CLINICAL QUIZ (p188) ANSWER

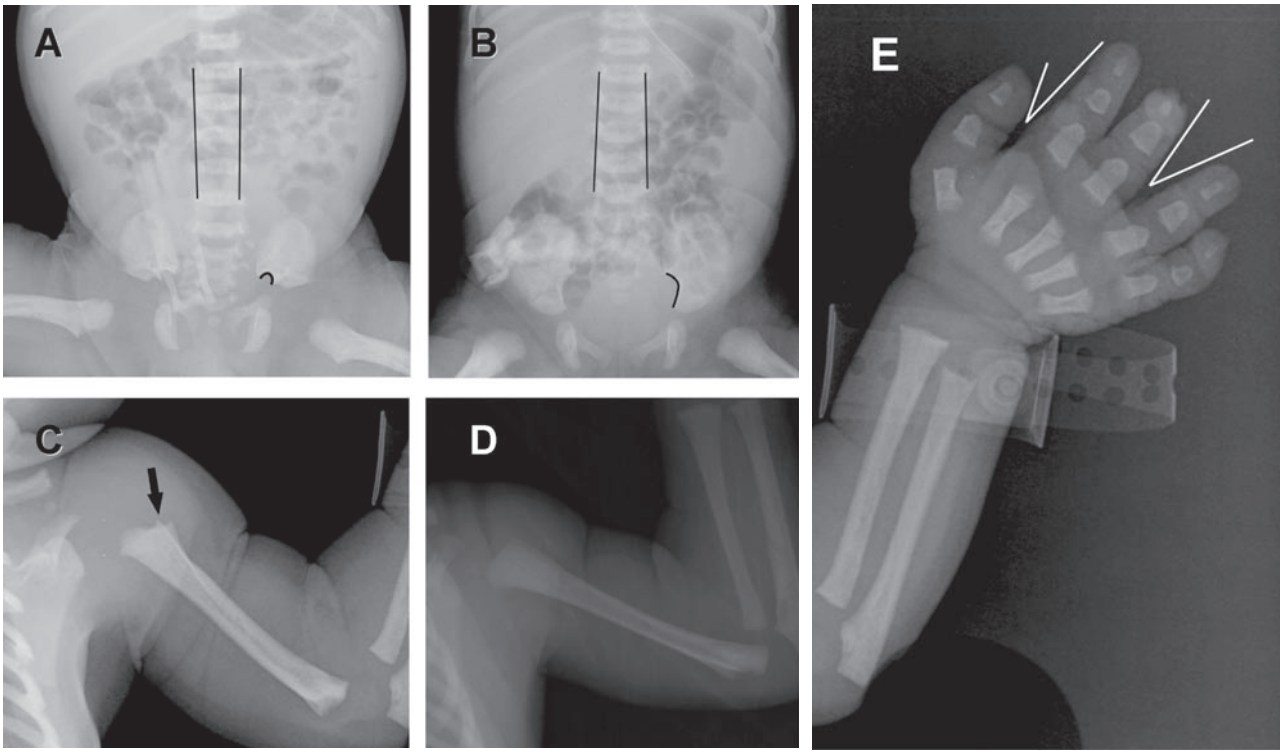
1. The babygram is abnormal for narrow sacrosciatic notches, radiolucent band over femoral heads, trident hand (more prominent over the left side), excessive skin folds over rhizomelic segments of long bones indicating mild rhizomelic shortening, decreased vertebral height, failure of progression of interpedicular distance over the lumbar segment, and bony spurs at metaphyses. Calvarium is large relative to the hypoplastic facial bones, but no definite long bone shortening is seen. These findings are compatible with the group of skeletal dysplasia related to FGFR3 (Fibroblast Growth Factor Receptor 3) mutations, in particular, hypochondroplasia or attenuated form of achondroplasia. Genetic study by DNA sequencing on PCR amplified fragments of exons 7, 9, 10, 13, 15 and 19 of the FGFR3 gene detected heterozygous 1138 G → A transition, confirming the diagnosis of achondroplasia.

2. FGFR3-related chondrodysplasia, Group 1 of the latest Nosology and Classification of Genetic Skeletal Disorders,[1] comprises a spectrum from the lethal thanatophoric dysplasia (type I and II), achondroplasia to the mildest form known as hypochondroplasia. Typical infants with achondroplasia display disproportionately short stature with rhizomelic shortening, absolute macrocephaly, contracted skull base and trident hands. 1138 G → A (mutation in the index patient) together with 1138G → C constitutes more than 98% of cases in achondroplasia, both resulting in a switch from Glycine to Arginine at codon 380; 80% of these mutations are de novo with advanced paternal age (greater or equal to 35 years of age), while the rest are inherited in an autosomal dominant manner with complete penetrance. Considerable overlap occurs between the 3 phenotypes due to the shared underlying molecular defect. In at risk pregnancies, prenatal diagnosis is available by genetic testing on samples obtained by chorionic villus sampling or amniocentesis. Typical features might only become apparent on antenatal ultrasonography starting from the second trimester.

3. The parents of our index patient received genetic counseling with regards to the diagnosis, natural history, management and underlying genetics. Reassurance was offered concerning the low risk of recurrence in future pregnancies. According to the guidelines on health supervision for children with achondroplasia issued by the American Academy of Pediatrics,[2] during infancy, serial monitoring of head circumference is essential in the detection of hydrocephalus, whereas magnetic resonance imaging is useful in the early identification of neural tissue compression by a small foramen magnum. Disease specific growth charts are available, with the expected average adult height for male and female being 131 cm and 124 cm respectively. Further morbidities will include motor delay, obstructive sleep apnea, otitis media with effusion, thoracic gibbus, lumbar lordosis and spinal stenosis, a multidisciplinary approach is adopted in the long term care for these children.

References

1. Superti-Furga A, Unger S. Nosology and classification of genetic skeletal disorders: 2006 revision. Am J Med Genet A 2007;143:1-18.
2. Trotter TL, Hall JG; American Academy of Pediatrics Committee on Genetics. Health supervision for children with achondroplasia. Pediatrics 2005;116:771-83.



Figures A (Patient) and **B** (Normal) demonstrate the failure of progression in interpedicular distance over the lumbar spine, and the narrow sacrosciatic notches. **Figures C** (Patient) and **D** (Normal) show abnormal bony spur at the metaphyseal region (arrow). The trident hand configuration is depicted on **Figure E**.

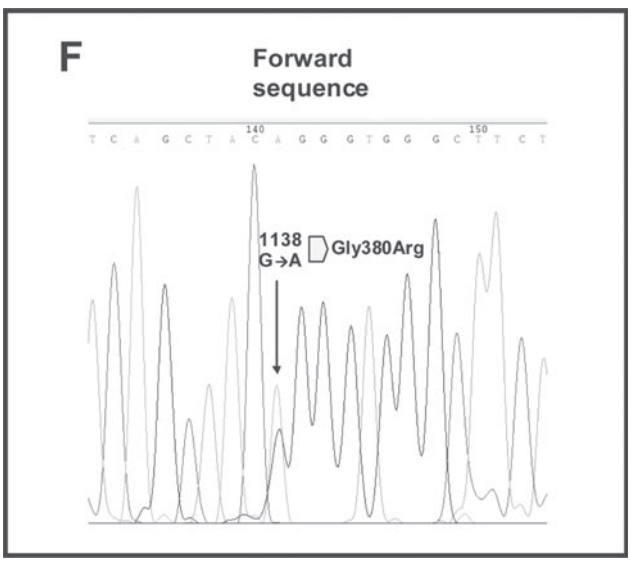


Figure F 1138 G → A mutation in the FGFR3 gene resulting in a switch from Glycine to Arginine at codon 380.