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Molecular analysis of SRY gene in patients with mixed gonadal dysgenesis. F. Alvarez-Nava[1], R. Ortiz[2], A. Rojas[2], A. Revol[2], I. Martínez[2], S. Martínez[2], M. Soto[1], L. Borjas[1], H. Barrera[2]. [1]Unidad de Genética Médica of Univ. of Zulia, Maracaibo, Venezuela and [2]Unidad de Laboratorios de Ingeniería y Expresión Genética, Univ. Nuevo León, Monterrey, México.

Mixed gonadal dysgenesis (MGD) encompasses a group of heterogeneous conditions consisting in presence of a dysgenetic testis with a streak gonad. MGD is probably due to an disturb in the determination/ differentiation testicular. The purpose of this study is to analyze SRY gene in MGD patients. A molecular investigation was undertaken in fifteen patients with disorder in an attempt to determine mutations in SRY through polymerase chain reaction, single strand conformational polymorphism and direct sequencing. Ten patients showed 45,X/46,XY and five 46,XY karyotype. Mutations in SRY gene were shown to be absent in 45,X/46,XY and 46,XY patients. This study confirm the findings of other studies. The primary etiology of MGD is heterogeneous, and cyotogenetic mosaicism typically seen in these patients may be a cause of this condition, although the presence of muations in testicular organizing genes downstream of SRY is still to rule out.

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Molecular analysis in true hermaphroditism. F. Alvarez-Nava[1], R. Ortiz[2], A. Rojas[2], M. Soto[1], L. Borjas[1], H. Barrera[2]. [1]Unidad de Genética Médica of Univ. of Zulia, Maracaibo, Venezuela and [2]Unidad de Laboratorios de Ingeniería y Expresión Genética, Univ. Nuevo León, Monterrey, México.

A true hermaphrodite (TH) is defined as an individual in whom both testicular and ovarian tissues are present. The diagnosis must be made histologically. The typical karyotype is 46,XX but about 30% of patients are chimeras 46,XX/46,XY. A small percentage of TH are 46,XY. Six documented histologically cases of TH have seen in the de Medical Genetic Unit of University of Zulia, Maracaibo, Venezuela, since 1985 to 1997. A molecular investigation was undertaken in an attempt to determine the cause of this disorder. Y-specific sequences, including SRY gene, were analyzed through polymerase chain reaction, single strand conformational polymorphism and direct sequencing. Three patients showed positive Y-sequences (two with 46,XX/46,XY and one with 46,XY karyotypes). These three patients did not have mutations in the amplified SRY fragments. In other three patients (46,XX karyotype), Y-sequences were shown to be absent from lymphocytes, genital skin fibroblasts or ovarian and testicular components of both ovotestes. Our data demonstrate that this phenotype does not always correlate with the presence or absence of Y-sequences in the genome, and confirm that TH is a genetically heterogeneous condition, suggesting that other genes working independently of SRY may also determine testicular differentiation.

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Prevalence of common mutations of the MTHFR gene in a Puerto Rican population

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Methylenetetrahydrofolate reductase (MTHFR) is a key enzyme in the metabolism of folate to methionine. Fourteen severe mutations of the MTHFR gene have been found to result in only a 0-20 percent activity of the control MTHFR protein (Goyette, 1995). A common mutation (C677T), which results in high homocysteine and low plasma folate levels, has been associated with a thermolabile form of the MTHFR enzyme, therefore being a risk factor for cardiovascular diseases and neural tube defects (NTD) in the homozygous form (Frosst, 1995). Another mutation in the human MTHFR gene (A1298C) has been found to destroy an MboII recognition site and results in decreased MTHFR activity. Plasma and homocysteine levels are not altered with the A1298C mutation, however this mutation seems to be a risk factor when combined with the C677T mutation (Van der Put NM, 1998).

In a prevalence study of the common C677T mutation screening in healthy women and newborn samples was performed we found that 8.6% of the individuals where homozygous for the mutation. These results compare with those found for Ohio Caucasian and Dublin populations (McAndrew, Kirke; 1996). Thirty NTD affected and control families were also analyzed in our laboratory for the C677T and A1298C mutations. Analysis of the A1298C mutation in 51 and 62 individuals from the control and NTD affected families, respectively, resulted in 8 control and 0 NTD affected individuals homozygous for the mutation. Taken together, the results of this study indicates that the Puerto Rican population has a low frecuency of the C677T mutation and confirms that homozygocity for the A1298C mutation does not present a direct risk for NTD.

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Incomplete X-linked congenital stationary night blindness: Characterization of mutations in the *CACNA1F* gene and an assessment of clinical variability. K.M. Boycott[1], W.G. Pearce[1,2], and N.T. Bech-Hansen[1]. [1]University of Calgary, Calgary, AB, Canada, [2]University of Alberta, Edmonton, AB, Canada.

X-linked congenital stationary night blindness (CSNB) is a clinically and genetically heterogeneous non-progressive retinal disorder characterized by impaired night vision, decreased visual acuity, myopia, nystagmus, and strabismus. Two loci for CSNB exist on the X chromosome. The locus for complete CSNB (nonrecordable scotopic b-wave and lack of rod dark adaptation) has been mapped to Xp11.4 (Boycott et al. AJHG 62:865-875, 1998), while the gene responsible for incomplete CSNB (subnormal scotopic b-wave and mildly elevated rod adaptation),*CACNA1F*, has been identified in Xp11.23 (Bech-Hansen et al. Nature Genet. 19:264-267). Our analysis of this retina-specific L-type calcium channel α_1-subunit gene has identified a total of 17 different mutations (two-thirds of which are predicted to cause a loss-of-function) in 36 families with incomplete CSNB. One of these mutations, L1045insC, is seen in 15 families of Mennonite ancestry from Western Canada. Clinical variability was examined in 66 patients from these families in terms of night blindness, myopia, visual acuity, congenital nystagmus, and strabismus. In 80% of the patients at least one of the main features of CSNB (night blindness, myopia, and nystagmus) was absent. The only clinical feature present in all 66 patients tested was impaired visual acuity. Among these patients who shared the common *CACNA1F* mutation, considerable variability in clinical expression is evident and suggests the presence of genetic modifiers.

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