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Mapping of the 21-Hydroxylase Deficiency Gene Within the HLA Complex.

In order to map the gene for 21-hydroxylase deficiency within the HLA complex on the 6th chromosome we have conducted studies of two additional HLA linked genetic markers. The studies involved the genetic polymorphic traits Bf (Factor B of the alternate complement pathway) and GLO-I (Glyoxalyse-I polymorphism) and was performed in 32 families of patients with congenital adrenal hyperplasia (CAH) of the 21-hydroxylase type (21-OH-def). Two families demonstrated genetic recombination between HLA-B and GLO-I. In one family with three HLA genotypically identical siblings who all were affected with CAH it was found that one child had either a maternal HLA-B, Bf: GLO-I or HLA-B:Bf, GLO-I recombinant haplotype. In the second family with two affected children one affected sib had a paternal HLA-D:GLO-I recombinant haplotype. This child was HLA-B, Bf, D genotypically identical with the other affected sib. These studies map the 21-OH-def gene between the HLA-A locus and the GLO-I locus.

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Close Genetic Linkage Between Congenital Adrenal Hyperplasia (21-hydroxylase deficiency) and HLA.

We report on a combined study of 32 families from NY and Zurich with a total of 46 patients with CAH. It was found that all patients were HLA genotypically different from the healthy sibs and that 2 or more affected children in the same sibship were HLA identical. Lod Score analysis demonstrated a peak Lod Score of 4.2 for the recombinant fraction $(\theta) \approx 0.00$ between HLA-B and 21-OH-def. Close genetic linkage between HLA-B and 21-OH-def. was thus established. No HLA-A,B or C antigen was selectively increased among the 34 unrelated patients. These studies provide the basis for utilization of HLA genotyping in high risk families to identify heterozygous carriers of the 21-OH-def. gene among sibs and other relatives. On the basis of these studies it can be predicted that 31 sibs were heterozygous carriers and 11 sibs were genetically unaffected for the enzyme deficiency. Prenatal diagnosis of the disease in high risk families by HLA typing of cultured amniotic cells may be possible. This is the first example in which an enzymatic deficiency of steroid biosynthesis has been shown to be closely linked to HLA.

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Linkage studies between HLA-A,B,D alleles and congenital adrenal hyperplasia (CAH).

The observation by Dupont et al. of close linkage between CAH and the HLA-complex prompted us to study the inheritance of HLA-haplotypes and the deficiency of C21-Hydroxylase (C21-H) in 12 families with CAH children. All family members were tested for CAH heterozygosity by the increase of plasma 17-OHP after ACTH stimulation. An increase of 17-OHP > 200 ng/dl was taken as evidence for CAH-heterozygosity. HLA-A,B,D typing was done by established serological and cellular methods. In 3 families with 2 CAH cases, we found identical HLA-A,B,D in the affected siblings. There was a good correlation between the results of the heterozygosity test and the segregation of HLA-haplotypes, in some cases over 3 generations. The distribution of HLA-A,B,D alleles in the 12 unrelated CAH-patients was not significantly different from controls, indicating that there is no positive association between C21-H deficiency and antigens of the HLA-series. Our data support the concept of close linkage of CAH and HLA allowing more precise prenatal diagnosis of CAH and identification of heterozygotes.

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Genetic Linkage between HLA and 21-Hydroxylase Deficiency

Seven families with one or more children with 21-hydroxylase deficiency (congenital adrenal hyperplasia C.A.H.) were typed for HLA-A, B and C antigens by the standard two stage NIH lymphocytotoxicity test. Salt-losing C.A.H. was present in five families and non-salt-losing C.A.H. in two families. No recombination between the HLA-B locus and the gene for C.A.H. was observed in twenty-one children. In one family a child with a recombinant haplotype "escaped" the disease demonstrating segregation with the HLA-B locus rather than the HLA-A locus. An adult male non-salt-loser was identified by HLA-typing and subsequently diagnosed biochemically.

More certain prenatal diagnosis of affected siblings of children with 21-hydroxylase deficiency and identification of heterozygotes may now be made.

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ABSENCE OF LINKAGE BETWEEN C-11 OH DEFICIENT CONGENITAL ADRENAL HYPERPLASIA AND HLA.

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A collaborative study revealed an unusually high frequency of congenital adrenal hyperplasia (CAH) due to C-11 OH deficiency in Israel. Seventeen families with 24 affected individuals were identified, mostly originating from North Africa. The diagnosis was based on clinical features and confirmed by the presence of high levels of urinary tetrahydro 11-deoxycortisol. Since both the C-11 and C-21 hydroxylating enzymes participate in the same adrenal biosynthetic pathways of steroids and 21-OH has been shown to be linked to HLA, we investigated the HLA antigens in our families. HLA antigens of the A, B and C loci were determined in 11 families which included 13 affected and 19 healthy children. Analysis of the data revealed that affected sibs did not share both haplotypes, and in addition, in several families unaffected siblings shared both haplotypes with the patients. Thus, no linkage between the C-11 OH variant of CAH and the HLA system was observed.

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Hormones from gut and pancreas in term neonates: response to fetal distress and different alimentary stimuli.

There is little information on gut hormone levels in the human neonate. We compare levels of gastrin, motilin, gastric inhibitory peptide (GIP), vasoactive intestinal peptide (VIP), pancreatic polypeptide (PP), pancreatic glucagon, enteroglucagon and insulin in cord blood of 19 normal neonates and 7 neonates with fetal distress, and report enteroinsular hormone release during the first feed of breast milk or 10% dextrose in 21 infants. Fetal distress caused significantly elevated mean cord levels of motilin, P.P., VIP and pancreatic glucagon. The first feed of human milk (5ml/kg) caused a rise in blood glucose, insulin, gastrin and enteroglucagon, but no change in GIP or pancreatic glucagon. 10% dextrose feeds (5mls/kg) caused similar changes without the increase in enteroglucagon. We conclude 1) several important gut hormones are detectable in cord blood. 2) Fetal distress stimulates selective gastro-intestinal hormone release. 3) Neonates differ from adults in their enteroinsular hormone response to feeding.