What causes BWCFF syndrome?
Changes (mutations) in the \textit{ACTB} and \textit{ACTG1} genes cause BWCFF syndrome. These genes code for proteins that have a crucial role in many functions of the cells of the body. Changes in \textit{ACTB} and \textit{ACTG1} that result in the production of altered proteins interfere with these functions. For example, these genes are required to make proteins which are needed for the normal development of brain cells (neurons). So far the majority of children and adults with BWCFF have been found to have mutations in \textit{ACTB}. However, there are no obvious differences between people with mutations in either gene. Changes to \textit{ACTB} that results in the loss of the \textit{ACTB} protein (as opposed to an altered \textit{ACTB} protein being made) causes a different outcome.

Why did this happen?
When children are conceived your genetic material is copied in the egg and sperm that make a new child. The biological copying method is not perfect and occasionally random rare changes occur in the genetic code of children that are not seen in the DNA of their parents. These types of changes happen naturally in all species, including humans, and are not due to your lifestyle or anything you did. BWCFF syndrome occurs when one of these random changes affects the \textit{ACTB} or \textit{ACTG1} genes. In most families, these changes occur out of the blue (\textit{de novo}). In a minority of families, one parent may have the same genetic change as their child, but this is very rare.

Can it happen again?
The risk of having another child affected by a rare gene disorder depends on the genetic code of the parents. For BWCFF syndrome, where parents do not carry the genetic change, the chance of having another child is almost always very low. If the genetic analysis of the parents of a child with BWCFF shows they carry the same variant, the chance of it happening again is much higher. Each family situation is different and a clinical geneticist can give you specific advice for your family.

Can it be cured?
BWCFF syndrome cannot be cured at the present time. However, treatment is available for many of the medical problems, like epilepsy, which can be associated with the condition.

Families say ...
“Having a diagnosis was daunting at first, however we realised that as there is such a wide spectrum of difficulties and such a small number of individuals diagnosed, it gives our son the chance to reach his full potential, whatever that might be.”

“We were told the future was uncertain in regards to intellectual disability but that stimulation was key to our son reaching his full potential. We have therefore provided him with as many opportunities to develop as possible, engaging fully with therapies as well as normal baby groups. He is continuing to surprise the professionals everyday with his progress.”

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This guide is not a substitute for personal medical advice. Families should consult a medically qualified clinician in all matters relating to genetic diagnosis, management and health. Information on genetic changes is a very fast-moving field and while the information in this guide is believed to be the best available at the time of publication, some facts may later change. Unique does its best to keep abreast of changing information and to review its published guides as needed. This guide was written by Professor Daniela Plz, Consultant Clinical Geneticist, Oxford University Hospitals, UK.

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What is BWCFF syndrome?
Baraitser-Winter Cerbebrofrontofacial syndrome (BWCFF) is a genetic condition, caused by changes in the \(ACTB\) and \(ACTG1\) genes that cause production of proteins with altered function. It is associated with distinct face and eye anomalies, intellectual disability and abnormal development of the grey matter of the brain.
The \(ACTB\) gene is found on chromosome 7, in the band numbered \(7p22.1\), between base pairs 5,527,147 and 5,530,600. The \(ACTG1\) gene is found on chromosome 17 in the band numbered \(q25.3\) between base pairs 81,509,970 and 81,512,865. Base pairs are the chemicals in DNA that form the ends of the ‘rungs’ of its ladder-like structure. There are millions of base pairs in every chromosome.

Other names
The term Baraitser-Winter Cerebrofrontofacial syndrome includes several conditions which were previously known by different names, before the gene changes underlying the disorders were discovered. The syndrome was first named Baraitser-Winter syndrome (BWS) after the doctors who described it in 1988. Another two conditions, Cerebrofrontofacial syndrome (types 1 and 3) and Fryns-Aftimos syndrome are now known to also be caused by changes in the same genes, \(ACTB\) and \(ATCG1\), as BWCFF, and they are considered part of the same syndrome.

Most people with BWCFF have:
- Intellectual disability or slow learning
- Developmental delay and learning difficulties (degree differs between individuals)
- Characteristic facial features, such as hypertelorism (widely spaced eyes)
- P toes (drooping of the eye lids)
- Pachygyria (thickened grey matter of the brain with reduced folds).

Medical concerns
- **Vision (ptosis and coloboma)**
  Drooping eyelids (ptosis) are very common. Significant ptosis may require surgery to lift the eye lid. Coloboma is a gap in the eye structure, for example the iris, or the retina (the back of the eye). Depending on the location of the coloboma in the eye, vision may be affected. A few children have small eyes (microphthalmia), a squint or are short-sighted.
- **Hearing**
  Variable sensorineural hearing loss (permanent nerve deafness) can develop, and can be progressive. Hearing aids may be required.
- **Epilepsy**
  If there are any anomalies of the brain structure, particularly pachygyria, it is likely a child with BWCFF will develop epilepsy. This is a seizure disorder, which usually needs to be treated with medication. Seizures commonly start before the age of five years. No cases of epilepsy have been seen when the brain scan looked normal.
- **Heart anomalies**
  Several different heart conditions are known to be associated with BWCFF. These are present from birth. They may require surgery and/or medication.
- **Cleft lip and palate**
  Some babies are born with a gap in the lip and/or roof of the mouth that requires surgical repair.
- **Hernia**
  Some babies are born with a hernia, or this appears later. Usually it is an umbilical hernia, which is seen as a swelling around the navel (tummy button). They mostly close on their own after a few years, but sometimes an operation is required.
- **Kidneys**
  Structural anomalies of the kidneys and urinary system have been found in a small number of children with BWCFF. This includes hydronephrosis – swelling of the kidneys – which has many causes; the treatment depends on the cause.

Is there a typical facial appearance?
Children and adults with BWCFF usually have a distinct appearance. Common features include a ridge down the middle of the forehead (metopic ridge) and a narrow forehead (trigonocephaly); arched eyebrows; ptosis; a short nose; a flat tip of the nose; a long philtrum (the area between the nose and upper lip) and a wide mouth.

Development
- **Learning**
  Developmental delay and intellectual disability is very variable, ranging from mild to severe. The degree of severity often corresponds to the amount of structural/grey matter change in the brain. Children and adults with a normal brain structure appear to have only mild to moderate problems.
- **Behaviour**
  Specific behavioural challenges have so far not been distinguished in children with BWCFF syndrome.
- **Speech**
  Speech development is commonly delayed, and in some children does not develop, or remains limited.
- **Growth**
  Some children may have a mild to moderate short stature and mild microcephaly (small head).
- **Physical development**
  Kyphosis (rounding of the back or spine) and scoliosis (curvature of the spine) can develop in some children. Some adults develop a ‘rounded back’ posture with forward facing shoulders and slightly bent elbows and knees. This is thought to be a muscular problem. Some adults may develop increasing problems with walking, possibly due to very gradually progressive muscle weakness.

Hearing problems can be progressive.

Management recommendations
At the time of diagnosis, screening for colobomas, hearing problems, and heart and kidney anomalies should be undertaken, if not done previously. A brain scan is important if seizures are present, and/or moderate to severe developmental delay/learning difficulties; with only mild delay, the need for a brain scan can be discussed.