# Medical history of children enrolled in PROPEL: A prospective clinical assessment study in children with achondroplasia

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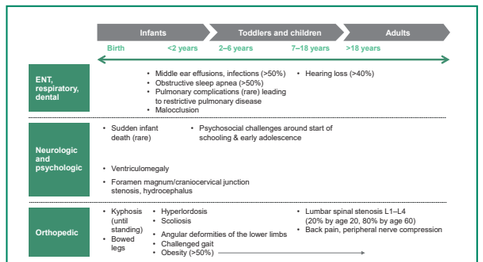
## Background

- Achondroplasia (ACH) is the most common short-limbed skeletal dysplasia, affecting between 1 in 15,000 to 1 in 30,000 live births in the US, with an estimated global prevalence of 250,000.[1,2]
- Characteristic clinical features of ACH are as follows: disproportionately short stature; smaller than average chest; macrocephaly with frontal bossing; midface hypoplasia; curvature of the spine; hypermobile joints; leg bowing; and shortening of the fingers and toes.[3]
- Individuals with ACH experience a variety of physical, functional, and psychosocial complications and challenges throughout their lifetime (see Figure 1).
- ACH is characterized by defective endochondral ossification resulting from gain of function pathogenic variants in the fibroblast growth factor receptor-3 gene (*FGFR3*),[5,6] which is a negative regulator of endochondral bone formation.
- FGFR3 is particularly prevalent on the surface of chondrocytes that give rise to cartilaginous bone.[7]

**Figure 1. Medical complications associated with ACH[4]**




## PROPEL study

- PROPEL (NCT04035811) is an ongoing, prospective, non-interventional clinical assessment study designed to collect baseline growth data and to characterize the natural history of ACH in children being considered for future enrollment in interventional studies with infigratinib sponsored by QED Therapeutics (Table 1).
- Children with ACH between the ages of 2.5 and 10 years are eligible for enrollment in PROPEL and are evaluated at screening/baseline, month 3, month 6, and every 6 months thereafter.

## Objectives

- Here we describe the medical complications reported as medical history in the PROPEL study.
- Medical history collected at screening/baseline is summarized using system organ class (SOC) and preferred/lower level terms:
  - Individual subjects are counted once within an SOC, even if they presented more than one event within that SOC.
  - Individual subjects are counted once if they presented more than one event with the same preferred term, but are counted more than once if they presented events in more than one preferred term.

**Table 1. PROPEL study key inclusion/exclusion criteria**

| Key inclusion criteria |
|---|
| • Signed informed consent by study participant or parent(s) or legally authorized representative (LAR) and signed informed assent by the study participant (when applicable) |
| • Age 2.5 to 10 years (inclusive) at study entry |
| • Diagnosis of ACH (as confirmed by the Principal Investigator, Co-principal Investigator, or other qualified clinical geneticist) |
| • Ambulatory and able to stand without assistance |
| **Key exclusion criteria** |
| • Hypochondroplasia or short stature condition other than ACH |
| • Females who have had their menarche |
| • Annualized height velocity ≤1.5 cm/year over a period ≥6 months prior to screening |
| • Concurrent disease or condition that, in the view of the investigator and/or study sponsor, may impact growth or where the treatment is known to impact growth |
| • Significant abnormality in screening laboratory results |
| • Treatment with growth hormone, insulin-like growth factor-1, or anabolic steroids in the previous 6 months or long-term treatment (>3 months) at any time |
| • Treatment with a C-type natriuretic peptide analog or treatment targeting FGFR inhibition at any time |
| • Regular long-term treatment (>1 month) with oral corticosteroids (low-dose ongoing inhaled steroid for asthma is acceptable) |
| • Previous limb-lengthening surgery |

## Results

- A total of 86 children with ACH enrolled as of January 2022 at 19 sites in Europe, Australia and North America have been included.
- Of the 86 subjects enrolled, 73 (84.9%) had molecular confirmation of their diagnosis.
- Overall, 79.1% of cases (n=68) were sporadic, whereas 11.6% (n=10) had another family member with diagnosis of ACH. Baseline characteristics are summarized in Table 2.
- The most common conditions reported in the medical histories of subjects are summarized in Table 3.

**Table 2. Baseline patient characteristics**

| Characteristic | Total (n=86) |
|---|---|
| **Age, years** | |
| Mean (SD) | 6.1 (2.5) |
| Median (range) | 6.2 (2.5–10.8) |
| **Age group**, n (%) | |
| <3 years | 12 (14.0) |
| 3 to <5 years | 22 (25.6) |
| 5 to <8 years | 26 (30.2) |
| ≥8 years | 26 (30.2) |
| **Sex**, n (%) | |
| Male | 34 (39.5) |
| Female | 52 (60.5) |
| **Race**, n (%) | |
| White | 54 (62.8) |
| Asian | 8 (9.3) |
| Black or African American | 4 (4.7) |
| Other | 7 (8.1) |
| Not reported | 13 (15.1) |

## Conditions/events reported as medical history

- A total of 58 children had undergone surgical or medical procedures, with a mean of 2.9 procedures per individual (1–11 interventions per child; Table 4).
- The most common types of surgery/procedure were:
  - Adenoidectomy, adenotonsillectomy, and tonsillectomy (34 children with 53 procedures; 1–4 surgeries per child).
  - Ear-related procedures (32 children with 58 procedures; 1–5 procedures per child).
  - Twenty-one children (24.4%) had undergone at least one surgery (1–5 surgeries per child) for spinal or cranial decompression (Table 4).
- A history of infections and infestations was reported in 46 children (53.5%; Table 5A):
  - The most common infections were ear infections (n=43; 50%).
- A history of respiratory disorders was reported in 40 children (46.5%):
  - The most common respiratory, thoracic, and mediastinal disorder was sleep apnea (n=35; 40.7%).
- A total of 33 children (38.4%) had a history of musculoskeletal disorders (Table 5B), the most common of which was kyphosis (n=18; 20.9%).
- Ear and labyrinth disorders were found in 15 children (17.4%), all of whom presented hearing impairment (Table 5C).
- Disorders in the central nervous system were reported in 16 children (Table 5D). Two children had hydrocephalus and four had ventriculomegaly without intracranial hypertension. Two children had spinal cord compression.
- Congenital cardiovascular abnormalities were found in four children, two of whom presented with patent ductus arteriosus and two with patent foramen ovale.

**Table 3. Most common conditions/complications from medical histories (by SOC)**

| Characteristic | Number of subjects (%) |
|---|---|
| Surgical and medical procedures | 58 (67.4) |
| Infections and infestations | 46 (53.5) |
| Respiratory, thoracic, and mediastinal disorders | 40 (46.5) |
| Musculoskeletal and connective tissue disorders | 33 (38.4) |
| Congenital, familial, and genetic disorders | 31 (36.0) |
| Nervous system disorders | 16 (18.6) |
| Ear and labyrinth disorder | 15 (17.4) |

**Table 4. Surgical and medical procedures occurring in ≥1 subject**

| Characteristic | Number of subjects (%)* |
|---|---|
| **Adenoidectomy/adenotonsillectomy/tonsillectomy** | 34 (39.5) |
| **Spinal and cranial surgeries** | 21 (24.4) |
| Decompressive craniectomy | 14 (16.3) |
| Spinal decompression | 5 (5.8) |
| Spinal laminectomy | 3 (3.5) |
| Foraminotomy | 1 (1.2) |
| Spinal fusion surgery | 1 (1.2) |
| Spinal operation | 1 (1.2) |
| **Ear procedures and operations** | 32 (37.2) |
| Ear tube insertion | 32 (37.2) |
| Myringotomy | 3 (3.5) |
| Middle ear operation | 1 (1.2) |
| Ear tube removal | 1 (1.2) |
| **Orthopedic procedures** | 6 (7.0) |
| Device therapy | 3 (3.5) |
| Meniscus operation | 1 (1.2) |
| Orthopedic procedure | 1 (1.2) |
| Osteotomy | 1 (1.2) |
| Rhizolysis | 1 (1.2) |
| **Ventriculo-peritoneal shunt** | 2 (2.3) |
| **Mechanical ventilation** | 2 (2.3) |
| **Palatal implant** | 2 (2.3) |
| **Turbinectomy** | 2 (2.3) |

*Subjects could be counted more than once if they underwent ≥1 procedure

**Table 5. Conditions/events reported as medical history**

| A) Ear infections, n (%) | |
|---|---|
| Otitis media serous | 12 (14.0) |
| Otitis | 5 (5.8) |
| Glue ear | 4 (4.7) |
| Otitis media chronic | 4 (4.7) |
| Otitis media recurrent | 4 (4.7) |
| Bilateral otitis media | 3 (3.5) |
| Ear infection | 3 (3.5) |
| Otitis media | 3 (3.5) |
| Otitis media acute | 3 (3.5) |
| Otitis media with effusion | 2 (2.3) |
| Right otitis externa | 1 (1.2) |
| Acute suppurative otitis media | 1 (1.2) |
| Chronic mucoid otitis media | 1 (1.2) |
| Chronic serous otitis media | 1 (1.2) |

| B) Musculoskeletal disorders, n (%) | |
|---|---|
| Kyphosis | 18 (20.9) |
| Genu varum | 6 (7.0) |
| Lumbar hyperlordosis | 5 (5.8) |
| Bow legs | 3 (3.5) |
| Spinal stenosis | 3 (3.5) |
| Lumbar spinal stenosis | 2 (2.3) |
| Tibia vara | 2 (2.3) |
| Knee pain | 2 (2.3) |
| Cervical spinal stenosis | 2 (2.3) |
| Contracture | 1 (1.2) |
| Elbow deformity | 1 (1.2) |
| Enlarged fontanelle | 1 (1.2) |
| Genu valgum | 1 (1.2) |
| Hyperlordosis | 1 (1.2) |
| Joint dysfunction | 1 (1.2) |
| Joint instability | 1 (1.2) |
| Joint laxity | 1 (1.2) |
| Leg pain | 1 (1.2) |
| Low back pain | 1 (1.2) |
| Lumbar scoliosis | 1 (1.2) |
| Muscle weakness | 1 (1.2) |
| Nose deformity | 1 (1.2) |
| Spinal canal stenosis | 1 (1.2) |
| Thoracic spinal stenosis | 1 (1.2) |

| C) Ear and labyrinth disorders, n (%) | |
|---|---|
| Hearing loss | 6 (7.0) |
| Conductive hearing loss | 5 (5.8) |
| Hypoacusis | 1 (1.2) |
| Middle ear effusion | 1 (1.2) |
| Hypoacusis | 1 (1.2) |
| Middle ear effusion | 1 (1.2) |
| Dysfunction of Eustachian tube | 1 (1.2) |

| D) CNS disorders, n (%) | |
|---|---|
| Cerebral ventricle dilatation | 4 (4.7) |
| Hydrocephalus | 2 (2.3) |
| Gross motor delay | 2 (2.3) |
| Speech disorder developmental | 2 (2.3) |
| Spinal cord compression | 2 (2.3) |
| Balance disorder | 1 (1.2) |
| Cervical cord compression | 1 (1.2) |
| Dysarthria | 1 (1.2) |
| Febrile convulsion | 1 (1.2) |
| Hypotonia | 1 (1.2) |
| Paraesthesia | 1 (1.2) |
| Radiculopathy | 1 (1.2) |

## Current status

- The PROPEL study is ongoing and enrolling participants as of March 2022.
- The PROPEL study is expected to characterize the natural history of ACH and lead to sufficient enrollment in Phase 2 (PROPEL 2) and/or Phase 3 interventional trials of infigratinib in children with ACH.
- Please refer to ENDO 2022 posters #PSAT105 and #PSAT106 for further details on the PROPEL and PROPEL 2 studies.

## Conclusions

- The PROPEL study has a planned total enrollment of 200 children and seeks to contribute to the deeper understanding of the natural history of ACH.
- Data described in this poster highlight the significant complications and high number of interventions that children with ACH undergo throughout infancy and childhood. This stresses the importance of expert management of this complex condition.

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