PREFACE:

All parents hope that their families will be healthy and normal. They are naturally concerned and upset when they find out that their child has a medical condition but anxious to learn more about the condition. You may have been told recently that your child has Albright Hereditary Osteodystrophy (also known as Pseudohypoparathyroidism or Pseudopseudohypoparathyroidism) or you may have known this for sometime. In either case, you may still have unanswered questions about this condition. We have prepared this booklet to provide additional help and information. The purpose is to answer a number of the frequently asked questions and to act as a pointer to other sources of information.

We hope this information will give you a better understanding of your child’s condition and so help you in looking after your child.

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1) What is Albright Hereditary Osteodystrophy (AHO)?

Professor Fuller Albright, an American doctor, first described this condition in 1942. Hereditary’ implies either being born with a condition or the inheritance of a condition from parent to child through gene material. The word ‘oste’ means bone; ‘dystrophy’ means changes or abnormalities.

2) AHO may also be called Pseudohypoparathyroidism (PHP). What are PHP and PPHP?

The terms ‘Pseudo’ implies similar to but not the same as. ‘Hypo’ means too little. ‘Parathyroidism’ means related to parathyroid hormone (which controls calcium levels).

At first because calcium levels in the blood were sometimes found to be low, AHO was thought to be due to parathyroid hormone deficiency (hypoparathyroidism). Later it was found that the parathyroid hormone levels were normal or even high. We now know that these unusual findings of PHP are caused by a peculiarity in the way that parathyroid hormone works as explained later.

Some members of affected families may have similar physical features as PHP, but serum levels of calcium and phosphorous are normal. This variant of PHP is called Pseudopseudohypoparathyroidism (PPHP).

3) What are the parathyroid glands and parathyroid hormone (PTH)?

The parathyroids are glands in the neck lying close to or within another gland called the thyroid gland. The thyroid gland lies in the front of the neck just below the Adam’s apple. Parathyroid glands produce the hormone called parathyroid hormone (PTH).

4) What does the parathyroid hormone (PTH) do?

PTH is responsible for maintaining normal calcium levels in the blood. Calcium is needed to maintain normal structure of bone and teeth and also helps in contraction of muscles. These are just two of the many important functions of calcium in our body.

5) How does parathyroid hormone (PTH) act?

PTH is released from the parathyroid glands when blood calcium levels are low. PTH along with Vitamin D acts on bone and intestine to increase blood calcium levels.
Many processes in the body require the outside of a cell to speak to the inside. This is usually achieved by hormones (acting as the **key**) working through receptors (**locks**) that sit on the cell wall or outer cell membrane. Once the key is in position, the lock can be opened, but the message requires another component which acts as **messenger** to inform the inside of the cell that the **key** has opened the **lock**.

Parathyroid hormone (**key**) acts on the cell receptor (**lock**) and the **messenger** to inform the inside of the cell is called G protein. G proteins are family of proteins with three subtypes **Gsα**, **Gsβ** and **Gsγ**. The s stands for stimulatory.

In the context of AHO, the hormone (**key**) is PTH and the **lock** is PTH receptor on cell wall. The defect in AHO is a deficiency in the activity of **Gsα** messenger. As a result, parathyroid hormone fails to signal efficiently.

**6) What happens when Gsα is not working in PHP?**

Because **Gsα** is not working properly, PTH is less active and so cannot control calcium levels correctly. In AHO, this may result in low blood calcium levels.

**Gsα** is also important in controlling the way in which other hormones work, including thyroid stimulating hormone (TSH) and sex stimulating hormones (LH, FSH). This may result in some features of an underactive thyroid hormone and/or sex hormones around the time of puberty.

**7) Why does your child have PHP?**

Our blueprint for life, known as inherited material or DNA, is packaged into chromosomes. We have 23 pairs of chromosomes, one set inherited from each parent. Each member of the pair consists of blocks of DNA forming ‘genes’. Genes provide instructions to the body with details of how and when activities should take place.

G proteins are each made by a separate gene. **Gsα** is made by the GNAS gene on chromosome 20.

The genetic problem in AHO/PHP/PPHP is a copying error (often called mutation) in the GNAS gene. This leads to alterations in the normal activity of the Gsα protein and impaired ability of the body to respond to the normal hormone/receptor (lock and key) signals.

A child develops PHP or PPHP because the gene mutation is either passed on from one of the parents or a new mutation has been formed when the baby was conceived.

There is some evidence to suggest that **Gsα** mutation is paternally transmitted in PPHP and maternally transmitted in PHP.

**8) What is the risk of your next child having PHP?**

This will depend upon a number of factors. The most important being dependant upon whether genetic alterations that cause altered G-protein activity in your child are also present in yourselves and this can be investigated these days with a
If you as parents do not have a genetic abnormality, your child must have had a new mutation and your next child will have the same risk as general population and not higher.

If, on the other hand, if either of you have the same genetic abnormalities, there is a 50% chance of passing on the condition to another boy or girl child.

9) Is your grandchild at risk for PHP?

In view of the clinical condition, your child may have problems with fertility in the first instance. As your son or daughter has the genetic mutation, your grandchild has a 50% chance of inheriting the condition.

10) What are the features of PHP?

PHP affects people in many different ways. Some children and adults are affected very minimally, some moderately and some more severely. Some of the common described physical features are given below. One need not necessarily have all the features to make a diagnosis.

- Usually heavy, stocky build and most often short. Occasionally normal or tall stature but overweight.
- Round face with low flattened nasal bridge
- Bony changes in hands and feet-
  - Short bones in fingers and toes giving short stubby hands and feet (Fig 1)
  - Short bones in palm of hand (the metacarpals) usually corresponding to 4th and 5th fingers. (Fig 2)
  - On making a fist this gives a dimpling instead of a prominence on back of hand at the 4th and 5th knuckles (Fig 3). Index finger is rarely involved making index finger sometimes longer than middle finger.
  - Short bones in the feet (the metatarsals) usually corresponding to 3rd and 4th toes (Fig 4)

_Figure 1:_ Hand of a child with AHO showing short stubby fingers
**Figure 2:** Hands of a child with AHO showing marked shortening of the fourth metacarpal in the right hand and third metacarpal in the left hand

![Hands of a child with AHO](image1)

**Figure 3:** Hands of an adult with AHO showing knuckle dimples in the clenched fists

![Hands of an adult with AHO](image2)

**Figure 4:** Feet of a child with AHO showing extreme shortening of the metatarsals corresponding to the 3rd and 4th toes.

![Feet of a child with AHO](image3)
• Learning and school difficulties in varying severity.
• Calcification (hard swellings) under the skin.
• Cataract
• Bony swellings, bowing of bones
• In girls- delayed puberty, absent, delayed onset or scanty periods, sometimes reduced fertility
• In boys- delayed puberty, sometimes reduced fertility.

11) **What tests are available to diagnose PHP?**

In addition to the above physical features blood tests, urine tests, X-rays and genetic tests can help in the diagnosis of PHP.

• Blood tests may reveal low calcium, elevated parathyroid hormone levels and elevated thyroid stimulating hormone, FSH and LH levels. Sometimes low thyroxine and sex hormone levels may be identified.

• Specialised urine tests occasionally help in showing deficient PTH action on cells.

• X-ray of the hand and feet may demonstrate short bones in the palm of the hand (metacarpal) and feet (metatarsal). *(Figure 4)*

• Genetic tests using blood samples to examine DNA demonstrates genetic mutation of the GNAS gene on chromosome 20.

*Figure 5: X-ray of the hand in a child with AHO demonstrating extreme shortening of the 4th palm bone (metacarpal).*
12) Can the doctors be sure that your child has PHP?

Usually yes - there are genetic tests available, which are only performed in a few specialised laboratories in the UK and the results may take weeks or months to be available. These DNA tests are of course helpful if positive, but negative results (no mutation found) does not totally exclude the diagnosis.

13) What are the treatment options available?

- If calcium levels drop to low levels, vitamin D can be given as medicine or tablets to improve this.
- The thyroid hormones will need monitoring and in some cases thyroxine tablets might be helpful.
- Most importantly, the school development and progress needs monitoring and special educational help is sometimes required.

14) Does the treatment need to be lifelong?

Calcium/Vitamin D treatment is lifelong. Other hormonal treatment may be required such as lifelong thyroid treatment or puberty hormones during adolescence.

15) Are there family support groups?

Yes. They are CLIMB (Children Living with Inherited MetaBolic Diseases [http://www.climb.org.uk/]) in UK and HYPOPARATHYROIDISM ([http://www.hypoparathyroidism.org](http://www.hypoparathyroidism.org)) in USA.

It may be helpful to speak to or meet another family who has a similar affected child with PHP. The best way to organise this is to speak to your child’s Geneticist, Paediatrician or other Specialists.

CONCLUSION:

We hope this booklet has helped you understand your child’s condition and answered some of your questions. We have tried to cover most of the important points. If you have any further questions you can always contact your child’s Specialist or Consultant for further advice.

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