Results: In TACR3, 19 probands harbored 13 distinct coding sequence rare nucleotide variants (3 nonsense mutations, 6 non-synonymous, 4 synonymous [one predicted to affect splicing]). In TAC3, one homozygous single base pair deletion was identified, resulting in complete loss of the neurokinin B decapeptide. Phenotypic information was available on 16 males and 7 females with coding sequence variants in TACR3/TAC3. Of the 16 males, 15 had microphallus; none of the females had spontaneous thelarche. Seven of the 16 males and 5/7 females were assessed after discontinuation of therapy and 6/7 males and 4/5 females demonstrated evidence for reversibility of their hypogonadotropism.

Conclusions: Mutations in the neurokinin B pathway are relatively common as causes of hypogonadism. While the neurokinin B pathway appears essential during early sexual development, its importance in sustaining the integrity of the hypothalamic-pituitary-gonadal axis appears attenuated over time.

Mutations of the KISS1 Gene Associated with Central Precocious Puberty
(J Clin Endocrinol Metab, 10.1210/jc.2009-2421)

ABSTRACT
Context: Kisspeptin, encoded by the KISS1 gene, is a key stimulatory factor of GnRH secretion and puberty onset. Inactivating mutations of its receptor (KISS1R) cause isolated hypogonadotropic hypogonadism (IHH). A unique KISS1R activating mutation was described in central precocious puberty (CPP).
Objective: To investigate KISS1 mutations in patients with idiopathic CPP and normosmic IHH.
Patients: Eighty-three children with CPP (77 girls) and 61 patients with IHH (40 men) were studied. The control group consisted of 200 individuals with normal pubertal development.
Methods: The promoter region and the 3 exons of KISS1 were amplified and sequenced. Cells expressing KISS1R were stimulated with synthetic human wild-type or mutant kisspeptin-54 (kp54) and inositol phosphate accumulation was measured. In a second set of experiments, kp54 was pre-incubated in human serum prior to stimulation of the cells.
Results: Two novel KISS1 missense mutations, p.P74S and p.H90D, were identified in three unrelated children with idiopathic CPP. Both mutations were absent in 400 control alleles. The p.P74S mutation was identified in the heterozygous state in a boy who developed CPP at 1 yr of age. The p.H90D mutation was identified in the homozygous state in two unrelated girls with CPP. In vitro studies revealed that the capacity of the P74S and H90D mutants to stimulate IP production was similar to the wild-type. After pre-incubation of wild-type and mutant kp54's in human serum, the capacity to stimulate signal transduction was significantly greater for P74S compared to the wild-type, suggesting that the p.P74S variant is more stable. Only polymorphisms were found in the IHH group.
Conclusion: Two KISS1 mutations were identified in unrelated patients with idiopathic CPP. The p.P74S variant was associated with higher kisspeptin resistance to degradation in comparison to the wild-type, suggesting a role for this mutation in the precocious puberty phenotype.

Infants of Women with Polycystic Ovary Syndrome have Lower Cord Blood Androstenedione and Estradiol Levels
Helen Anderson, Naomi Fogel, Stefan K. Grebe, Ravinder J. Singh, Robert L. Taylor, and Andrea Dunaif
(J Clin Endocrinol Metab, 10.1210/jc.2009-2651)

ABSTRACT
Context: Prenatal androgen excess can cause a phenocopy of polycystic ovary syndrome (PCOS) in mammals. Retrospective studies have suggested that girls at risk for PCOS have low birth weight and prospective studies have suggested an increased prevalence of small for gestational age offspring in women with PCOS.
Objective: To determine whether infants of women with PCOS have reduced birth weight or increased intrauterine androgen levels.
Design: Prospective case-control study.
Participants: Thirty-nine PCOS and 31 control women and their infants.

Main outcome measures: Birth weight and mixed cord blood testosterone, androstenedione (A), dehydroepiandrosterone, 17-hydroxyprogesterone, estradiol (E2), and dihydrotestosterone levels.

Results: Mean birth weight did not differ but there was a significant increase in the prevalence of large for gestational age infants in the PCOS group. Cord blood E2 and A levels were lower (p < 0.05) but testosterone:E2 ratios did not differ in female PCOS compared to control offspring. There was no difference in 17-hydroxyprogesterone or in other androgen levels in either male or female PCOS offspring compared to their respective control group.

Conclusion: Infants of women with PCOS were more likely to be large for gestational age. Female offspring of affected women have lower cord blood A levels; other cord blood androgen levels do not differ compared to female control offspring. Cord blood E2 levels are also significantly decreased in PCOS, without any difference in the testosterone:E2 ratio, suggesting decreased fetal or placental production of steroids.

A Heterozygous Mutation of the Insulin-Like Growth Factor-I Receptor Causes Retention of the Nascent Protein in the Endoplasmic Reticulum and Results in Intrauterine and Postnatal Growth Retardation

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ABSTRACT

Background: Mutations in the IGF-I receptor (IGF1R) gene can be responsible for intrauterine and postnatal growth disorders.

Objective: Here we report on a novel mutation in the IGF1R gene in a female patient. The aim of our study was to analyze the functional impact of this mutation.

Patient: At birth, the girl’s length was 47 cm [−1.82 sd score (SDS)], and her weight was 2250 g (−2.26 SDS). Clinical examination revealed microcephaly and retarded cognitive development. She showed no postnatal catch-up growth but had relatively high IGF-I levels (+1.83 to +2.17 SDS).

Results: Denaturing HPLC screening and direct DNA sequencing disclosed a heterozygous missense mutation resulting in an amino acid exchange from valine to glutamic acid at position 599 (V599E-IGF1R). Using various cell systems, we found that the V599E-IGF1R mutant was not tyrosine phosphorylated and had an impaired downstream signaling in the presence of IGF-I. Flow cytometry and live cell confocal laser scanning microscopy revealed a lack of cell surface expression due to an extensive retention of V599E-IGF1R proteins within the endoplasmic reticulum.

Conclusion: The V599E-IGF1R mutation interferes with the receptor’s trafficking path, thereby abrogating proreceptor processing and plasma membrane localization. Diminished cell surface receptor density solely expressed from the patient’s wild-type allele is supposed to lead to insufficient IGF-I signaling. We hypothesize that this mechanism results in intrauterine and postnatal growth retardation of the affected patient. The reported retention of the nascent IGF1R in the endoplasmic reticulum presents a novel mechanism of IGF-I resistance.

Chemerin, A Novel Adipokine in the Regulation of Angiogenesis


(J Clin Endocrinol Metab, 10.1210/jc.2010-0042)

ABSTRACT

Context: Chemerin is a new adipokine associated with obesity and the metabolic syndrome. Gene expression levels of chemerin were elevated in the adipose depots of obese compared with lean animals and was markedly elevated during differentiation of fibroblasts into mature adipocytes.

Objective: To identify factors that affect the regulation and potential function of chemerin using a genetics approach.

Design, setting, patients and intervention: Plasma chemerin levels were measured in subjects from the San Antonio Family Heart Study (SAFHS), a large family-based genetic epidemiological study including 1354 Mexican American individuals. Individuals were randomly sampled without regard to phenotype or disease status.