

IS THE WAARDENBURG I SYNDROME GENE LOCATED ON CHROMOSOME 9?

Elias O. da Silva¹, Francisco M. Salzano² and Tania A. Weimer²

ABSTRACT

Studies involving the locus of Waardenburg I syndrome and two others on chromosome 9 (ABO system and adenylate kinase-1) were performed on two large kindreds from northeastern Brazil. The ABO data do not agree with previous investigations, since they are not suggestive of linkage.

INTRODUCTION

The classical Waardenburg Syndrome (WS) is characterized by telecanthus with lateral displacement of lower lacrimal puncta, hyperplastic nasal root, hyperplastic eyebrows with synophrys, sensorineural deafness, heterochromia iridis, white forelock, premature greying and hypopigmented skin lesions. Frequencies of the syndrome varying between 1:32,400 and 1:42,000 were calculated by some investigators in different countries (Waardenburg, 1951; Hageman, 1978; Hanta and Azumi, 1967, cited by Ishikiriyama *et al.*, 1989).

Two types of WS are recognized. Telecanthus, a major component of the classical or type I syndrome (WIS), is not a manifestation of the type II syndrome. Considering that WIS is one of the most typical autosomal dominant syndromes, with

¹ Departamento de Biologia Geral, Laboratório de Genética, Universidade Federal de Pernambuco and Instituto Materno-Infantil de Pernambuco (IMIP), Rua dos coelhos 300, Boa Vista, 50070 Recife, PE, Brasil. Send correspondence to E.O.S.

² Departamento de Genética, Instituto de Biociências, Universidade Federal do Rio Grande do Sul, Caixa Postal 1953, 90001 Porto Alegre, RS, Brasil.

virtually 100% penetrance, and that many large affected kindreds have been reported, it is surprising that only a few linkage studies have been performed. The available data suggested genetic linkage between the WIS and the ABO *loci* (Simpson *et al.*, 1974; Arias *et al.*, 1975). The ABO and AK systems are located on human chromosome 9 (Cook *et al.*, 1978; Spence and Tsui, 1987).

MATERIAL AND METHODS

In this work, the relationship between both *loci* was investigated in two large Northeastern kindreds, one being from the State of Rio Grande do Norte (kindred 1) and the other from Pernambuco (kindred 2). A study of the adenylate kinase (AK) *locus* was also performed.

Blood samples from a total of 70 individuals in three generations of both kindreds were analysed. The tests for the ABO blood group were done using the tube method, according to the instructions given by the serum manufacturers (Biotest), and those for adenylate kinase-1 (AK-1) were performed as described by Fildes and Harris (1966).

The lod score for kindred 1 was calculated according to standard methods (McKusick and Ruddle, 1977).

RESULTS AND DISCUSSION

Illustrative cases of WIS in the Northeastern kindreds are shown in Figure 1. There is no evidence that these kindreds are biologically related.

The results of the tests for the ABO system are presented in the partial pedigrees shown in Figures 2 (kindred 1) and 3 (kindred 2). Patients III-7 (kindred 1) and II-9 (kindred 2) are heterozygous for both the WIS and ABO system *loci*.

Assuming the hypothesis of linkage between both *loci* in a phase-unknown pedigree (kindred 1), individual IV-5, one of the five children of patient III-7, must be a recombinant. Therefore, the recombination fraction, based only on this small segment of the pedigree (since the others are not informative), would be 0.20, with a lod score of 0.12*. Considering kindred 2, patient III-9, one of the two children of II-9, could be either a recombinant or a product of independent segregation. Our data, therefore, do not support the claims of Simpson *et al.* (1974) and Arias *et al.* (1975).

In a recent article, Ishikiriyama *et al.* (1989) reported a sporadic case of WIS associated with a *de novo* paracentric inversion of chromosome 2 [inv (2) (q35 q37.3)]

$$0.5 [(0.2)(0.8)^4] + 0.5 [(0.2)^4(0.8)]$$

$$* \log_{10} \frac{\quad}{(0.5)^5} = 0.12$$

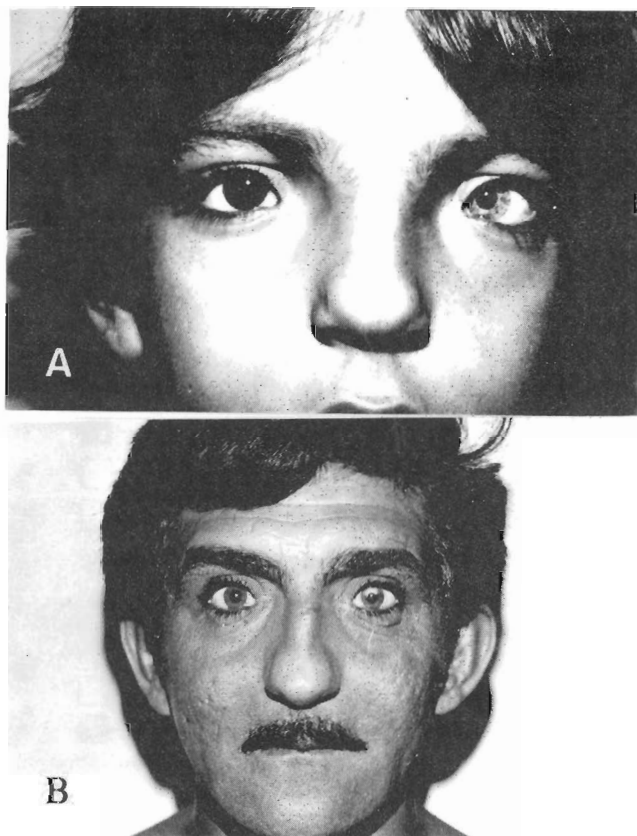


Figure 1 - Typical cases of Waardenburg I syndrome. A, patient III-24 of kindred 1 and B, patient II-5 of kindred 2. Note the presence of telecanthus (A and B), binocular (A) and monocular (B) heterochromia iridis, and hyperplastic nasal root and eyebrows (A and B). (The hair of patient II-5 is dyed because of premature greying).

and suggested that the *locus* for WIS may be at either one of the breakpoints. As the authors pointed out, further family linkage studies are necessary to confirm or deny this tentative assignment.

The results of the tests for AK-1 were not informative, since there was no variation at this *locus*, all the analysed blood samples being of the 1-1 type.

Note added in proof: Recently Foy *et al.* (1990) reported the assignment of the *locus* for Waardenburg I syndrome to chromosome 2q37

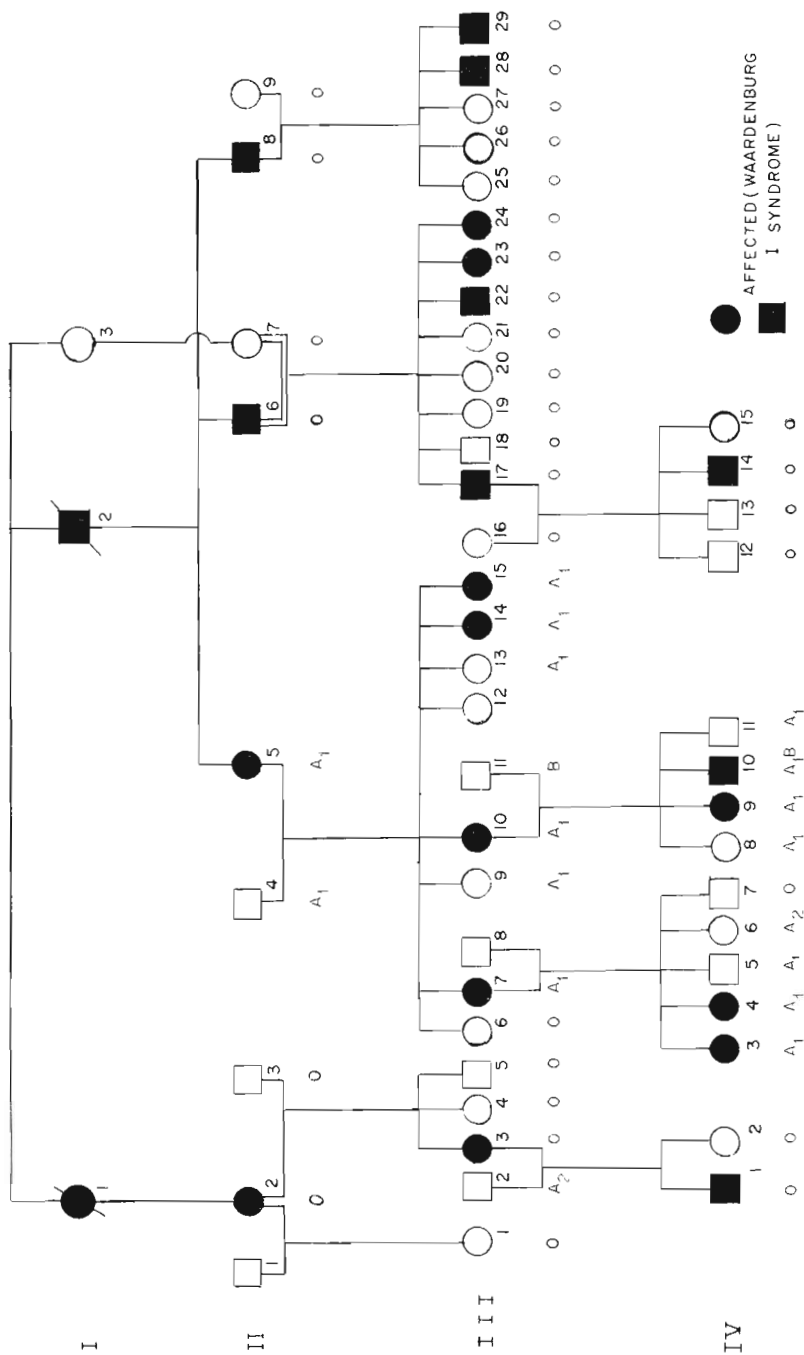


Figure 2 - Partial pedigree of kindred 1, showing the ABO blood groups of the individuals.

ACKNOWLEDGMENTS

We thank Paula S.C. Arruda, for bibliographic help, and Girley V. Simões and Rumi R. Kubo, for laboratory assistance.

This work was supported in part by Grant 401426/88-2 from CNPq.

RESUMO

Estudos envolvendo o *locus* da síndrome de Waardenburg I e dois outros localizados no cromossomo 9 (sistema ABO e adenilato quinase-1) foram realizados em duas grandes famílias nordestinas. Os resultados reais ao sistema ABO não estão de acordo com investigações prévias, desde que não são sugestivos de ligação.

REFERENCES

- Arias, S., Mota, M., Yáñez, A. and Bolivar, M. (1975). Possible linkage between the ABO *locus* and Waardenburg syndrome type I. *Humangenetik* 27: 145-149.
- Cook, P.J.L., Robson, E.B., Buckton, K.E., Slaughter, C.A., Gray, J.E., Blank, C.E., James, F.E., Ridler, M.A.C., Inslay, J. and Hultén, M. (1978). Segregation of ABO, AK1 and ACONs in families with abnormalities of chromosome 9. *Ann. Hum. Genet.* 41: 365-377.
- Fildes, R.A. and Harris, H. (1966). Genetically determined variation of adenylate kinase in man. *Nature* 209: 261-263.
- Foy, C., Newton, V., Wellesley, D., Harris, R. and Read, A.P. (1990). Assignment of the *locus* for Waardenburg syndrome type I to human chromosome 2q37 and possible homology to the splotch mouse. *Am. J. Hum. Genet.* 46: 1017-1023.
- Hageman, M.J. (1978). Waardenburg's syndrome in Kenyan Africans. *Trop. Geogr. Med.* 30: 45-55.
- Ishikiriya, S., Tonoki, H., Shibuya, Y., Chin, S., Harada, N., Abe, K. and Niikawa, N. (1989). Waardenburg syndrome type I in a child with *de novo* inversion (2) (q35q37.3). *Am. J. Med. Genet.* 33: 505-507.
- McKusick, V.A. and Ruddle, F.H. (1977). The status of the gene map of the human chromosomes. *Science* 196: 390-405.
- Simpson, J.L., Falk, C.T., Morillo-Cucci, G., Allen, Jr., F.H. and German, J. (1974). Analysis for possible linkage between the *loci* for the Waardenburg syndrome and various blood groups and serological traits. *Humangenetik* 23: 45-50.
- Spence, M.A. and Tsui, L.C. (1987). Report of the committee on the genetic constitution of chromosome 7, 8 and 9. *Cytogenet. Cell Genet.* 46: 170-187.
- Waardenburg, P.J. (1951). A new syndrome combining developmental anomalies of the eyelids, eyebrows and nose root with pigmentary defects of the iris and head hair and with congenital deafness. *Am. J. Hum. Genet.* 3: 195-253.