead to increased pressure within the skull (intracranial pressure). Premature fusion of the skull bones can cause several characteristic facial features in people with Carpenter syndrome. Distinctive facial features may include a flat nasal bridge, outside corners of the eyes that point downward (down-slanting palpebral fissures), low-set and abnormally shaped ears, underdeveloped upper and lower jaws, and abnormal eye shape. Some affected individuals also have dental abnormalities including small primary (baby) teeth. Vision problems also frequently occur.Abnormalities of the fingers and toes include fusion of the skin between two or more fingers or toes (cutaneous syndactyly), unusually short fingers or toes (brachydactyly), or extra fingers or toes (polydactyly). In Carpenter syndrome, cutaneous syndactyly is most common between the third (middle) and fourth (ring) fingers, and polydactyly frequently occurs next to the big or second toe or the fifth (pinky) finger.

Keywords: Carpenter Syndrome, Genetic Disease, craniosynostosis.

Nomination of Scietific Medical Terms-1

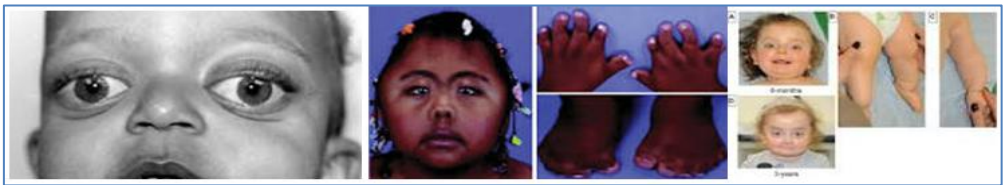
Medical Terms	Other Names	Learn More: HPO ID
100% of people have these symptoms		
Brachydactyly	Short fingers or toes	0001156
Finger syndactyly		0006101
Toe syndactyly	Fused toes [more]	0001770

INTRODUCTION

People with Carpenter syndrome often have intellectual disability, which can range from mild to profound. However, some individuals with this condition have normal intelligence. The cause of intellectual disability is unknown, as the severity of craniosynostosis does not appear to be related to the severity of intellectual disability. Other features of Carpenter syndrome include obesity that begins in childhood, a soft out-pouching around the belly-button (umbilical hernia), hearing loss, and heart defects. Additional skeletal abnormalities such as deformed hips, a rounded upper back that also curves to the side (kyphoscoliosis), and knees that are angled inward (genu valgum) frequently occur. Nearly all affected males have genital abnormalities, most frequently undescended testes (cryptorchidism).A few people with Carpenter syndrome have organs or tissues within their chest and abdomen that are in mirror-image reversed positions. This abnormal placement may affect

several internal organs (situs inversus); just the heart (dextrocardia), placing the heart on the right side of the body instead of on the left; or only the major (great) arteries of the heart, altering blood flow.The signs and symptoms of this disorder vary considerably, even within the same family. The life expectancy for individuals with Carpenter syndrome is shortened but extremely variable.The signs and symptoms of Carpenter syndrome are similar to another genetic condition called Greig cephalopolysyndactyly syndrome. The overlapping features, which include craniosynostosis, polydactyly, and heart abnormalities, can cause these two conditions to be misdiagnosed; genetic testing is often required for an accurate diagnosis. Carpenter syndrome is thought to be a rare condition; approximately 70 cases have been described in the scientific literature.

Clinical symptoms



Nomination of scietific medicalterms-2

LAST UPDATED: 11/1/2019

Medical Terms	**Other Names**	**Learn More: HPO ID**
80%-99% of people have these symptoms		
Craniosynostosis		0001363
Cryptorchidism	Undescended testes [more]	0000028
External genital hypoplasia	Underdevelopment of external reproductive organs	0003241
Intellectual disability	Mental deficiency [more]	0001249
Obesity	Having too much body fat	0001513
Oxycephaly		0000263
30%-79% of people have these symptoms		
Abnormal cornea morphology		0000481
Broad thumb	Broad thumbs [more]	0011304
Cloverleaf skull		0002676
Genu valgum	Knock knees	0002857
Postaxial hand polydactyly	Extra little finger [more]	0001162
Preaxial foot polydactyly		0001841
5%-29% of people have these symptoms		
Kyphoscoliosis		0002751
Patent ductus arteriosus		0001643
Polysplenia	Multiple small spleens	0001748
Talipes equinovarus	Club feet [more]	0001762
Umbilical hernia		0001537
Percent of people who have these symptoms is not available through HPO		
Abnormality of the pinna	Abnormally shaped ears [more]	0000377
Agenesis of permanent teeth	Failure of development of permanent teeth [more]	0006349
Aplasia/Hypoplasia of the corpus callosum		0007370
Aplasia/Hypoplasia of the middle phalanges of the hand	Absent/small middle finger bone of the hand [more]	0009843
Aplasia/Hypoplasia of the middle phalanges of the toes	Absent/small middle bones of toe [more]	0010194
Atrial septal defect	An opening in the wall separating the top two chambers of the heart [more]	0001631
Autosomal recessive inheritance		0000007
Brachycephaly	Short and broad skull	0000248
Camptodactyly	Permanent flexion of the finger or toe	0012385
Cerebral atrophy	Degeneration of cerebrum	0002059
Clinodactyly of the 5th finger	Permanent curving of the pinkie finger	0004209
Complete duplication of proximal phalanx of the thumb	Complete duplication of the innermost bone of the thumb	0009608
Conductive hearing impairment	Conductive deafness [more]	0000405
Coronal craniosynostosis		0004440
Coxa valga		0002673
Depressed nasal bridge	Depressed bridge of nose [more]	0005280

SYMPTOMS AND COMPLICATIONS

It is characterized by the number of features which include:

- Craniofacial malformations,,raniosynostoses,Kleeblattschädel (cloverleaf skull) ,Obesity ,Congenital cardiac anomalies
- Umbilical herniation ,
- Hypogenitalism ,Cryptorchidism ,Mental retardation ,Limb anomalies ,Genu valgum +/- lateral patella displacement ,Coxa valga
- Pes varus
- Syndactyly: typically soft tissue 3 ,Polydactyly: typically preaxial 3 ,Double ossification center of proximal phalanx of the thumb
- Broad first metatarsal

CAUSES

There are two types of carpenter syndrome.

Mutations in the rab23 or megf8 gene cause carpenter syndrome.

TYPE-1: The *RAB23* gene provides instructions for making a protein that is involved in a process called vesicle trafficking, which moves proteins and other molecules within cells in sac-like structures called vesicles. The Rab23 protein transports vesicles from the cell membrane to their proper location inside the cell. Vesicle trafficking is important for the transport of materials that are needed to trigger signaling during development. For example, the Rab23 protein regulates a developmental pathway called the hedgehog signaling pathway that is critical in cell growth (proliferation), cell specialization, and the normal shaping (patterning) of many parts of the body.

TYPE-2: The *MEGF8* gene provides instructions for making a protein whose function is unclear. Based on its structure, the Megf8 protein may be involved in cell processes such as sticking cells together (cell adhesion) and helping proteins interact with each other. Researchers also suspect that the Megf8 protein plays a role in normal body patterning. Mutations in the *RAB23* or *MEGF8* gene lead to the production of proteins with little or no function. It is unclear how disruptions in protein function lead to the features of Carpenter syndrome, but it is likely that interference with normal body patterning plays a role. For reasons that are unknown, people with *MEGF8* gene mutations are more likely to have dextrocardia and other organ positioning abnormalities and less severe craniosynostosis than individuals with *RAB23* gene mutations. This condition is inherited in an autosomal recessive pattern, which means both copies of the gene in each cell have mutations. The parents of an individual with an autosomal recessive condition each carry one copy of the mutated gene, but they typically do not show signs and symptoms of the condition.

RISK FACTORS

Carpenter syndrome is a genetic condition, caused by a mutation (change) on a specific gene. Research has identified the affected genes as the RAB23 gene or MEGF8 gene. Both these genes affect how certain cells in the body – including bone cells – grow, divide and die.

DIAGNOSIS

The diagnosis of Carpenter Syndrome is made based on the presence of the bicoronal and sagittal skull malformations, which results in a pointed, cone-shaped or short, broad head. The diagnosis is also made based on the presence of extra or fused digits. X rays and/ or CT scans of the skull may be performed in order to accurately diagnose the individual; however, other genetic disorders, which have available genetic tests, are also characterized by skull malformations. A positive result on these tests can rule out a Carpenter Syndrome diagnosis.

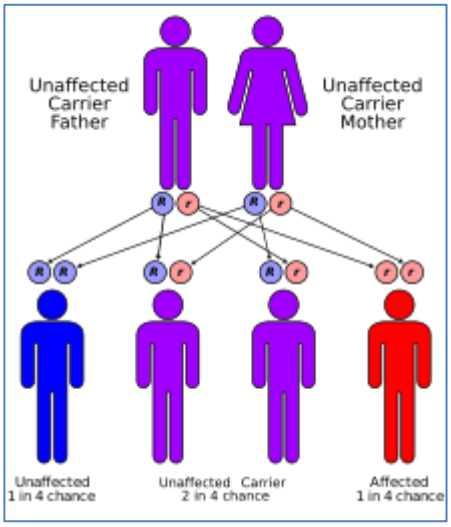
TYPES

The primary diagnostic factor is a malformation of the skull. The two most common types of craniosynostosis are sagittal and bicoronal. Sagittal craniosynostosis manifests itself by causing a long narrow skull, resembling a football. It is quantitatively determined by measuring the anterior to posterior (front to back) diameter of the skull. An increased A-P diameter indicates a malformed fusion of the sagittal suture. Individuals affected with sagittal craniosynostosis have narrow, prominent foreheads and the back of the head is much larger than normal. The "soft spot" is very small or missing altogether with this particular type of craniosynostosis.The second common type of skull malformation is bicoronal craniosynostosis is characterized by a wide, short skull. In this particular type of craniosynostosis the A-P diameter is smaller than in normal individuals. These individuals have malformed eye sockets and foreheads. The eye sockets are much smaller than normal and often cause visual impairment. Complications may include damage to the optic nerve, resulting in a decrease in visual clarity, bulging eyeballs as a result of shallow eye orbits which usually causes some sort of damage to the cornea (the outer layer of the eye). Bicoronal craniosynostosis may also result in widely spaced eyes and narrowing of the sinuses and tear ducts that may result in inflammation of the mucous membranes of the exposed portion of the eye. In addition to the previously named complications of bicoronal craniosynostosis, many babies will also be affected by hydrocephalus, more commonly known as water on the brain. Hydrocephalus results in increased pressure on the brain which can cause permanent brain damage if not treated promptly. An abnormally highly arched palate is also seen in affected individuals causing dental problems and the thrusting forward of the lower jaw. Individuals affected by Carpenter syndrome often experience cutaneous syndactyly (fusion of the digits) or polydactyly (presence of extra

digits) of the toes more often than fingers. Individuals also have short fingers. Approximately one third of individuals born with Carpenter Syndrome have a type of heart defect. Commonly seen heart defects may include: narrowing of the pulmonary artery, transposition of the major blood vessels, or the presence of an abnormally large vena cava, which delivers blood back to the heart from the head, neck, and upper limbs. The testes of males affected by Carpenter Syndrome may also fail to descend (Paul A. Johnson, 2002).

OCCURRENCE

There are approximately three hundred known cases of Carpenter Syndrome in the United States. Only 1 in 1 million live births will result in an infant affected by Carpenter Syndrome (RN, 2007).Carpenter Syndrome is an autosomal recessive disease which means both parents must have the faulty genes in order to pass the disease onto their children. Even if both parents possess the faulty gene there is still only a twenty five percent chance that they will produce a child affected by the syndrome. Their children who do not have the disease will still be carriers and possess the ability to pass the disease onto their offspring if their spouse is also a carrier of the particular gene[8].



TREATMENT

Specialists often initiate treatment to correct abnormal skull shape between the age of 6 and 12 months. Infants born with this genetic disorder may also need surgery to correct heart defects. The removal of extra digits and separation of fingers and toes can also be beneficial. Operations to correct the malformations of the skull should be performed within the first year of infancy in patients affected by Carpenter Syndrome. Performing surgery at a young age increases the likelihood of obtaining a greatly improved appearance of the head because modifying bone is much easier to do when the skull is still constantly growing and changing[8]. In surgery the doctor breaks the fused sutures to allow for brain growth. Doctors remove the cranial plates of the skull, reshape them and replace them back onto the skull in an attempt to reshape the head to appear more normal. Although the sutures are broken during surgery they will quickly refuse, and in some cases holes form in the plates allowing cerebral spinal fluid to escape into cyst like structures on the external surface of the head.If an individual with Carpenter Syndrome has a serious heart defect they will require surgery to correct the malformation of the heart. Other elective surgeries may also be performed. Some parents opt to have their child's webbed fingers or toes separated which improves their appearance but not necessarily the functionality of the digits. In order to address the occupational challenges of the disease, many children with Carpenter Syndrome go through speech and occupational therapy in order to achieve more independence in everyday tasks and activities (RN, 2007). In order to address the vision problems that are associated with bicoronal craniosynostosis, the individual must seek consultation from an ophthalmologist. If the palate is severely affected dental consultation may be necessary to correct the malformation. Obesity is often associated with Carpenter Syndrome, so a lifelong diet plan is often utilized to maintain a healthy weight. In addition surgery must be performed if the testes fail to descend (Paul A. Johnson, 2002). If the procedure is not performed the individual will become infertile.

REFERENCES

1. Carpenter, G. (1901). Two sisters showing malformations of the skull and other congenital abnormalities. *Report of the Society for the Study of Disease in Children (London)*, *1*, 110.
2. Carpenter, G. (1909). Case of acrocephaly with other congenital malformations. *Proceedings of the Royal Society of Medicine*, *2*(45–53), 199–201.
3. Cohen, D. M., Green, J. G., Miller, J. (1987). Acrocephalopolysyndactyly type II-Carpenter syndrome: Clinical spectrum and an attempt at unification with goodman and summitt syndromes. *American Journal of Medical Genetics*, *28*, 311–324.
4. Cohen, M. M., Jr. (2009). Perspectives on craniosynostosis: Sutural biology, some well-known syndromes, and some unusual syndromes. *The Journal of Craniofacial Surgery*, *20*(Suppl 1), 646–651.
5. Der Kaloustian, V. M., Sinno, A. A., & Nassar, S. I. (1972). Acrocephalopolysyndactyly, type II (Carpenter syndrome). *American Journal of Diseases of Children*, *124*, 716.
6. Eaton, A. P., Sommer, A., Kontras, S. B. (1974). Carpenter syndrome-acrocephalopolysyndactyly type II. *Birth Defects Original Article Series*, *10*, 249–260.
7. Gershoni-Baruch, R. (1990). Carpenter syndrome: Marked variability of expression to include the summitt and goodman syndromes. *American Journal of Medical Genetics*, *35*, 236–240.

8. Jenkins, D., Seelow, D., Jehee, F. S. (2007). *RAB23* mutations in carpenter syndrome imply an unexpected note for hedgehog signaling in cranial suture development and obesity. *American Journal of Human Genetics, 80*, 1162–1170.
9. Marsh, J. L., & Vannier, M. W. (1995). *Comprehensive care for craniofacial deformities* (p. 208). St. Louis: Mosby.
10. Palacios, E., & Schimke, R. N. (1969). Craniosynostosis-syndactylism. *American Journal of Roentgenology, 106*, 144–155.
11. Perlyin, C. A., & Marsh, J. L. (2008). Craniofacial dysmorphology of Carpenter syndrome: Lessons from three affected siblings. *Plastic and Reconstructive Surgery, 121*, 971–981.
12. Poole, M. D. (1993). Surgical caution with Carpenter's syndrome. *Journal of Cranio-Maxillo-Facial Surgery, 21*, 93.
13. Puri, V., Thirupuram, S., Jain, T. S. (1980). Acrocephalosyndactyly type II (Carpenter's syndrome). *Indian Pediatrics, 17*, 175.
14. Robinson, L. K., James, H. E., Mubarak, S. J. (1985). Carpenter syndrome: Natural history and clinical spectrum. *American Journal of Medical Genetics, 20*, 461–469.
15. Temtamy, S. A. (1966). Carpenter's syndrome: Acrocephalopolysyndactyly. An autosomal recessive syndrome. *Journal of Pediatrics, 69*, 111–120.