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JOURNAL ARTICLE

Larger trinucleotide repeat size in the androgen receptor gene of infertile men with extremely severe oligozoospermia

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Androgens are significant regulators of human spermatogenesis. Their action is mediated through the androgen receptor (AR), which binds to the androgen responsive element on DNA and regulates gene transcription. Men become infertile with spinobulbar muscular atrophy (Kennedy disease) caused by a trinucleotide repeat expansion, > or = 40 CAG repeats, in the AR gene located on the X chromosome. In this prospective study, we investigated whether the variable size, larger repeats, of this trinucleotide could alter AR function and result in impaired spermatogenesis. A total of 69 infertile men were studied. Clinical and laboratory analysis showed idiopathic, nonobstructive azoospermia in 16 men, extremely severe oligozoospermia in 27 men (< 1 million sperm/mL), and severe oligozoospermia in 26 men (1 to 5 million sperm/mL). Fertile control men (n = 45) were selected by documented paternity proven by linkage analysis. Leukocyte DNA was analyzed by polymerase chain reaction (PCR) amplification across the AR repeat region. Accurate size determination of the PCR product using an ABI 373 DNA sequencer allowed precise calculation of CAG repeat sizes. The AR gene was not analyzed for other types of mutations. The difference in CAG repeat size between infertile men and proven fertile controls was statistically significant, P = .03. Patients with extremely severe oligozoospermia had significantly longer CAG repeat tracts (mean, 25.4 +/- 4.0; P = .0005; range 20-39) than controls (mean, 22 +/- 2.8; range 12-30) or patients with severe oligozoospermia (mean, 22.2 +/- 2.3; range 18-26). None of the 26 infertile men with sperm counts < 1 million/mL had < or = 19 CAG repeats compared with 6 out of 45 controls (13%; P = .06). This study suggests that some men with severe impairment of spermatogenesis have longer trinucleotide repeats in the AR gene. Although direct evidence is missing, lower affinity between androgen and the AR protein or decreased AR protein availability with longer repeats could be responsible for a diminished androgen effect on spermatogenesis. Two of the patients in the extremely severe oligozoospermia group had 35 and 39 CAG repeats, respectively (normal range is 11 to 33). Although not yet considered a mutation, longer trinucleotide repeats are unstable and might either expand or contract between generations. If they expand, conception through the use of intracytoplasmic sperm injection (ICSI), could result in the son of an

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