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50 Years Ago in *The Journal of Pediatrics*

Hand-Foot-Genital Syndrome and Its Multiple Genetic Mechanisms

Stern M, Hall JC, Perry BL, Stimson CW, Weitkamp LR, Poznanski AK. The hand-foot-uterus syndrome: a new hereditary disorder characterized by hand and foot dysplasia, dermatoglyphic abnormalities, and partial duplication of the female genital tract. J Pediatr 1970;77:109-16.

A unique autosomal dominant syndrome was described in 1970 by Stern et al in which affected members in a large multigeneration family displayed phenotypic variability and had malformed thumbs, a hypoplastic thenar eminence, and clinodactyly of the fifth digit. There was shortening of the first metacarpal and metatarsal on radiograph examination. In addition to the previously described skeletal features, 4 females in 3 consecutive generations had duplication anomalies of the uterus, including a bifid uterus with single cervix, a double uterus and double cervix with a subseptate vagina, and a double uterus and septate vagina. Affected individuals had similar dermatoglyphic findings. The expanded phenotypic spectrum includes hypospadias in males and urinary tract abnormalities, such as vesicoureteral reflux, ectopic ureteric orifice, and ureteropelvic junction obstruction, resulting in renaming of the condition to "hand-foot-genital" syndrome (HFGS). Although the skeletal features display complete penetrance, the genital features are characterized by incomplete penetrance with phenotypic variability.

HFGS is caused by mutations in the homeobox gene *HOXA13*, a DNA-binding transcription factor involved with morphogenesis involving distal limb and lower urinary tract development. *HOXA13* is localized to the *HOXA* gene cluster on chromosome 7 and the second *HOX* gene reported to be associated with a human malformation syndrome. Mutation mechanisms in *HOXA13* causing HFGS include protein truncation, polyalanine tract expansion, and missense resulting in amino acid substitution and 7p15.2 microdeletions.[1] Protein truncating mutations are thought to function as null alleles. There are 5 polyalanine tracts in exon 1 with 15-18 amino acid residues and expanded alleles containing 7-15 meiotically stable extra alanine residues. The mechanism(s) associated with *HOXA13* polyalanine tract expansion include gain of function and protein inactivation causing a dominant negative effect. Missense mutations may alter *HOXA13* target DNA binding. Deletions in 7p15.2 containing the *HOXA* gene cluster resulting in hapoinsufficiency for *HOXA13* have been reported.[2] The presence of distal limb malformations in a child should prompt an investigation for urogenital anomalies.

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