**HLA class II distribution in Congolese with hyperthyroidism: preliminary results**

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**OBJECTIVE**

The incidence of the hyperthyroidism is not certain genes operate in hyperthyroidism, to determine whether the susceptibility to hyperthyroidism. No studies in the distribution of the alleles of HLA, PCR, SSOP, susceptibility to hyperthyroidism, Rép. Dém. du Congo.

**INTRODUCTION**

For many years, hyperthyroidism was considered as very rare in the African Black people. Since, this affection is one of the most frequent in our outpatients in the service of Endocrinology and Metabolism at the Hospital Clinic of Kinshasa. Indeed, the incidence of this disease passed from 0.42% in 1960 to 5% in 1999, with a prevalence of 2 for thousand [3]. The most common clinical form encountered in this study is made of a diffuse or multinodular goiter, a unilateral or bilateral ophtalmopathy, associated or not to an infiltrative dermopathy, high levels of total thyroxin (T4) and total tri-iodothyronin (T3), and an undetectable TSH or a very low value of this hormone. Sometimes, the ignorance of genetic and immunologic risk factors to the Graves disease may make more difficult the classification of the patients, as well as the choice of an efficient regimen of treatment [1, 7, 19, 20, 27].

Many studies performed in China [17], in Caucasian White people [28], in United Kingdom [9], in Italy [5] and in the USA [31] showed important geographic, racial or ethnic variations in the distribution of the susceptibility to hyperthyroidism. No study was undertaken in our countries, in the manner of those made in USA [26, 31], in Mediterranean [15], in Europe [17, 24] and in Asiatic [35] populations, to determine whether or not certain genes operate in hyper-

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**La distribution des gènes HLA de classe II chez les hyperthyroïdiens congolais : résultats préliminaires**

M Bidingija, A Galgani, R Buzzetti, M Ditu

**Ann. Endocrinol.**, 2006 ; 67, 6 : 596-603

**Objectif :** L’incidence de l’hyperthyroïdie ne cesse d’augmenter à nos consultations externes, alors que nos connaissances sur les facteurs favorisant son apparition dans notre milieu ne sont que superficielles. C’est pour palier à cette lacune que la présente étude a été entreprise, en vue d’identifier les gènes HLA dans la population Congolaise et de déterminer la susceptibilité génétique de l’hyperthyroïdie aux Cliniques Universitaires de Kinshasa.

**Matériels et Méthodes :** Neuf femmes Congolaises souffrant d’hyperthyroïdie et 13 témoins (3 femmes et 10 hommes) sans pathologie thyroïdienne connue, ont été examinés et comparés pour l’analyse des gènes HLA-DR et HLA-DQ, du mois d’Août 2000 au mois d’Août 2002. La technique de la Polymerase Chain Reaction (PCR) et les sondes des séquences spécifiques d’oligonucléotides fixes (test SSOP HLA-DRB) ont été utilisées pour identifier les allèles des loci HLA-DRB1 et HLA-DQB1.

**Résultats :** Dans le groupe des femmes hyperthyroïdiennes, 3 allèles (HLA-DR1, HLA-DR2, HLA-DR3) et un groupe allélique (HLA-DR11,13,14) ont été détectés au locus DRB1, alors qu’un seul allèle (HLA-DQB1*0602) a été identifié au locus DQB1. Le groupe allélique DR11,13,14 était le plus fréquent, avec une fréquence allélique de 0,50, suivi par l’allèle HLA-DR3 avec une fréquence allélique de 0,222 ; 6 haplotypes ont été détectés, avec prédominance de l’haplotype DR3/DR11,13,14 (fréquence génotypique = 0,333), suivi de l’haplotype DR11,13,14/DR11,13,14-DQB1*0602 (fréquence génotypique = 0,222). Dans le groupe témoin, trois allèles, HLA-DR2, HLA-DQB1*0602 et DR2/DR2-DQB1*0,602 exerceront un rôle protecteur contre le développement de l’hyperthyroïdie chez les porteurs de ces gènes, tandis que les gènes DR3, le groupe allélique DR11,13,14 ainsi que l’haplotype HLA-DR3/DR11,13,14 seraient des facteurs de prédisposition à la maladie et à l’exophtalmie basedowienne. Des études plus approfondies sont nécessaires pour confirmer ou infirmer ces résultats préliminaires.

**Conclusions :** HLA-DR2, HLA-DQB1*0602 et DR2/DR2-DQB1*0,602 exercent un rôle protecteur contre le développement de l’hyperthyroïdie chez les porteurs de ces gènes, tandis que les gènes DR3, le groupe allélique DR11,13,14 ainsi que l’haplotype HLA-DR3/DR11,13,14 seraient des facteurs de prédisposition à la maladie et à l’exophtalmie basedowienne. Des études plus approfondies sont nécessaires pour confirmer ou infirmer ces résultats préliminaires.

**Mots-clés :** HLA, PCR, SSOP, susceptibilité à l’hyperthyroïdie, Rép. Dém. du Congo.
Objective: Incidence of the hyperthyroidism is continuously increasing, whereas our knowledge concerning the facilitating or etiologic factors of this increase are still partial. To evaluate some of these unknown factors, we started this preliminary study, in order to identify HLA genes in hyperthyroid Congolese, and to determine their susceptibility in the appearance and development of hyperthyroidism at the Hospital Clinic of Kinshasa.

Materials and Methods: Nine Congolese women with hyperthyroidism, and thirteen healthy controls (3 women and 10 men) were examined and compared for HLA-DR and HLA-DQ genes analyses, from August 2000 to August 2002. DRB1 and DQB1 alleles were identified, using the Polymerase Chain Reaction (PCR) and immobilized sequence-specific oligonucleotide (SSO HLA-DRB1 and DQB1 test) probes assays.

Results: In the group with hyperthyroidism, three alleles (HLA-DR1, HLA-DR2, HLA-DR3) and an allele group (HLA-DR11,13,14) were found for DRB1 locus, while only one allele (HLA-DQB1*0602) was identified for DQB1 locus; allele group HLA-DR11,13,14 was the most frequent (allele frequency=0.50), followed by HLA-DR3 allele (allele frequency=0.222); 6 haplotypes were observed, with predominance of haplotype DR3/DR11,13,14 (genotype frequency=0.333), followed by haplotype DR11,13,14/DR11,13,14-DQB1*0602 (genotype frequency=0.222). In the group of healthy controls, three alleles (HLA-DR2, HLA-DR3, HLA-DR4) and an allele group (HLA-DR11,13,14) were identified for DRB1; HLA-DR2 allele was predominant (allele frequency=0.615), followed by allele group HLA-DR11,13,14 (allele frequency=0.231); a statistic significant difference was observed between the frequencies of DR2 allele and allele group DR11,13,14 in the healthy controls compared to those of hyperthyroid patients (p=0.02); 6 haplotypes were also detected in this group, the most frequent haplotype being HLA-DR2/DR2-DQB1*0602 (genotype frequency=0.540 versus 0.333 in the hyperthyroid group) (p=0.048). HLA-DQB1*0602 was dominant in the healthy controls group (allele frequency=0.890), versus HLA-DQB1*0302 (allele frequency=0.110).

Conclusions: HLA-DR2, HLA-DQB1*0602 and DR2/DR2-DQB1*0.602 would play a protective role against the hyperthyroidism, while DR3 allele, allele group DR11,13,14 and haplotype HLA-DR3/DR11,13,14 would predispose to this disease or to Graves’ exophthalmopathy. A large and profound study is needed to confirm our preliminary results.

Key words: HLA, PCR, SSOP, susceptibility to hyperthyroidism, Dem. Rep. of Congo.
are compared to those from 13 healthy subjects, designed as “control group”.

**Blood sample collection and DNA extraction**

Ten milliliters sample of blood was drawn from an antecubital vein using EDTA as coagulant, and was stored at \(-18^\circ C\) until its use for genomic DNA extraction by a trained personnel. Every plastic tube was carefully handled and tagged to avoid the contamination of the blood samples and the confusion of the names of the patients. DNA extraction was performed according to the instructions given in the QIAamp DNA Mini Kit and QIAamp DNA Blood Mini kit 09/2001, cat.51304, from QIAGEN Distributors.

**HLA typing**

HLA typing was performed in the Department of Clinical Sciences, at the Policlinico Umberto I/Rome. HLA-DRB1 and -DQB1 locus typing data was generated using sequence-specific oligonucleotide (SSO) technology with immobilized probe assays (non commercial) kindly provided by Dr. Erlich’s group of the Roche Molecular Systems (Alameda, CA, USA). The three main steps of the technique are the following:

- amplification of the specific target DNA sequences by Polymerase Chain Reaction (PCR),
- hybridization of the amplified products (amplicons) to a array of immobilized sequence-specific oligonucleotide probes,
- detection of the probe-bound amplified product by colour formation [14].

**HIV serologic test**

A HIV test was realized on each of the samples by a trained personnel, from the Transfusion Blood Bank at the Hospital Clinic of Kinshasa, using the Microelisa system kit, Vironostika HIV-Uni-Form II plus O, from Biomérieux Firm. Two patients whose test was positive were excluded from the study.

**Statistic analyses**

Allelic frequency was obtained by addition of the number of each single allele in the population and was expressed as a frequency, according to the following formula, for a population with N diploid individuals: frequency of allele A=(2nAA+nAa)/2N, where n is the number of individuals with a genotype written in index [34]. Expected genotype frequency is predicted by the Hardy-Weinberg equation, p^2+2pq+q^2=1, which was verified in every case [34]. Approach relative risk (Odds ratio) (OR) was calculated in order to evaluate the risk of developing the hyperthyroidism by the HLA predisposed subjects, and Fisher test was used to determine the statistic validity of the relative risk value calculated, with a confidence interval (CI) of 95%. Arithmetic average was used to calculate the mean age of the subjects.

**RESULTS**

From the 118 blood samples drawn, 2 samples were excluded because of the positive serologic HIV test. On the 116 DNA extracts remaining, 90 extracts were excluded because of alterations during their transport and storage, 4 extracts from the well-being siblings of the hyperthyroid subjects were also excluded in order to avoid the selection bias. Only 22 of 118 DNA extracts (18.6%) were analysed for the HLA-DRB1 and HLA-DQB1 loci. These 22 extracts belong to 9 hyperthyroid patients (41%) and 13 healthy subjects without parental relation with the hyperthyroid patients (59%), and constitute the human material for the present study. *Table I* summarizes the principal characteristics of these 22 subjects.

**Allele frequencies**

Allele frequencies observed in the 22 subjects for the DRB1 locus are shown in *table II*. Three alleles (HLA-DR1, HLA-DR2, HLA-DR3) and an allele group (HLA-DR11,13,14) were found. It was not possible to separate different components of the allele group DR11,13,14, since the probe used was appropriated for investigation of the

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Hyperthyroid patients (n=9)</th>
<th>Healthy non relative subjects (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years+1sd)</td>
<td>40.66±12.61</td>
<td>29.27±3.5</td>
</tr>
<tr>
<td>Genre</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— female</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>— male</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Family antecedent of goiter in :</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— mother’s parents</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>— mother</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>— siblings</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Exophthalmia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— in the patient</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>— in the family</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
genetic risk in the diabetes mellitus and not in the hyperthyroidism. Nevertheless, this allele group was dominant in the hyperthyroid patients compared to controls (50% vs 29.4% respectively; p=0.04). Otherwise, HLA-DR2 allele was predominant in the control group compared to the hyperthyroid patients (59% vs 17% respectively; p=0.05).

As for the allele group DR11,13,14, it was also difficult to detect other alleles than HLA-DQB1*0602 and DQB1*0302 alleles in the DQB1 locus with the probe used. In the hyperthyroid patients, only HLA-DQB1*0602 allele was detected, with an allele frequency of 27.7% (28%). In the healthy control group, the allele frequency of HLA-DQB1*0602 allele was 89% (Odds ratio=0.781; Fisher: p=0.32), and HLA-DQB1*0302 allele frequency was 11%.

Distribution of the genotypes according to the clinical state

Six different genotypes were found in the control group as well as in the hyperthyroid group. Table III shows the respective genotype frequencies for the control subjects and the hyperthyroid patients, as detected for DRB1 and DQB1 loci.

Exophtalmopathy and HLA genes

Association between exophtalmopathy and genotypes HLA in the hyperthyroid patients is shown on table IV. This table shows that 6 of 9 patients with hyperthyroidism (66.6%) have an exophtalmopathy, and that DR3 allele or allele group DR11,13,14 are present in 83.3% of these patients.

Characteristic genes

The analysis of 22 DNA extracts in our patients let us suspect the following genes or allele group as playing a role in the susceptibility or in the resistance to hyperthyroidism: HLA-DR3 gene (O.R: 9.6; Fisher: p=0.06) and HLA-DR11,13,14 allele group (O.R: 11.7; Fisher: p=0.02) seem to predispose to the hyperthyroidism, whereas HLA-DR2 gene (O.R:0.20; Fisher: p=0.016) seems to protect against this disease.
DISCUSSION

Role of the HLA system

Susceptibility to Graves disease, the most common cause of hyperthyroidism, is associated both to the individual sex, to a Major Complex of Histocompatibility (MHC), and to a gene coding for heavy chains of Immunoglobulins [9, 12]. Through the clonage of the T Lymphocytes Receptor genes (TCR), it was shown that the function of TCR is to allow the T lymphocytes to recognize the antigen bound to the Antigen-Presentative membrane Cell (APC), in the context of the class II HLA molecules [12].

So, HLA molecules act as receptors of foreign antigens, and present them to CD4+ T lymphocytes in the context of the class II HLA antigens, or to the CD8+ T lymphocytes in the context of the class I HLA antigens [8, 25]. In the case of Graves’ disease, foreign molecule may be a Thyroglobulin (Tg) or a TSH receptor (TSH-R) [10, 11, 32]. It is also known, after Sai-Ching JY in 2002, that thyroid epithelial cells abnormally express HLA-DR antigens at their surfaces (26). Other studies showed that a low proportion of circulating B lymphocytes was able to bind a radioactive thyroglobulin or a DNA on their membrane receptor [10, 11, 32]. Indeed, when the presentation of antigen to T lymphocytes by the APC is correct, these lymphocytes “see” the antigen in the context of HLA molecules and begin to proliferate by two ways:

— if the T helper lymphocytes are in concern, their proliferation results in the genetically predisposed subjects and in the presence of autoreactive T lymphocytes, in the synthesis of the lymphokines which stimulate differentiation and antigen activation of other immuno-competent cells, specially the B lymphocytes. These autoreactive lymphocytes grow into plasmocytes and secrete various antibodies directed against the TSH receptor. One of the properties of these auto-antibodies is to stimulate synthesis and secretion of thyroid hormones, independently to the negative feed-back mechanisms, with as consequence the development of hyperthyroidism due to Graves disease.

— If the cytotoxic T cells are concerned, proliferation leads to a cytolysis of the thyroid cells and explain the occurrence of auto-immune thyroiditis, such as the Hashimoto thyroiditis, which shares several common characteristics with the Graves’ disease.

HLA genes distribution

Our results show, in the control group, a net predominance of HLA-DR2 allele (f_q=61.5%), followed by an allele group DR11,13,14 (f_q=23.1% for the DRB1 locus. In the hyperthyroid subjects in contrary, gene allele group DR11,13,14 represents 50% of the patients, followed by HLA-DR3 allele (22.2%). No significant difference was observed between the frequencies of DQB1*0602 allele in the control group (89%) and hyperthyroid group (27.7%) (p=0.32).

HLA-DR2 Gene

HLA-DR2 frequency detected by Mbayo was 20.9% by the serologic method, and 20.88% by the PCR technique [21]. It is a little difficult to compare our results to those of the author, because of the reduced number of our respective studies, and also, because we do not know whether his patients were or not in an euthyroid state. However, HLA-DR2 gene is predominant in the two series. Frequency of HLA-DR2 gene is approximately the same in Nigerians (21,73%) and in Zimbabweans (21.60%) as in Congolese population studied by Mbayo, while it is low in South-African Blacks (11.5%) (p<0.05) [21].

Positive susceptibility association between HLA-DR2 and hyperthyroidism has not been demonstrated in Caucasian White and Asiatic populations yet. However, our results seem to indicate that DR2 gene would be a protector factor against the development of hyperthyroidism (Odds ratio[OR]=0.18 ; p=0.02). Finally, it is more tempting to presume, in the manner of diabetes mellitus type 1, that this gene would play the same role as in diabetes mellitus, alone, or in association with an other DR2 or DQB1*0602 allele.

Indeed, this gene combines with a very high affinity to thyrotropic oligonucleotide; this combination results in an abnormal molecule configuration on the CPA membrane cell, and makes the complex molecule unable to stimulate hyperthyroidism.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Exophthalmopathy</th>
<th>HLA genotypes</th>
</tr>
</thead>
<tbody>
<tr>
<td>K.B.</td>
<td>absent</td>
<td>DR2/DR11,13,14-DQB1*0602</td>
</tr>
<tr>
<td>B.N.</td>
<td>present</td>
<td>DR2/DR2-DQB1*0602</td>
</tr>
<tr>
<td>M.S.</td>
<td>present</td>
<td>DR3/DR11,13,14</td>
</tr>
<tr>
<td>M.L.</td>
<td>absent</td>
<td>DR1/DR3</td>
</tr>
<tr>
<td>L.N.</td>
<td>present</td>
<td>DR1/DR11,13,14-DQB1*0602</td>
</tr>
<tr>
<td>M.K.</td>
<td>present</td>
<td>DR3/DR11,13,14</td>
</tr>
<tr>
<td>B.E.</td>
<td>absent</td>
<td>DR11,13,14/DR11,13,14-DQB1*0602</td>
</tr>
<tr>
<td>B.M.</td>
<td>present</td>
<td>DR3/DR11,13,14</td>
</tr>
<tr>
<td>B.D.</td>
<td>present</td>
<td>DR11,13,14/DR11,13,14-DQB1*0602</td>
</tr>
</tbody>
</table>
HLA class II distribution in Congolese with hyperthyroidism: preliminary results

HLA-DR3 allele was detected in 7.7% of the cases in our control group, whereas its frequency is 22.2% in the hyperthyroid group. The low frequency of HLA-DR3 gene was also demonstrated by Mbayo, who found frequencies of 9.5% by the serologic method and 10.44% by the biologic molecular technique using the PCR [21]. In spite of its low frequency, this gene is very often implicated in the thyroid diseases in the Caucasian populations. The relative risk of atrophic form of Hashimoto thyroiditis is multiplied by 2.6, whereas the relative risk for Graves’ disease varies from 3.5 to 3.7 in the European patients [4, 6]. Our results suggest that hyperthyroidism susceptibility would be more often associated to HLA-DR3/DR11,13, DR14 genotype (33.3% of our cases) than to a single HLA-DR3 allele or a homozygote HLA-DR3/DR3 (0 case in our series).

Association between exophthalmopathy and genotypes HLA in the hyperthyroid patients is shown in tableau IV. This table shows that 6 of 9 patients with hyperthyroidism (66.6%) have an exophthalmopathy, and that DR3 allele or allele group DR11,14,14 are present in 83.3% of these patients.

In spite of a controversy about the implication of HLA genes in the development of the Graves’ ophthalmpathy [29, 30, 33], the study showed that the majority of our hyperthyroid patients with ophtalmopathy (66.7%) have, either DR3 allele, or allele group DR11,13,14 in their respective genotype. Indeed, Villaneuva and al. [31] failed to demonstrate a positive correlation between HLA-DR3 and severe ophthalmpathy in the patients with hyperthyroidism, in comparison with the hyperthyroid patients or control-subjects who have the same alleles, but are free of ophthalmpathy. Authors suspected other environmental factors (particularly smoking) to be operating in the development of hyperthyroidism in genetically predisposed individuals. This drug was not mentioned as an isolated precipitating or a trigger factor in our patients, but results of our preliminary study strongly agree with an important role of DR3 and DR11,13,14 alleles in the developement of Graves’ophthalmpathy.

**Potential susceptibility Genes**

This limited series of patients has shown a relatively high frequency of DR11,13,14 allele group, HLA-DR3 allele, and DR3/DR11,DR13,DR14 genotype in hyperthyroid patients (tableau II). Homozygote HLA-DR3/DR3 subject (1 case) was free of hyperthyroidism, unlike a high relative risk of the disease induced by this haplotype in the Caucasian White populations [6, 10, 11].

Susceptibility to hyperthyroidism would be more often associated to the DR3/DR11,13,14 genotype than to a single DR3 allele or to the DR3/DR3 homozygote. The two clearly separated in our sample) and thyroid disease are rare in the Caucasian people, except for the aforesaid association between HLA-DR5 allele and the hypertrophic form of lymphocytic chronic thyroiditis (Hashimoto thyroiditis) on the one hand and, on the other hand, between the atrophic form of this disease and HLA-DR3 allele [26, 32]. Thus, data from this preliminary study suggest that allele group DR11,13,14 would play an important role in the development of the Graves’disease in Congolese population in Kinshasa. Up to day, little is known about the role of allele group HLA-DR13,14 (or DR6) in the genesis and development of hyperthyroidism, even in the industrialized countries.

**DQB1*0602 and DQB1*0302 alleles**

Badenhoop and al. [2] demonstrated that a significant susceptibility to the Graves’ disease or to Hashimoto thyroiditis was associated to the HLA-DQ2 allele, and that this susceptibility was more pronounced when transmitted by the father to his daughter. Thus, authors proposed the existence of interaction between a chromosome-X factor and HLA-DQ haplotypes in the appearance of Graves’ disease, Hashimoto thyroiditis and diabetes mellitus type 1.

Genotype HLA-DR2/DR2-DQB1*0602 was detected in 54% of our control group, whereas only 11,1% of the hyperthyroid patients have this genotype (O.R: 0.110; Fisher: p=0.048). Indeed, in the case of diabetes mellitus type 1, and in opposition to the DQB1*0302 allele, DQB1*0602 allele could bind with high affinity the diabetogenic oligonucleotide and “isolate” it from susceptibility gene, even if this gene is included in the same haplotype. This “isolation” results in abnormal configuration of the molecule which must be presented to the lymphocytes by the APC, and makes it unable to activate the immune system. According to this hypothesis, DQB1*0602 allele would be a protective factor against the development of hyperthyroidism in the subjects with allelic group DR11,13,14, in the manner of DR2 allele in diabetes mellitus type 1 in the White Caucasians [13].

**HLA-DR11,13,14 Genes**

Allele group DR11,13,14 was detected in 50% of hyperthyroid patients, instead of 23.1% in the healthy individuals group (p=0,02). Data indicating the correlation between HLA-DR5 allele (or allele group DR11,12 not

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following alleles, DR2 and DQB1*0602, as well as the genotype HLA-DR2/DR2-DQB1*0602, may be considered, in our series, as resistance genes to Basedow/Graves’ disease, or to hyperthyroidism in general.

CONCLUSIONS

These preliminary results have shown the predominance of HLA-DR2 and HLA-DQB1*0602 alleles in the control group, with respective frequencies of 61.5% and 89%. Allele group DR11,13,14 is dominant in the hyperthyroid group and represents 50% of the patients. Our results suggest that HLA-DR2, HLA-DQB1*0602 alleles and DR2/DR2-DQB1*0602 haplotype would constitute the resistance factors against the hyperthyroidism. DR3 allele, allele group DR11,13,14 and genotype HLA-DR3/DR11,13,14 would be considered as susceptibility factors to hyperthyroidism or to Graves’exophthalmopathy. Nevertheless, a large and profound study is necessary to confirm our results.

ACKNOWLEDGEMENTS

Authors are very grateful to the professors Raffaella Buzzetti and Alberto Signore, all from the University of Roma, Italy, for their encouragement and for the reagents necessary for the realization of this study. Thanks to doctor Andrea Galgani, from the Department of Clinical Science Endocrinology at Polyclinico Umberto I, Rome,Italy, for analysing of our DNA extracts. We are also grateful to ISORBE for the financial support granted for this first part of our researches in the thyroid domain. Thanks to madam H. Nzuzi, from the Regional Center of Nuclear Studies of Kinshasa (CREN-K) for the preparation of our samples before their shipment to Roma.

RÉFÉRENCES


