Clinical features of ACH include:
- Relatively short chest with overly compliant ribs.
- Relatively short waist with a barrel-shaped abdomen.
- Fixed flexion of the elbows and knees.
- Midfacial retrusion due to the under-development of cartilaginous bones.
- Increased incidence of scoliosis.
- Restricted pulmonary function.
- Congenital heart defects.
- Genetic variants in ACH include substitutions in the transmembrane domain of FGFR3. Eighty percent of affected individuals represent a de novo event.

Growth velocity (4–5 cm/year) for children with ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor 3 (FGFR3) gene, which 95% of cases result from single amino acid substitutions in the transmembrane domain of FGFR3. Eighty percent of affected individuals represent a de novo event.

Linear growth is slower in ACH children compared with average stature children (Table 1).

Study body height at birth is approximately between –1.4 and –2 SDS for non-ACH reference tables.

During infancy and childhood, height falls progressively and delay even further from average stature data to a low but steady growth spurt. Final height is approximately 131 cm for males and 124 cm for females. The height of children with ACH is approximately 32% less than that of normal controls.

Rate of growth in ACH children drops from 10 to 15 cm/year at birth to 10 cm/year at age 2 years. Lower limb growth falls in a range of 8–10 cm/year for the first 2 years of life, which can lead to long-term complications and also improve long bone growth that could improve the activity of daily living.

FGFR3 inhibitors are orally bioavailable and selective FGFR2/3 selective tyrosine kinase inhibitor in development for FGFR-related diseases. Infigratinib inhibits FGFR downstream signaling, offering a direct therapeutic strategy to counteract the hyperactivity of FGFR3 in ACH.

Preliminary data in a Fgfr3<sup>Y367C/+</sup> mouse model of ACH<sup>2</sup> showed that:
- Low doses of infigratinib (0.5, 2.5 and 10 mg/kg reduced FGFR phosphorylation, restored the activity of FGFR3 downstream signaling pathways to levels observed in wild type mice.
- Mice also exhibited substantially improved skeletal parameters in the upper and lower limbs, and improvement in the foramen magnum.
- No toxic effects were observed at these low but efficacious doses.

These preclinical data indicate that low doses of infigratinib administrated to children with ACH have the potential to substantially ameliorate skeletal abnormalities that can lead to long-term complications and also improve long bone growth that could improve the activity of daily living.

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Other objectives

Assess ACH-related medical events (e.g., obstructive sleep apnea, middle ear infections, lumbar spinal stenosis, cranial base anomalies)...