CLINICAL AND MOLECULAR CHARACTERISTICS OF THAI PATIENTS WITH ACHONDROPLASIA

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Abstract. Achondroplasia is an autosomal dominant disorder characterized by disproportionately short stature, frontal bossing, rhizomelia, and trident hands. Most patients appear sporadically resulting from a *de novo* mutation associated with advanced paternal age. A glycine to arginine mutation at codon 380 (G380R) of the fibroblast growth factor receptor 3 gene (*FGFR3*) was found to be the most common cause of achondroplasia in various populations. We identified and clinically characterized 3 Thai patients with achondroplasia. In all of them, we also successfully identified the G380R mutation supporting the observation that this is the most common mutation in achondroplasia across different ethnic groups including Thai.

INTRODUCTION

Patients with short stature display an extremely long list of differential diagnoses. Achondroplasia is one of them. Clinical manifestations and molecular defects of patients with achondroplasia have been described in various ethnic groups. Here we report three Thai patients with achondroplasia whose molecular abnormalities were successfully identified, providing a specific method for molecular diagnosis of patients and for prenatal diagnosis in families at risk.

MATERIALS AND METHODS

Case reports: Three patients coming to the Genetics Clinic at King Chulalongkorn Memorial Hospital were diagnosed with achondroplasia. Patient 1 was born at term to a 37 year-old G3P2 Thai mother and a 43 year-old unrelated Thai father. Neither the parents nor the two elder sisters of patient 1 were affected. Pregnancy and delivery were uncomplicated. His birth weight was 3,590 g (+1 SD), length 47 cm (-2 SD), and head circumference 38.5 cm (+3 SD). In addition to short stature, physical examination revealed increased upper to lower trunk ratio (2.2:1) (normal 1.7:1), frontal bossing, rhizomelia, trident hands, left hydrocele, and lordosis (Fig 1A). Achondroplasia was diagnosed soon after birth. At 8 months of age, his head circumference was 49 cm (+4 SD). Due to the rapid increase of his head size, a CT scan of the brain was performed revealing hydrocephalus. A ventriculoperitoneal shunt was placed. Developmental assessment by the Gesell Developmental schedule showed a developmental quotient of 73 at the chronological age of 1 year and 8 months. The left hydrocele was surgically repaired at 1 year and 9 months. Polysomnography performed at 2 years and 6 months was normal. At 4 years and 6 months, growth hormone provocative tests by insulin and clonidine showed maximum growth hormone levels of 1.9 and 6.4 ng/ml, respectively, indicating growth hormone deficiency. The IQ test by WISC III revealed verbal IQ, performance IQ and full IQ of 84, 103, 93 respectively at 8 years of age. Radiography of the lumbar spine showed caudal narrowing

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of the spinal canal with short pedicles (Fig 2A). At his last follow-up at 8 years and 1 month, his height was 100.2 cm (-4 SD), weight 19.6 kg (-1 SD), and head circumference 56 cm (+2.5 SD).

Patient 2 was born at term to a 27-year-old G1P0 Thai mother and a 27-year-old unrelated Thai father. The parents were unaffected. Pregnancy, labor and delivery were unremarkable. His birth weight was 3,500 g and his length 47 cm. Physical examination at 4 months of age revealed macrocephaly with a head circumference of 43 cm (+2 SD), increased upper to lower trunk ratio (40:19.5 = 2.05:1), large anterior fontanel, frontal bossing, depressed nasal bridge, trident hands, and rhizomelia (Fig 1B). Radiography revealed decreased interpeduncular distances of his lumbar vertebrae. A diagnosis of achondroplasia was made. CT scan of the brain at 10 months revealed hydrocephalus requiring ventriculoperitoneal shunt. Developmental assessment by the Gesell Developmental schedule showed a mental age of 39 weeks at the chronological age of 79 weeks. The IQ test according to Stanford Binet revealed an IQ of 82 at 5 years of age. Echocardiogram performed at 2 years and an eye examination at 3 years were unremarkable. Noisy breathing was developed at the age of 5 years. Obstructive sleep apnea was found by polysomnography and his hypertrophied tonsils and adenoids were removed at the age of 5 years and 10 months. The following tests were normal: blood cell counts, blood sugar, BUN, Cr, electrolytes, prothrombin time, and partial thromboplastin time. At his last visit at the age of 6 years and 10 months his height was 99.3 cm (-2.5 SD), weight 31.4 kg (+2.5 SD), and head circumference 54 cm (+1.5 SD).

Patient 3 was born at term after uncom-

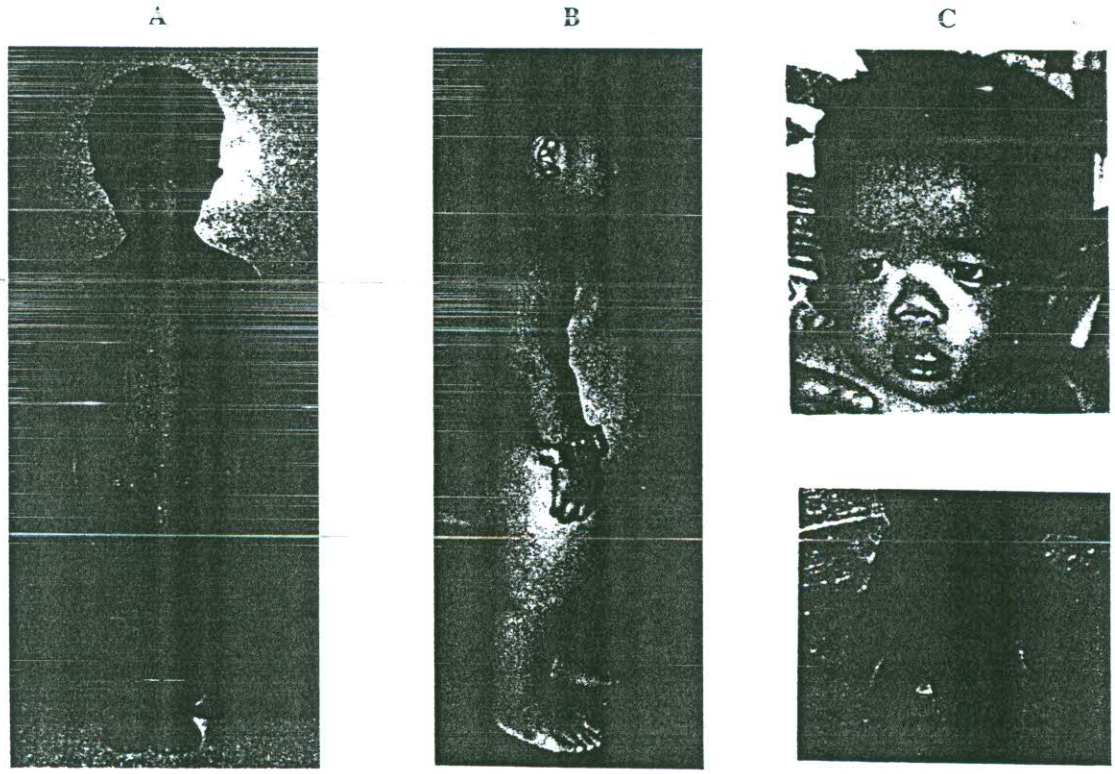

Fig 1–Clinical features. A. Patient 1 at 7 years of age showing disproportionate short stature with rhizomelia. B. Patient 2 at 6 years old revealing frontal bossing, overweight, and lumbar lordosis. C. Patient 3 at 11 months old showing maxillary hypoplasia (upper panel) and a trident hand (lower panel).