Genetic abnormalities in polycystic ovary syndrome

Anomalies génétiques dans le syndrome des ovaires polykystiques

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RÉSUMÉ - Le syndrome des ovaires polykystiques (SOPK) est une endocrinopathie très fréquente et la cause majeure de dysfertilité. Il est aussi associé à un risque accru de diabète de type 2 dans la 2e partie de la vie. Malgré cette évidente importance pronostique de cette affection, l’étiologie de la maladie reste encore bien mal connue. Compte tenu du lien familial bien connu dans de nombreux cas, nous avons entrepris, au sein de notre département, des études génétiques afin d’identifier les gènes majeurs impliqués dans la survenue de la maladie. Nous avons mis en évidence que le SOPK est associé à un polymorphisme dans la zone de régulation de CYP11a (codant pour la rupture de la chaîne latérale de Cholesterol P 450, enzyme fortement impliqué dans la voie chimique de la stéroïdogenèse). L’étude du gène de l’insuline (INS) nous a permis de constater, dans 3 groupes séparés, qu’il existait une association entre SOPK et les allèles de classe III de l’INS-VNTR (situé dans la zone de régulation du gène de l’insuline). Des anomalies dans la même région ont été associées à l’apparition du diabète de type 2. Nous suggérons que le SOPK est une anomalie oligogénique, dans laquelle un petit nombre de gènes majeurs sont susceptibles d’interagir avec des facteurs environnementaux (notamment alimentaires) déterminant ainsi le phénotype clinique et biochimique, par essence hétérogène, de la maladie.

SUMMARY - Polycystic ovary syndrome (PCOS) is a very common endocrinopathy and is the major cause of anovulatory infertility. It is also associated with an increased risk of non insulin dependent diabetes (NIDDM) in later life. Despite the importance of PCOS to women’s health, little is known about its aetiology. Because of the well-known familial clustering of cases of PCOS, recent studies in our department have focused on clinical and molecular genetic studies in an attempt to identify key genes which may be involved in its aetiology. We have found evidence that a polymorphism in the regulatory region of CYP11a (encoding P450 cholesterol side chain cleavage, also an important enzyme in the steroidogenic pathway) is associated with and linked to PCOS. In examination of the insulin gene (INS), we have shown, in three separate populations, that class III alleles in the INS-VNTR (the minisatellite in the regulatory region of the insulin gene) are associated with PCOS. Variation in this element has also been implicated in the aetiology of NIDDM. We propose that PCOS is an oligogenic disorder in which a small number of key genes interact with environmental factors (notably dietary), the balance of which factors determine the, typically heterogeneous, clinical and biochemical phenotype.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders, being a major cause of anovulatory infertility and of hirsutism [5]. It is now recognised that, in addition to the reproductive implications, PCOS is associated with a characteristic metabolic disturbance of which hyperinsulinaemia and insulin resistance are the central features.
A bnormalities of insulin secretion and/or action may be related to the mechanism of anovulation in PCOS. The importance of the metabolic disorder is further illustrated by the finding that women with PCOS have an estimated 6-fold increase in risk of non-insulin-dependent diabetes (NIDDM) in later life [1]. Despite the clinical significance of PCOS, its aetiology remains uncertain but the high prevalence of cases within the families of affected cases suggests that there is a major genetic cause. Most of the clinical genetic studies published to date, including our own, have concluded that the most likely mode of inheritance is autosomal dominant but recent studies at our centre suggest that PCOS may represent a complex trait involving the interaction of a small number of genes with environmental — principally nutritional — factors [3, 9, 12].

CANDIDATE GENES IN PCOS

A lthough the biochemical features of PCOS are variable, certain abnormalities are consistent in the endocrine presentation of PCOS and these point towards possible candidate biochemical pathways in the search for the genetic basis of the syndrome. Hyperandrogenaemia is perhaps the most frequently observed abnormality and is common to all groups of subjects with polycystic ovaries regardless of the mode of presentation [3]. The weight of evidence suggests that hyperandrogenism in PCOS is primarily the result of constitutive hypersecretion of ovarian androgens, thus raising the possibility of a genetically-determined abnormality in the androgen biosynthetic pathway.

Hyperinsulinaemia and insulin resistance are the central features of the « metabolic syndrome » in women with polycystic ovaries. Although it is possible that there are primary abnormalities of both insulin action and insulin secretion [2], recent data demonstrate that whilst insulin sensitivity is restored towards normal by diet, derangement of first-phase insulin secretion persists after calorie restriction [7]. This phenomenon suggests that there is an intrinsic abnormality of pancreatic β-cell function in PCOS and that the insulin gene itself is a candidate in its aetiology. One important additional point is that hyperinsulinaemia is predominantly a feature of anovulatory women with PCOS and does not occur to the same degree in equally hyperandrogenaemic women with polycystic ovaries and regular cycles [10].

THE 17-HYDROXYLASE, 17/20-LYASE GENE (CYP17)

A bnormalities in the regulation of key genes in the androgen biosynthetic pathway have also been discovered. Because of the reported abnormalities in regulation of 17-hydroxylase/17-20 lyase in PCOS [11], our initial studies focused on the role of CYP17 (coding for P450c17α). Results of a preliminary case-control study suggested that a variant form of CYP17 was associated with PCOS but there was no relationship between genotype and serum testosterone levels. Furthermore, subsequent, larger, case-control studies — from our own group as well as from other centres — have been unable to confirm the putative association [4]. In addition, linkage analysis excluded CYP17 as a major susceptibility gene for PCOS within families.

THE CHOLESTEROL SIDE-CHAIN CLEAVAGE GENE (CYP11A)

W e then examined CYP11a (coding for P450 cholesterol side chain cleavage). A polymorphic sequence (a pentanucleotide repeat) in the 5' regulatory region of CYP11a was identified and both case-control association studies and non-parametric linkage analysis were performed. The most common genotype (designated 216-) was significantly associated with PCOS and serum testosterone [6]. We examined the segregation of CYP11a in 20 families. With the aid of a number of polymorphic markers in the region of CYP11a, we carried out non-parametric linkage analysis using the GENEHUNTER (multipoint linkage) program [8]. We found evidence for excess allele sharing (i.e. linkage) at the CYP11a locus. Thus, data from both association and linkage studies suggest that this is a major susceptibility locus for hyperandrogenism in PCOS.

THE INSULIN GENE VARIABLE NUMBER TANDEM REPEAT (INS-VNTR)

W e also have evidence that the insulin gene (INS) variable number tandem repeat (VNTR) is a major susceptibility locus for PCOS [13]. The INS-VNTR is in the 5' regulatory region of the gene; it has been shown to be involved in insulin secretion and has been implicated in the aetiology of NIDDM. We found that class III alleles in the VNTR were associated with anovulatory PCOS in
two independent populations and using two
different methods of analysis (case-control
studies and by the use of affected family
based controls; AFBAC). With the aid of the
GENEHUNTER linkage analysis pro-
gramme which allowed both parametric and
non-parametric analyses, we established that
there was excess allele sharing at the INS-
VNTR locus. The geometric mean of fasting
serum insulin concentrations was significantly
higher in families in which linkage was
demonstrated than in those families without
evidence of linkage. This suggests a functional
role for the VNTR variant in the expression
of hyperinsulinaemia/insulin resistance in
PCOS.

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