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Genetic inheritance pattern in prurigo Hebra

Siti Aisah Boediardja,[1] Wahyuning Ramelan,[2] Santoso Cornain[3]

[1]Departement of Dermato-Venereology, Faculty of Medicine, University of Indonesia;[2]Department of Biology Faculty of Medicine, University of Indonesia;[4]Department of Pathology, Faculty of Medicine, University of Indonesia.

ABSTRACT A study was conducted to analyze the multifactorial genetic inheritance pattern in prurigo Hebra (PH). Fifty probands (PH patients) consisting of 11 males and 39 females, with age ranged from 5-30 years were included in this study. A three-generation family tree was obtained from each subject, from which a total of 79 families were eligible for analysis. For each family the possible mode of inheritance, namely autosomal dominant (AD) or autosomal recessive (AR), was predicted. The families were then grouped according to the mode of inheritance. Analysis was conducted using Chi-square test, comparing the observed occurrence of PH and the expected value for each mode. To rule out mutation, the second method was applied, which only families with more than one affected child were analyzed, was used. The genetic inheritance pattern was not consistently compatible either with AR or AD. This finding, and other supporting facts, such as female preponderace, the role of HLA and the lower morbidity rate compared to the expected rate in AR or AD mode, indicated that the genetic inheritance of PH follows a multi-factorial pattern. **[Paediatr Indones 2001:41:76-81]**

Keywords: *prurigo Hebra, multifactorial gene inheritance, pedigree analysis*

PURIGO HEBRA (PH) IS A CHRONIC SKIN INFLAMMATORY disease that mostly affects children. The diagnosis is readily established based on the skin morphology, especially the characteristic prurigo papules on the extensor extremities and face, which at times may be extended to the buttocks and abdomen, with symmetrical distribution.[1-5] Acute lesions of PH appear as dome-shaped papules on erythematous base with tiny vesicle on their top, when ruptures is followed by erosion and crust. The chronic stage shows hyperpigmented and hyperkeratotic skin with lichenifications. In 1997, PH ranked high among the ten most common skin diseases at the Department of Dermato-veneorology, Dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

Correspondence: Siti Aisah Boediardja, M.D., Ph.D. Department of Dermatoveneorologi, Medical School, University of Indonesia, Jalan Salemba No. 6, Jakarta 104330, Indonesia

The pathogenesis of PH has not been completely understood. [1-5] There has never been a study on the role of genetic inheritance reported so far. Most investigators assume that the inheritance follows a multifactorial mode, based on the frequent occurrence among members of an affected family and the presence of influencing factors such as bad hygiene, poor nutrition, and hypersensitivity to insect bite.[1-7] The multifactorial trait is determined by multiple causes of extrinsic (environment) and intrinsic (genetic) factors. The general formula has been given as f = g+e, where f stands for phenotype, g for genetic and e for environment.[8-11] We analyzed the pedigree of PH patients treated at Dr. Cipto Mangunkusumo Hospital to determine the mode of inheritance of the disease.

Methods

The subjects (probands) were PH patients at the Department of Dermato-Venereology, Dr. Cipto Ma-

TABLE 1. PREDICTED MODE OF INHERITANCE IN 79 FAMILIES OF PRORIGO HEBRA PROBANDS

Group	Predicted inheritance & the genotypes	Total no. of family	Total affected children	Total healthy children	Total children	Expected risk
A	AR (H><H/ Rr><Rr)	40	59 (29%)	144 (71%)	203	25%
B	AR (H><PH)/Rr><rr)	4	1 (20%)	5 (50%)	5	50%
C	AR or AD (H><PH: Rr><rr or dd><Dd)	15	19 (40%)	30 (60%)	49	50%
D	AR or M (H><H/Rr><Rr)	20	20 (20%)	79 (80%)	99	25%
	Total	79	99 (28%)	257 (72%)	356	-

Note: AR = automal recessive; AD = autosomal dominant;
M = mutation; H = healthy; PH = Prurigo Hebra

ngunkusumo Hospital, Jakarta. A family tree comprising three generations of each proband was obtained. Should there any family member suspected of having PH, clinical examination was carried out to confirm the diagnosis.

The inheritance mode of autosomal recessive (AR), autosomal dominant (AD), or mutation (M) was predicted, based on the morbidity status of the parents of the affected persons. The phenotype of an affected individual was coded PH and normal individual was coded H. The genotype in AR mode of inheritance was labeled RR, Rr, or rr, with R represented for healthy allele and r recessive (sick) allele. Thus, the genotype of affected individual in AR was rr. The genotype in AD inheritance pattern was labeled DD, Dd, or dd, with D represented for dominant (sick) allele. The genotype of affected individuals in AD was either heterozygote (Dd) or homozygote (DD).[12-16]

The affected families were pooled into groups of possible patterns, i.e., AR, AD, both AR and AD, and M. We used two methods to determine the mode of inheritance. The first method included all families for statistical analysis, while the second, to rule out mutation, only families with more than one 1 affected child were analyzed. The figure was subtracted by one. Statistical analysis comparing the observed risk (O) and the expected risk (E) for each mode was carried out using SPSS 7.5 program f/w and confidence interval analysis (CIA). Significance difference was defined at $p<0.05$.

Results

A total of 50 prurigo Hebra patients (probands) were included, consisted of 11 males and 39 females, with the age ranged from 5 to 30 years with mean 17 (SD 7) years, body weight 39 (SD 14) kg, and height 141 (SD 19)cm.

All probands and affected children had history and clinical manifestations of mosquito bite hypersensitivity, such as papular-urticaria reaction. The mean duration of illness was 9 (SD 6) years, most of them (40%) had suffered for 6-10 years. Forty probands (80%) had good nutritional status using NCHS standard. Females were predominant with female-to-male ratio among unaffected children was 66:33, while among probands it was 39:11.

There were 79 nuclear families total from 50 probands, with 99 family member affected out of 514 total number families and children. The morbidity rate was 18.6%.

Seventy-nine families were distributed in 4 groups, based on the predicted genetic inheritance patterns and the parents' possible genotype (Table 1). The expected risk of each group was the calculated natural risk of having affected children under that particular mode of inheritance.

A. The first method analysis

Data for the first method analysis included all families of affected children, and are summarized in Table 1 for analysis.

1. Group A. The forty families had a total of 203 children, consisted of 59 affected and 144 healthy children. Naturally in AR pattern with healthy heterozygous parents (Rr >< Rr), the expected morbidity risk was 25% so that the expected number of affected children should be 25% x 203 children = 50.75 (Table 2). The mode of inheritance in this group was consistent with AR pattern.

TABLE 2. GROUP A: AR PATTERN, HEALTHY PARENTS (Rr><Rr)

Children	O	E	X^2	p	RSR	95%CI
Affected	59	50.75	1.34	>0.05	1.23	0.892; 1.68
Healthy	144	153.25				
Total	203	203.00				

Note: O = observed; E = expected; RSR = ratio between 2 standardized ratios.

2. Group B. There was only 1 affected child and 4 healthy children observed in 4 families. In this group, one of the parents was affected. If the genotypes of the parents were Rr (heterozygous) and rr (homozygous), the expected risk of inheritance should be 50% (Table 3). Since the data were small, Fisher exact test for continuity was applied.

TABLE 3. GROUP B: AR PATTERN, ONE AFFECTED PARENT

Children	O	E	X^2	p	RSR	95%CI
Affected	1	2.5	0.90	>0.05	0.25	0.005; 2.53
Healthy	4	2.5				
Total	5	5.0				

Note: See note of Table 2.

The results did not show any significant difference between the observed and the expected (AR pattern).

3. Group C. In this group of 15 families, the two possible mode of inheritance AR or AD could not yet be predicted. Both patterns had 50% risk of affected children. The statistical analysis revealed no significant difference between observed and expected value, p>0.05, thus the inheritance mode followed either AR or AD pattern. (Table 4).

TABLE 4. GROUP C: AR OR AD PATTERN, ONE AFFECTED PARENT (RR><RR/DD><DD)

Children	O	E	X^2	p	RSR	95%CI
Affected	19	24.50	0.42	>0.05	0.63	0.34; 1.16
Healthy	30	24.50				
Total	49	49.00				

Note: See note of Table 2.

4. Group D. In this group AR or M mode of inheritance was predicted. Mutation was suspected if there was only one affected child in the whole family and no other members affected in three generations. In AR pattern, if the genotypes of healthy parents were RR or Rr the risk of morbidity would be 0%; but if both parents were heterozygous (Rr), then the expected risk would be 25% (Table 5).

TABLE 5. GROUP D: AR PATTERN, BOTH PARENTS HEALTHY RR><RR

Children	O	E	X^2	p	RSR	95%CI
Affected	20	24.75	0.96	>0.05	0.66	0.38; 1.10
Healthy	79	24.75				
Total	99	99.00				

Note: See not of Table 2.

It shows that there was no significant difference between the observed and expected values ($p>0.05$), and the genetic inheritance was consistent with AR pattern.

B. The second method analysis

The aim of the second method analysis was to rule out the occurrence of mutation in the affected families. Thus, the number of affected children in each family was reduced by one prior to statistical analysis. Families with only one affected child were automatically excluded.

1. Group A. After reduction one child from every each family, there were 17 families left for analysis, with 19 affected children and 144 healthy children (Table 6).

TABLE 6. GROUP A: AR PATTERN, HEALTHY PARENTS (RR><RR)

Children	O	E	X^2	p	RSR	95%CI
Affected	19	40.75	22.21	<0.01	0.397	0.121; 0.642
Healthy	144	122.25				
Total	163	163.00				

Note: see not for Table 2.

A highly significant difference was found between the observed and the expected values ($p<0.001$). It is concluded that the genetic inheritance pattern in group A is incompatible with AR pattern.

2. Group B. After reduction, there was no affected child left for analysis.

3. Group C. After reduction there were 4 affected and 29 healthy children in 4 families (Table 7).Statistical analysis showed that there was a significant difference between the observed and the expected values ($p<0.05$), so that the genetic inheritance of 4 families of PH was incompatible with AR or AD patterns.

TABLE 7. C GROUP A: 4 FAMILIES PREDICTED AS AR (RR><RR), OR AD (DD><DD)

Children	O	E	X^2	p	RSR	95%CI
Affected	4	16.5	9.40	<0.05	0.138	0.035; 0.339
Healthy	29	16.5				
Total	33	33.0				

Note: see not for Table 2.

4. Group D. After reduction there was no affected child left. The analysis was impossible to conduct.

Discussion

The findings of the first and second method of analysis for all groups are summarized in Table 8.

The morbidity rate of prurigo Hebra in this study (18,6%) was less than the expected morbidity risk in AR (25%), if one of the parents was heterozygous, and in AD (50%) if both parents were heterozygous.

Using the first method, statistical analysis on group A did not show significant difference between the observed and expected value, $p>0.05$. Thus the genetic inheritance in 40 families in this group was compatible with AR pattern. Four families in group B were analyzed and there was no significant difference between the observed and expected value ($p>0.05$, Fisher exact test). The genetic inheritance was compatible with AR. Statistical analysis of 15 families in group C showed compatibility with AR and also with AD pattern, so that the genetic inheritance pattern in these families could not be determined. The mode of inheritance in group D was consistent with AR pattern.

The first method analysis revealed that all 64 families in group A,B, and D were compatible with AR, while 15 families in C group could not be concluded, and the possibility of mutation was not yet excluded. By using the second method analysis the possibility of mutation was ruled out. After reduction, seventeen families (group A) were incompatible with AR pattern. Four families (group C) were incompatible with either AR or AD pattern. So, it was con-

TABLE 8. RECAPITULATION OF GENETIC INHERITANCE ANALYSIS USING 2 METHODS

Group	no of families	1st method	Pattern (Compatibility)	No. of families	2 method	Pattern (Compatibility)
A	40	p>0.05	AR (C)	17	p<0.01	AR (I)
B	4	p>0.05	AR (C)	-	-	-
C	15	p>0.05	AD /AR (C)	4	p<0.05	AR or AD (I)
D	20	p>0.05	AR (C)	-	-	-
Total	163	163.00				

Note : C= Compatible, I= Incompatible; Significance level* at p<0.05
highly significance level** at p<0.01

cluded that the genetic inheritance pattern cannot be confirmed.

All probands and other affected family members had history and clinical manifestations of hypersensitivity to insect bite. Hypersensitivity to insect bite such as ant, bed bug, mite, and mosquito in prurigo patients had been proved by prick test, as reported by Occampo in 1975.[15]

Human leukocyte antigen (HLA) has been known to be associated with many skin diseases. 16-20 Concurrent with this study, the human leukocyte antigen (HLA) profile of 41 probands and 41 healthy normal persons was investigated in an unmatched case-control study. The study found that HLA-A10 was a significant immunogenetic risk factor in prurigo Hebra (RR=8 with 95%C.I.=1.67;8.87). Other types such as HLA-A 6602(10), HLA-B27, and HLA-B63(15) were associated with the severity, while HLA-B35 was found as a significant protective factor (RR=0.17 with 95% C.I.=0.04;0.65).[21] This indicated that there were multiple genes (polygenes) involved. The contribution of HLA genes supported the characteristics of multi-factorial inheritance pattern.[10] In this study female was predominant, RR = 2 (95% CI: 0.127;0.922), meaning that female had the risk twice higher than male to suffer from prurigo Hebra.[21] Naturally in AD and AR pattern, both sexes have the same possibility to be affected. This study showed sex liability; among probands female/male ratio was 39:11, while among affected members 99:33. It is known that sex liability is one of the characteristics of multi-factorial pattern of inheritance.[10]

We concluded that the mode of genetic inheritance in Prurigo Hebra follows the multifactorial pattern, based on the following findings: the pattern was not consistently compatible with either AR or AD patterns, morbidity risk was less than the risk in AR or AD patterns, sex liability, multiple genes (polygenes) of HLA were found as a risk factor and associated with the severity of the disease, hypersensitivity to mosquito bite was found in all patients.

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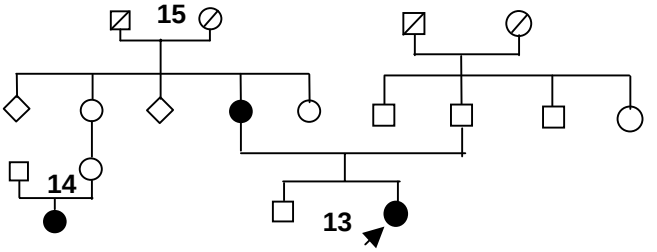
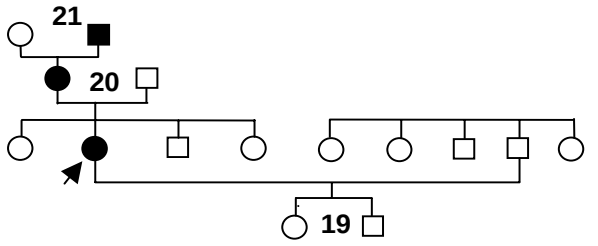
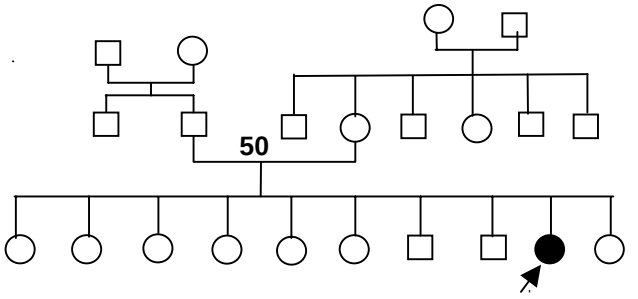
Appendix 1. Example of pedigrees of some probands



Proband No. IX: nuclear family-13 with one parent affected, predicted as autosomal dominant (AD) or autosomal recessive (AR) inheritance; nuclear family-14, both parents affected predicted as AR; nuclear family-15 both parents were healthy predicted as RA.



II. Proband No. XII: nuclear family-19, one parent affected, predicted as AD or AR; nuclear family-20 one parent affected, predicted as AD or AR; nuclear family-21one parent affected predicted as AD or AR.



III. Proband No XXXI: nuclear family-50 both parents were healthy, no one affected in 1st and 2nd generation, predicted as AR or Mutation.