Bone growth and achondroplasia

This document is intended to explore the impact of restricted bone growth in people with achondroplasia, and to showcase what benefits healthy bone growth could bring to people with the condition.

THE ROLE OF GENETICS

Like everything in the body, the shape, size and construction of the skeleton is largely determined by the plan laid down by the genes.

So, if there are changes in the genes that regulate bone growth then there is a high chance there will be changes in the skeleton too.

There are hundreds of skeletal disorders that have been traced back to genetic factors. These range from brittle bone disease to bowed or shortened limbs.

While still rare, achondroplasia is the most common of these genetic skeletal disorders, occurring in around one in 25,000 live births.[1]

While the disease affects nearly all the bones in the body–namely the endochondral bones–it is most obvious in the limbs.

On average people with achondroplasia will end up around 25% shorter than people of average height.[2,3]

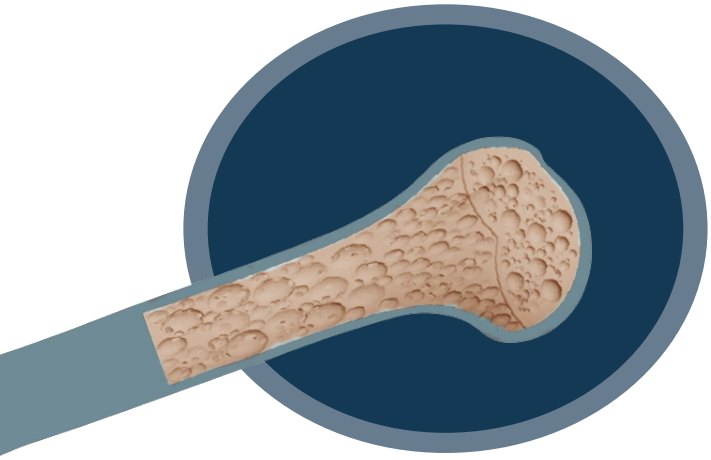
HOW BONES GROW

There are two different ways that bones form, but the type of growth that is affected in achondroplasia is called endochondral bone growth.

This is the main sort of growth responsible for lengthening bones and it only occurs in specific places all around the body, called the cartilage growth plates.

If we look within these growth plates, we see that a special sort of cartilage is growing and being replaced by hard bone.

If something slows that process down, this can result in abnormalites in the length and shape of the bones. Because these plates are the source of bone growth almost everywhere in the body, changes that slow down this growth result in shorter bones.



THE CARTILAGE GROWTH PLATES

Cartilage is comprised of thousands of individual cartilage cells carefully stacked in layers. By looking closely at growth plates we can get a better understanding for exactly how this process happens.

At the top of the plate the cartilage cells divide, below that they grow larger, then mature and are finally replaced by bone cells moving in from below.

As each new layer of bone forms at the bottom, more cells are dividing and growing at the top, adding layer upon layer of hard bone at the edge of the growth plate.

To ensure this process happens in a perfectly organised way, there are a large number of signals that regulate how fast and where this growth happens.

The signals themselves are often small molecules circulating around the body and the cells in these layers need a way to read and respond to them.

On each cell this process usually starts with what's known as a receptor, a special molecule that pokes through the cell surface and recognises these signals.

The combination of hundreds of different signals being recognised across millions of cells is what controls how, when and where bones grow.

ACHONDROPLASIA, BONE GROWTH, AND THE FGFR3 RECEPTOR

FGFR3 (fibroblast growth factor receptor 3): FGFR3 has major roles in endochondral bone formation, active mutations in FGFR3 are the cause of achondroplasia, hypochondroplasia and thanatophoric dysplasia.[4]

In people with achondroplasia the gene for one of the key receptors in regulating cartilage cell growth is altered – the Fibroblast growth factor 3 receptor or FGFR3.

To understand exactly how changes in the *FGFR3* gene causes bone growth to slow down and see how it interacts with some of the other growth controls, we have to look inside the cell.

The FGFR3 molecule itself lives on the surface of the cartilage cells. Normally the receptor is only activated when it joins with a signalling molecule from outside called a fibroblast growth factor or FGF. These FGF molecules fit into specific receptors like a lock and key.

When one of these FGF molecules slots into the receptor on the outside, it causes a change on the inside, setting off a chain of signals that tells the cell to stop growing. It's the FGF signal sticking on the outside that sets off the STOP lights for growth on the inside of the cell.

This is a normal process throughout the body, where signalling via these FGF molecules help to regulate the formation of the skeleton.

In someone with achondroplasia, a change in the FGFR3 receptor means that it's active even without an FGF molecule being in position on the outside. On the inside of the cell, this means the growth traffic light is stuck in the STOP position regardless of what signals FGFR3 sees outside.

And because FGFR3 is regulating bone growth in these cartilage cells everywhere, it doesn't just mean that bones in the legs are shorter. It means that all bones that grow by this type of ossification are shorter, and some can end up misshapen.

In fact, FGFR3 is present everywhere in the body, and while what it does outside of these growth plates isn't fully understood, it is very likely that this overactivity is responsible for some of the other associated conditions seen in people with achondroplasia.

Discover more about what to expect living with achondroplasia at achondroplasia.com

This document was created for educational purposes only. The content is not prescriptive and should not replace consultation with a trained healthcare provider. Information regarding achondroplasia is provided as a general overview and is not intended to be comprehensive.

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ACHONDROPLASIA, BONE GROWTH, AND THE NPRB RECEPTOR

NPRB receptors (natriuretic peptide receptor B): Part of a family of peptides that play an essential role on the regulation of blood pressure, the intravascular volume, and electrolyte homeostasis.[5]

C-type natriuretic peptide (CNP): CNP is produced by the endothelium and the heart and appears to play a prominent role in vascular and cardiac function, both physiologically and pathologically.[6]

Alongside the FGFR3 system, there are many other components that also control the bone growth in the body.

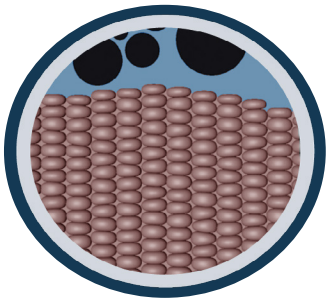
One of the most important is a receptor called NPRB which responds to a different signal from outside the cell, a molecule called CNP.

This NPRB actually acts as GO switch for bone growth, by turning off the STOP signal coming from FGFR3. So when CNP is present on the outside of the cell, this additional signal silences the STOP signal from FGFR3, allowing the cartilage cells to grow again and bones to get longer.[7]

Again this is a normal process and this balance between the FGFR3 and NPRB pathways is one of the things that helps to fine tune bone growth.

In people with achondroplasia the signal from the FGFR3 receptors is generally stronger, overriding the GO signal from CNP.

But what is particularly interesting about this CNP system is that it might give scientists a way to restore the balance between the two pathways in people with achondroplasia and release that bone growth STOP signal.



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