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Genetic epidemiology of host predisposition microfilaraemia in human loiasis

A. Garcia[1,2], L. Abel[2], M. Cot[1], P. Richard[3], S. Ranque[3], J. Feingold[4], F. Demenais[5], M. Boussinesq[3] and J-P. Chippaux[3]

1 *Institut de Recherche pour le Développement (IRD/ORSTOM), OCEAC, Yaoundé, Cameroun*
2 *Institut National de la Santé et de la Recherche Médicale (INSERM) – Unité 436, Hôpital Pitié-Salpétrière, Paris, France*
3 *IRD/ORSTOM, Centre Pasteur, Yaoundé, Cameroun*
4 *INSERM – Unité 155, Paris, France*
5 *INSERM – Unité 358, Paris, France*

Summary Evidence is accumulating from experimental and human studies that genetic factors are involved both in the control of infectious diseases and in the regulation of infection levels and clinical presentation. So far few studies have investigated the role of these genetic factors in human infection by the filarial parasite *Loa loa*. We present a segregation analysis on 74 nuclear families who live in the tropical rainforest of southern Cameroun and are exposed to homogeneous loiasis transmission. The results indicate that there is a genetic predisposition to be microfilaraemic and that predisposed subjects might be genetically unable to mount an efficient immune response against loiasis antigens. This individual susceptibility could explain at least in part why the prevalence of infection (microfilaraemic individuals) does not usually exceed 30% of the exposed population in hyperendemic regions. Further genetic studies, based on linkage analysis using both familial information and genetic markers, will help to identify the nature of the genetic factors predisposing to microfilaraemia.

keywords loiasis, genetic epidemiology, immunity

correspondence Dr A. Garcia, Institut Pierre Richet – OCCGE; BP 1500, Bouake. Côte d'Ivoire. E-mail: Andre.Garcia@orstom.ci

Introduction

The filarial parasite *Loa loa*, which is found in the tropical rainforests of Western and Central Africa, causes a chronic infection in humans with two characteristic clinical features, Calabar swelling and subconjunctival migration of adult worms (Klion *et al.* 1991). Rare but severe complications including endocardial fibrosis and nephropathies have been decribed (Andy *et al.* 1981; Ngu *et al.* 1985). Whereas exposure to *Loa loa* may approach 100% in endemic areas (Gordon *et al.* 1948; Eveland *et al.* 1975; Goussard *et al.* 1984), the prevalence rate of *Loa loa* carriers (microfilaraemic individuals) does not usually exceed 30% of the population. Repeated cross-sectional suveys have shown that microfilaraemic individuals generally remain identical over time (Van Hoegaerden *et al.* 1987; Noireau & Pichon 1992). These results were confirmed by a longitudinal epidemiological survey including several parasitological measurements per individual during a one-year follow-up, which showed important long-term stability of both the microfilarial status of subjects exposed to repeated infections (microfilaraemic/amicrofilaraemic) and the level of parasitaemia in microfilaraemic individuals (Garcia *et al.* 1995). It has been suggested that the absence of *Loa loa* microfilariae in a high proportion of the population and the long-term stability of the microfilarial status may be due to genetic factors involved in susceptibility or resistance to loiasis (Van Hoegaerden *et al.* 1987; Noireau & Pichon 1992). There is evidence for genetic control of susceptibility to parasitic infections in humans (Ottesen *et al.* 1981; Abel *et al.* 1991; Hill *et al.* 1991; Marquet *et al.* 1996; Garcia *et al.* 1998a), and experimental studies in animal models suggest that genetic factors could be involved in filarioses (Wakelin & Blackwell 1988; Folkard & Bianco 1995). However, to our knowledge no specific results have been reported concerning genetic factors involved in human loiasis.

Investigating the genetic susceptibility or resistance to human infection progressed along two complementary ways: case-control studies, mainly aimed at testing associations between clinical or immune responses to infection and genetic markers such as HLA antigens (Hill *et al.* 1991) and familial studies to explore the role of a major gene involved in human

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susceptibility or resistance to infection (Abel *et al.* 1992; Garcia *et al.* 1998a). The characteristic feature of familial studies is the statistical dependence of family data, and the modelling objective in genetic epidemiology is to explain these familial correlations in terms of biological relationships and shared environment. In familial studies segregation analysis is the first step in the effort to determine the mode of inheritance of a complex trait; this does not require typing of genetic markers. Segregation analysis is a statistical method that attempts to detect the existence of a single gene, called major gene, taking into account all other risk factors (individual, behavioural or environmental) significantly involved in the variability of a complex trait denoted as the phenotype. We refer to the gene as a major gene in a biometric sense, i.e. its effect on variability is large enough to be detected without assuming that it alone accounts for all the dependence among relatives. It is important to notice that a large number of genes, environmental and cultural factors can contribute to the variability of the trait, although only the effect of one or a few genetic loci may be discernible, at least statistically, in the phenotype.

Our study aimed at investigating the existence of a genetic control mechanism involved in the susceptibility or resistance to human *Loa loa* infection, with the main goal of verifying a genetically based ability to limit or eliminate microfilariae. Segregation analysis was performed on a qualitative phenotype denoted as the Individual Microfilarial Status (IMS) defined from several parasitological measurements taken during a 1-year follow-up.

Materials and methods

Study area and familial data

Between April 1992 and April 1993 an epidemiological survey was conducted in a Southern Camerounian village in the tropical rainforest to investigate the stability over time of the microfilarial status (microfilaraemic/nonmicrofilaraemic) of subjects permanently exposed to *Loa loa* transmission, and the factors influencing this microfilarial status. The population was clearly informed and the protocol of the study, including blood samples, was approved by traditional (chief and village committee), local and governmental authorities (Public Health Ministry). The characteristics of the village population, 667 individuals from the Ewondo ethnic group, are detailed in Garcia *et al.* (1995). The familial study involved a randomly selected sample of 74 nuclear families. Each family was composed of at least 3 subjects, and the entire family sample totaled 344 particpants. Inhabitants of the village not included in the family study were old people living alone, individuals with uncertain familial relationships and people who refused to participate.

Parasitological measurements and phenotype of interest (IMS)

Parasitological measurements were taken every two months during the 1-year follow-up from calibrated thick blood smears (30 μl) obtained by fingerprick between 1000h and 1500h. The blood smears were stained with Giemsa and microfilariae identified and counted to express parasite density as the number of microfilariae/30 μl. Since we were interested in the factors influencing the probability of being microfilaraemic, the outcome of each measurement was coded as a binary variable denoted Elementary Microfilarial Status (EMS) and coded 0 when no microfilariae were present in the thick blood smear, or as 1 when microfilariae were found. For more than 60% of the population the EMS was equal to 0, meaning that these subjects never harboured microfilariae in their blood during the 1-year follow-up. Of 128 individuals sampled 6 times, 107 (84%) never modified their EMS and of the 21 subjects who did, 11 modified their EMS only once over 6 measurements (Garcia *et al.* 1995).

To obtain a unique variable accounting for the overall degree of infection during the survey and taking into account the long-term stability of the EMS, a binary variable denoted as the Individual Microfilarial Status (IMS) was defined. For a given individual the IMS was coded as 0 when all the EMSs were equal to 0, and the IMS was coded as 1 if at least one EMS was equal to 1. Twelve individuals who presented no microfilariae in all measurements, except one with a very low number of microfilariae (less than 3), were classified as unknown IMS. Another 35 individuals were coded as unknown phenotype because they were sampled only once during follow-up. Finally, of 344 study subjects, 218 were classified amicrofilaraemic (all EMS = 0; IMS = 0), 79 as microfilaraemic ($\geq$ 1 EMS = 1 with an important number of microfilariae; IMS = 1), and 47 as unknown phenotype. The segregation analysis used the IMS as the binary phenotype of interest.

Factors influencing the individual microfilarial status

The variability of IMS can be explained by an unobserved genetic factor but also by individual, behavioural or environmental measured risk factors. Risk factors which have a significant influence on the IMS should be taken into account in segregation analysis. The five measured factors we tested as potentially influencing the IMS were: sex; area of residence (4 areas); activity: field workers spending several hours per day in the fields and forest, and nonfield workers (teachers, schoolchildren, older people, etc.); age in years, which was considered as a quantitative variable; and percentage of time spent indoors between 0600h and 2200h, denoted as indoor time and used as a binary variable (indoor time less or more

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than 50%). Indoor time was assessed by two Camerounian sociologists from the Camerounian University of Science who spent two months in the village living with the population. The influence of these measured risk factors on the IMS is described elsewhere (Garcia *et al.* 1995) and briefly summarized in the Results section.

Statistical methods

Effect of measured risk factors on IMS

Pearson χ^2 tests were used for univariate analyses, and multivariate analysis was performed by means of multiple logistic regression. BMDP statistical software (University of California, Los Angeles, CA) was used for all computations.

Segregation analysis

A regressive approach, classically used in epidemiology, was proposed by Bonney (1986) to construct comprehensive models by direct use of the biological relationships among relatives in defining simple patterns of familial dependence. These models specify a regressive relationship between each individual's phenotype (i.e. the probability of being microfilaraemic in our study) and explanatory variables including a major gene effect resulting from the segregation of two alleles (A, a); the phenotypes of older relatives (antecedents); and measured individual, behavioural or environmental covariates. For a binary phenotype, as the one we used (IMS = 0/IMS = 1), this relationship is expressed by means of a regressive logistic model (Bonney 1986). The parameters of the logistic model corresponding to these three classes of explanatory variables are summarized in Table 1.

The parameters of the major gene effect are q, the frequency of A, the allele predisposing to be microfilaraemic, and the three genotype-specific baseline risks adjusted on covariates, a_{AA}, a_{Aa} and a_{aa}, corresponding to the logic of the probability of being microfilaraemic for individuals with genotypes AA, Aa, and aa, respectively. Dominance of allele A is defined through constraints on the baseline risks, e.g. $a_{AA} = a_{Aa}$ (allele A is dominant), $a_{Aa} = a_{aa}$ (allele A is recessive), within the general case of codominance a_{AA}'a_{Aa}'a_{aa}. If the parent-offspring transmission of allele A is assumed to follow Mendelian laws, no additional parameters are necessary, and the major effect is due to the segregation of a major gene. However, the Mendelian transmission hypothesis should be tested against alternative hypotheses of parent-offspring transmission to avoid false conclusions regarding the presence of a major gene (Demenais *et al.* 1986). To perform these tests, three parameters, called transmission probabilities and noted $t_{AA->A}$, $t_{Aa->A}$ and $t_{aa->A}$, were defined (Elston & Stewart 1971); these parameters represent the probability of transmitting A to an offspring for individuals AA, Aa and aa, respectively. Under the Mendelian hypothesis, these probabilities are fixed to the following values: $t_{AA->A} = 1$, $t_{Aa->A} = 0.5$ and $t_{aa->A} = 0$, whereas under a general parent-offspring transmission hypothesis these probabilities are free parameters estimated between 0 and 1. This latter case corresponds to a parent-offspring transmission more complex than a single major gene, and is generally denoted as a major effect transmission. Furthermore, a no-parent-offspring transmission hypothesis has to be tested before to conclude Mendelian segregation of a major gene (Demenais *et al.* 1986). Under this hypothesis of no-parent-offspring transmission, the three transmission probabilities are equal ($t_{AA->A} = t_{Aa->A} = t_{aa->A}$), and family resemblances could be explained by the transmission of cultural (nutritional habits, smoking, etc.) or behavioural factors rather than by a single genetic model. To conclude the segregation of a major gene, two conditions must be met: the Mendelian hypothesis must hold when tested against the general parent-offspring transmission hypothesis; and the no parent-offspring transmission hypothesis fails when tested against the general parent-offspring transmission hypothesis.

Table 1 Parameters used in regressive models for segregation analysis

Effect	Parameters	Signification
Major effect	q	Frequency of allele A predisposing to be microfilaremic
	$\alpha_{AA}, \alpha_{Aa}, \alpha_{aa}$	Genotype-specific baseline risks for individuals AA, Aa and aa respectively
	$\tau_{AA->A}, \tau_{Aa->A}, \tau_{aa->A}$	Transmission probabilities†
Residual family dependences from major effect	$\gamma_{FM}, \gamma_{FO}, \gamma_{MO}, \gamma_{SS}$	Phenotype dependence between father-mother, father-offspring, mother-offspring and sib-sib respectively
Covariates	β_g‡	Regression coefficient

† When the transmission probabilities are fixed to their Mendelian values ($\tau_{AA->A} = 1$, $\tau_{Aa->A} = 0.5$, $\tau_{aa->A} = 0$, the major effect is a major gene. ‡ May vary with genotype in case of interaction between genotype and covariate (β_{AA}, β_{Aa}, β_{aa}).

The dependence of an individual's phenotype on antecedents' phenotypes is expressed in terms of residual family dependences which account for the observed phenotypic resemblance between relatives residual from the major gene effect, without assuming its behavioural, environmental or genetic origin. Different patterns of familial dependences can be considered, and in the class D model used in this study, 4 family dependences are specified (Bonney 1986): g_{FM}, the father-mother (or spouse) dependence; g_{FO}, the father-

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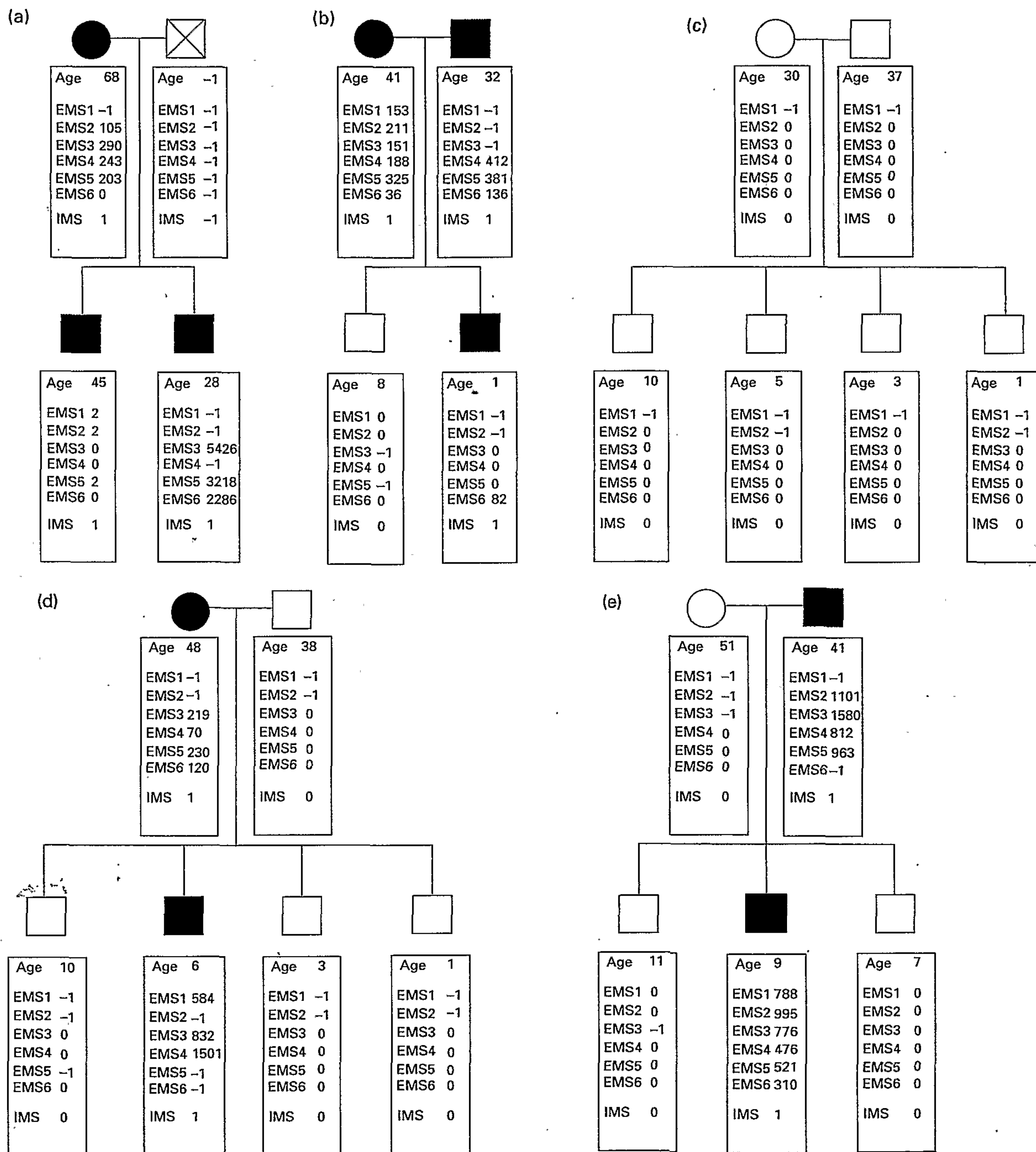

Figure 1 Five nuclear families (a–e) indicating for each person age (years), EMS for each measurement (1–6) expressed as the number of microfilariae counted in 30 μl of blood (–1 means that the person was not present) and the IMS. ■ Microfilaraemic individual (IMS=1); ☒ Individual with no measurement (unknown phenotype); □ Amicrofilaraemic individual (IMS=0).

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offspring dependence; g_{MO}, the mother-offspring dependence; and g_{SS}, the sib-sib dependence. In our analysis, g_{FM} was never significant and fixed equal to 0.

The effects of measured covariates are parametrized in terms of regression coefficients (bs) as usually done in linear regression. An interesting feature of the regressive models is that they allow to test for an interaction between a covariate and the major gene effect. For each covariate the genotype-specific regression coefficients are denoted b_g,with g = AA, Aa or aa. Under the hypothesis of no interaction, we have $b_{AA} = b_{Aa} = b_{aa}$, whereas the three bg parameters are estimated in the presence of interaction.

Whereas the b parameters can be easily interpreted in terms of odds ratio (OR) as usually done in logistic regression, the interpretation of the g parameters is much more complex, particularly when the proportion of unknown phenotypes in the population is important (Demenais *et al.* 1992). However, in some conditions corresponding to the precise pattern of familial dependences, g parameters could be interpreted in terms of conditional OR; for example, the conditional mother-offspring OR can be expressed from the mother-offspring dependence parameter as $OR_{MO} = \exp(g_{MO})$ (Abel *et al.* 1993).

The estimation of relevant parameters and the strategy of tests are based on maximum likelihood principles. The likelihood of the sample of families is computed under different hypotheses (or models), and nested hypotheses are tested by means of the likelihood ratio criterion: if the null hypothesis is true, minus twice the natural logarithm of the likelihood ratio is distributed as a c^2, the degrees of freedom (d.f.) being equal to the difference between the number of independent parameters estimated under the two hypotheses. As mentioned before, the parent-offspring transmission of the major effect should be tested. To conclude the presence of a *major gene* instead of a *major effect*, two conditions must be met: the null hypothesis of Mendelian transmission ($t_{AA->A} = 1, t_{Aa->A} = 0.5$ and $t_{aa->A} = 0$) must hold when compared to the general transmission hypothesis (free t's), and the no-parent-offspring transmission (equal t's) hypothesis must fail against the general transmission hypothesis (free t's). All computations were performed using the computer program REGRESS (Demenais & Lathrop 1994), which incorporates the regressive approach into the LINKAGE package (Lathrop *et al.* 1984).

Results

Descriptive results

From the whole population of 667 individuals 74 nuclear families totalling 297 subjects with known IMS were included in the familial study (Figure 1). Not all subjects attended every measurement (mean number of measurements per individual = 3.8; range 2–6), but no effect of the number of measurements on the variability of IMS was detected. The mean age of the familial population was 28.5 years (1–80) with a sex ratio (male:female) of 1.01. The prevalence of microfilaraemic individuals in the familial population (i.e. IMS = 1) was not significantly different from the prevalence in the whole population (26.6% and 28.3%, respectively).

Influence of measured risk factors on IMS

Using a univariate method, neither sex nor habitation area had a significant effect on the IMS. Several entomological surveys during the follow-up confirm the homogeneity of vectorial activity within the study area (Chippaux *et al.* personal communication). Microfilaraemic individuals were significantly older than nonmicrofilaraemic subjects ($P < 0.001$) with a mean age (SEM) of 37.9 years (1.54) and 23.9 years (1.01), respectively. Field workers were significantly more microfilaraemic than nonfield workers, 33% and 17% repectively ($P < 0.01$), and the proportion of microfilaraemic people was significantly higher in the population spending less than 50% of their time indoors ($P < 0.02$). Age may be considered a confounding factor since field workers and people with less than 50% indoor time are older and, when multivariate analysis was performed using logistic regression with age, activity and indoor time as explicative variables, age remained the only significant factor influencing the prob-

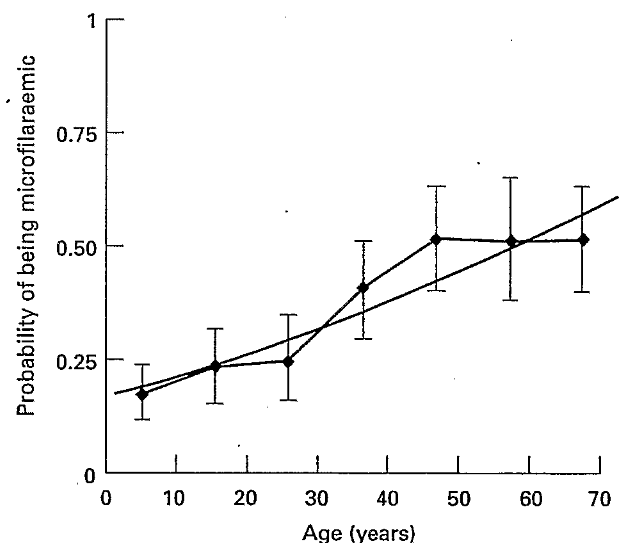

Figure 2 Influence of age (years) on the probability of being microfilaraemic. ● Observed proportion with 95% confidence intervals (------) of microfilaraemic subjects within seven age groups. —— Probability of being microfilaraemic predicted with the logistic model including age as a quantitative variable.

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Table 2 Contingency tables for father-offspring and mother-offspring IMS association

	Parent	
Offspring	IMS = 1	IMS = 0
Father to offspring IMS association		
IMS = 1	10	6
IMS = 0	48	49
OR_{FO} = 1.70; (95%CI = 0.57;5.04) (NS)		
Mother to offspring IMS association		
IMS = 1	12	12
IMS = 0	28	88
OR_{MO} = 3.14; (95%CI = 1.27;7.70) ($p < 0.01$)		

ability of being microfilaraemic ($P < 0.0001$). Figure 2 represents the evolution of the probability of being microfilaraemic with age. Consequently, age was the only covariate included in segregation analysis.

Familial analysis

Prior to segregation analysis we investigated the possibility of familial aggregation by constructing a contingency table according to the IMS status of parents and offsprings (Table 2). The results were consistent with a significant association ($P < 0.01$) between mother and offsprings IMS, with a mother-offspring OR (OR_{MO}) equal to 3.14 (95% confidence interval (CI_{95}) = 1.27; 7.70). The probability of being microfilaraemic for a child born to a microfilaraemic mother was 0.30 compared to 0.12 when the mother was amicrofilaraemic. No significant association was observed between father and child (OR_{FO} = 1.70; CI_{95} = 0.57; 5.04).

Segregation analysis was then performed and the results are presented in Table 3. When a model including father-offspring, mother-offspring and sib-sib dependences (II) was compared to a sporadic model without familial resemblance (I), there was no evidence for familial dependencies (model I *vs.* II; $c^2 = 1.44$, 3 d.f.; $P > 0.5$). However, the only parameter indicating a trend for a familial resemblance, although non-significant, was the mother-offspring dependency parameter ($g_{MO} = 0.62$) whereas the g_{FO} and g_{SS} parameters reached their bound 0. Considering that this scheme of familial dependence (isolated mother–offspring association) was described for other filariases (Hightower *et al.* 1993) and confirmed in our data (Table 2), and taking into account the difficulties of interpreting g parameters (Abel *et al.* 1993), we decided to further the segregation analysis. When estimating a co-dominant major gene model with residual mother-offspring dependency (model IIIa), the a_{Aa} parameter tended towards a_{aa} (i.e. the codominant model is equivalent to a dominant model), and g_{MO} reached its bound 0. Therefore the c^2 assessing the presence of a major gene (model II *vs.* III-a; $c^2 = 6.53$) has an indeterminate number of dfs comprised between 1 and 3. With a very conservative strategy considering 3 dfs, the test is nonsignificant at the 0.05 level ($P = 0.088$), whereas it is significant ($P = 0.038$) when considering 2 dfs (e.g. when testing the presence of a dominant gene). Therefore we pursued the analysis under the hypothesis of the best-fitting Mendelian model explaining the familial distribution of IMS, i.e. a dominant major gene with no residual familial correlation (IIIb). Note that interaction between age and genotype was never significant. The Mendelian transmission hypothesis of this dominant major gene ($t_{AA->A} = 1$, $t_{Aa->A} = 0.5$ and $t_{aa->A} = 0$) held compared to a general transmission hypothesis where the transmission probabilities were estimated (model IIIb *vs.* V; $c^2 = 1.29$, 3 d.f.; $P > 0.5$), and the hypothesis of no-parent-offspring transmission ($t_{AA->A} = t_{Aa->A} = t_{aa->A}$) was rejected (model IV *vs.* V; $c^2 = 8.8$, 2 d.f.; $P < 0.02$). Finally, the results of transmission tests are consistent with the existence of a dominant major gene predisposing individuals to be microfilaraemic. Under model IIIb, the frequency of allele A predisposing to be microfilaraemic was estimated at 36%, indicating that assuming Hardy–Weinberg equilibrium, 13% of AA homozygous individuals and 46% of Aa heterozygous individuals are predisposed to be microfilaraemic. The evolution of the cumulative probability to be microfilaraemic (penetrance) with age is presented in Figure 3. For AA and Aa predisposed subjects, penetrance is around 80% by the age of 50 whereas it remains less than 1% for aa resistant individuals by the same age.

Discussion

This familial study, investigating potential genetic control in human loiasis, is consistent with a host genetic predisposition to be microfilaraemic. Although our analysis did not permit a definitive conclusion as to the nature of the genetic model involved, the results are compatible with a dominant major gene model controlling the IMS. Under this latter hypothesis, parameter estimates indicate that around 59% of the population are predisposed to be microfilaraemic whereas 41% of the exposed population have a very low lifetime risk to harbour microfilariae. This genetic model could account for the observation that within hyperendemic regions, the prevalence of infection does not usually exceed 30% of the exposed population. Further analyses in larger family samples will overcome the difficulties of our analysis and precisely describe the nature of these genetic factors.

Whatever was the pattern of familial dependences tested, both the sib-sib parameter and the father-offspring parameter alway equalled 0, whereas the mother-offspring parameter

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Table 3 Segregation analysis of IMS using regressive model

Model	q	α_{aa}	α_{Aa}	α_{AA}	$\tau_{AA->A}$	$\tau_{Aa->A}$	$\tau_{aa->A}$	β_{age}	γ_{FO}	γ_{MO}	γ_{SS}	No. of estimated parameters	−2LnL*
I. Sporadic with age effect	(0)†	−1.85	$(=\alpha_{aa})$	$(=\alpha_{aa})$	–	–	–	0.03	–	–	–	2	317.47
II. Familial Dependencies (FD)	(0)	−1.68	$(=\alpha_{aa})$	$(=\alpha_{aa})$	–	–	–	0.03	0.0	0.62	0.0	5	316.03
III. Mendelian Major Gene (MG)													
III-a Codominant MG with residual FD and without interaction	0.36	−1.39	−1.39	−6.88	(1)	(0.5)	(0.0)	0.06	(0.0)	0.0	(0.0)	6	309.50
III-b Dominant MG without residual FD and without interaction	0.36	−1.39	(−1.39)	−6.88	(1)	(0.5)	(0.0)	0.06	(0.0)	(0.0)	(0.0)	4	309.50
IV. No parent-offspring transmission (equal τ's) without residual FD and without interaction	0.46	−1.55	(−1.55)	−14.9	0.47	(0.47)	(0.47)	0.06	(0.0)	(0.0)	(0.0)	5	317.01
V. General transmission (free τ's) without residual FD and without interaction	0.37	−1.31	(−1.31)	−22.8	0.55	0.56	0.0	0.04	(0.0)	(0.0)	(0.0)	7	308.21

† () indicates that the parameter is fixed at the corresponding value. *Minus twice the logarithm of the likelihood.

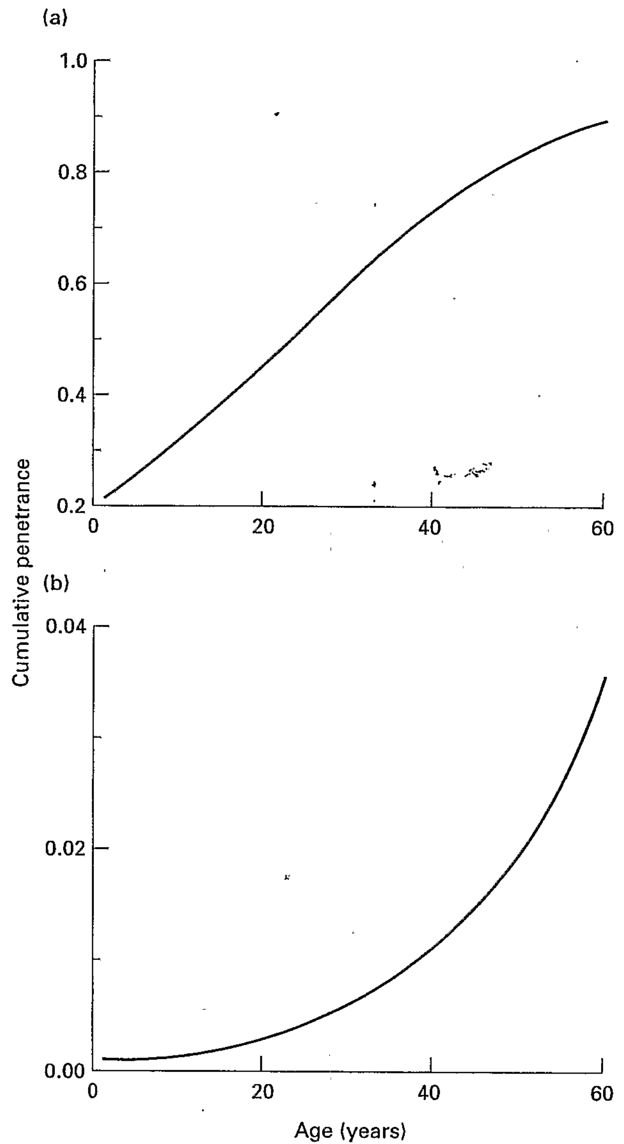

Figure 3 Evolution of the cumulative probability of being microfilaraemic (penetrance) with age (a) for individuals with genotype AA and Aa (predisposed to be microfilaraemic) and (b) for individuals with phenotype aa (not predisposed to be microfilaraemic).

estimation was consistent with a trend for mother-offspring dependence. Furthermore, using a more classical approach, the same pattern of mother-offspring aggregation was confirmed. The absence of significant familial dependency detected during segregation analysis may be explained, at least in part, by the lack of power of the analysis due not only to the small size of family sample, but also to the small number of families with at least two microfilaraemic individuals (30%). Furthermore, the important proportion of sub-

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jects with unknown phenotype in our family sample (14% of the whole population) may lead to difficulties in interpreting g parameters (Demenais *et al.* 1992). However, with the pattern of familial dependences in our data (i.e. $g_{FO} = 0$, $g_{SS} = 0$ and $g_{MO} = 0$) the mother-offspring dependence parameter may be interpreted in terms of conditional OR (Abel *et al.* 1993), and in that particular case, $\exp(g_{MO}) = 1.86$ represents the mother-offspring OR after conditioning each individual's phenotype on those of preceeding relatives. This conditional OR is lower than the marginal OR computed from the contingency table assuming that all observations are independent, which probably overestimates the actual value of familial aggregation (Hunt *et al.* 1986). The same scheme of familial aggregation was found, using the same statistical approach, for other parasitic diseases such as leishmaniasis (Cabello *et al.* 1995) and bancroftian filariasis (Lammie *et al.* 1991; Hightower *et al.* 1993). In the latter case, Hightower *et al.* (1993) showed that children in households with a microfilaraemic mother were more frequently microfilaraemic than offspring with an amicrofilaraemic mother ($P < 0.0001$), whereas no difference was noted in children according to paternal status. Although the mechanisms which underlie this increased risk are not yet clear, the influence of prenatal sensitization through transplacental transfer of specific filarial antigens has been put forward. One of the consequences of *in utero* repeated antigenic exposure may be the deletion of a restricted set of parasite antigen-specific T-cell clones, and thus the immune system of children born from microfilaraemic mothers could be unable to recognize and delete filarial antigens (Weil *et al.* 1983; Lammie *et al.* 1991; Carlier & Truyens 1995). However, even though this mechanism may be proposed for loiasis, no evidence for placental transfer of loiasis antigens was found in 92 mother-cord blood samples (Van Hoegaerden & Akue 1986). These observations also raise the problem that the mother's current infection status at the time of the surveys does not necessarily reflect her status at the time of the child's birth. The hypothesis of genetic acting on the host for controlling individual microfilarial status may also be invoked to explain mother-offspring dependence.

Experimental studies have shown the involvement of a genetically based ability to produce specific IgM after infection with *Dipetalonema vitae* (Wakelin & Blackwell 1988). Host immunity against a specific larval stage of the filarial parasite *Acanthocheilonema vitae* has also been put forward to explain the control of total worm burden after reinfection in jirds (Eisenbeiss *et al.* 1994). The same parasite-driven immune mechanism is proposed to explain the limited average individual burdens in people continuously infected with *Onchocerca volvulus* (Albiez *et al.* 1988). Considering the development of *Wuchereria bancrofti* infection, Gordon (1955) suggested a genetically mediated division of the population into 'good' hosts (presence of parasite and free of clinical manifestation) and 'bad' hosts (clinical disease and low or no parasitaemia), and Brengues (1975) added a third category defined as refractory (neither clinical manifestation nor microfilaraemia). In loiasis infection the same discordance between clinical manifestations and parasitaemia has been described (Nutman *et al.* 1986, 1988) as potentially due to differences in the modulation of immune response to parasite antigens (Klion *et al.* 1991). Wassom & Kelly (1990) reviewed the role of genetic control in susceptibility or resistance to parasitic diseases, and individuals genetically predisposed to microfilaraemia could be unable to mount an efficient immune response against loiasis antigens. It is likely that the HLA region (Rilley *et al.* 1991), but also non-HLA genes such as T cell receptor or immunoglobulin genes, are involved not only in human genetic regulation of immune responses to infection or vaccination (Beck *et al.* 1995), but also in modulation of disease (McGuire *et al.* 1994). A case control study in The Gambia showed that an HLA class I antigen and an HLA Class II haplotype were independently associated with protection from severe malaria (Hill *et al.* 1991, 1992) and the implications of genes independent of the HLA region were demonstrated by Ruwende *et al.* (1995). Familial studies also found evidence for the genetic control of parasite infection levels in human malaria (Abel *et al.* 1992; Garcia *et al.* 1998a) and schistosomiasis (Abel *et al.* 1991). The locus controlling the intensity of *Schistosoma mansoni* infection has been mapped to chromosome 5q31-q33, a region containing several candidate genes encoding immunological molecules (IL4, IL9 ...) (Marquet *et al.* 1996), and the same chromosomal region may be involved in the control of *Plasmodium falciparum* infection levels (Garcia *et al.* 1998b). For filarial diseases, discordant results exist concerning the involvement of HLA antigen in the control of the expression of infection. Chan *et al.* (1984) found a significant difference in the frequency of HLA-B15 antigen between patients with filarial elephantiasis and normal controls, whereas Ottesen *et al.* (1981) found evidence for a family clustering, compatible with genetic transmission of susceptibility to bancroftian filariasis, although it was not associated with the HLA-A or B locus.

These results emphasize the major role of genetic factors in the control of susceptibility or resistance to parasitic infections. Knowledge of such genetic factors could help improve our understanding of the physiopathology of filariasis and may have practical implications not only for new chemotherapies or vaccines, but also for control strategies, since microfilaraemic individuals are probably the only reserve of parasitic material available to the vector.

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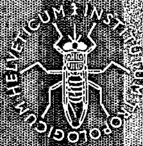

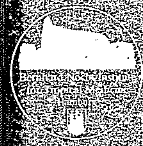

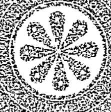

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