

Genetics of Familial Neuroblastoma: Long-Range Studies

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ABSTRACT: This is a longitudinal study of a family prone to neuroblastoma. The family was originally reported in 1975 when three children in a single generation were found to be affected. We now report the case of a fourth affected child, the sole child born in the succeeding generation. Cytogenetic studies have disclosed the segregation in the family of a paracentric inversion of the long (q) arm of chromosome No. 11 and a deletion of the short (p) arm of chromosome No. 21. However, the independent assortment of the inv(11q) and 21p- chromosomes with neuroblastoma permits us to exclude them as linkage markers for the neuroblastoma gene.

INTRODUCTION

A remarkable family with three instances of neuroblastoma was originally reported [1] in 1975. The probanda (index case) was ascertained because she had neuroblastoma at birth. Then it was learned by history that both her father and mother had had children, by previous matings, who had died with neuroblastoma. Chromosome studies with G-banding were included in the original report. These data were updated [2] in 1981.

A fourth child with neuroblastoma has recently been born into this family. The purpose of this note is to summarize information about this extraordinary family.

NEUROBLASTOMA CASES IN THE FAMILY

Case 1. The probanda (Fig. 1, III, 2) had neuroblastoma [1] and received chemotherapy. Now at age 8½ years she is well, without evidence of neuroblastoma.

Case 2. By a prior mating the mother had had a son (Fig. 1, III, 1) who died with neuroblastoma 1 hr after birth.

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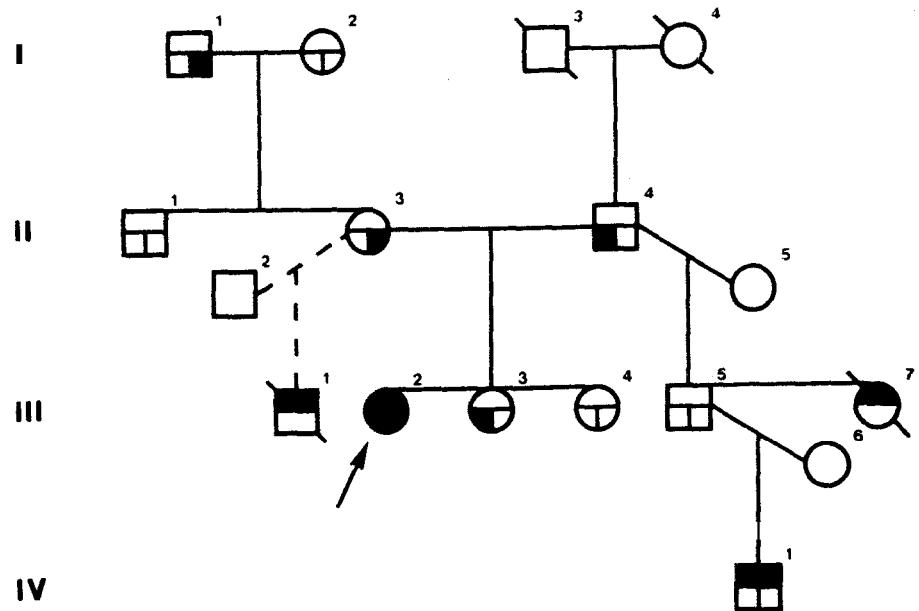


Figure 1 Pedigree of family with four cases of neuroblastoma. Segregation of chromosome No. 11 and 21 variants is shown (see text). Open lower half of squares (males) and circles (females) means no cytogenetic data are available. $\square$ = neuroblastoma, $\square$ = chromosome No. 11 variant, $\oplus$ = chromosome No. 21 variant, $\ominus$ = chromosomes normal. Arrow = probanda.

Case 3. By a prior marriage the father also had had a child, a daughter (Fig. 1, III, 7), who died with neuroblastoma at age 5 years.

Case 4. By the same prior marriage the father had had a phenotypically normal son (Fig. 1, III, 5) whose wife (Fig. 1, III, 6) gave birth in December 1981 to a girl (Fig. 1, IV, 1) with congenital metastatic neuroblastoma.

GENETIC AND ENVIRONMENTAL STUDIES

The family is Caucasian. The father (Fig. 1, II, 4) is of German ancestry, and the mother [Fig. 1, II, 3] is of Irish origin. They are not consanguineous and are not related to their previous mates. The father's son (Fig. 1, III, 5) and his wife are also unrelated.

There is no known genetic disease, aside from neuroblastoma, in this family. Physical examinations have not disclosed café-au-lait spots, cutaneous neurofibromas, or other signs of neurofibromatosis.

No other types of cancer, aside from neuroblastoma, have to our knowledge occurred in the family.

Chest and abdominal radiographs of the parents of the probanda showed no ectopic calcifications. Catecholamine excretion was also normal in the parents. The young man (Fig. 1, III, 5) who now has a daughter (Fig. 1, IV, 1) with neuroblastoma has not been studied in this regard.

A detailed environmental history failed to reveal unusual exposure to infections, chemicals, or other suspicious agents. The probanda and her deceased half-sib with neuroblastoma were conceived and born in California, whereas the most recently affected child (Fig. 1, IV, 1) was conceived and born in Arizona.

CYTOGENETIC STUDIES

Chromosome studies with G-banding were done on lymphocytes cultured with phytohemagglutinin from ten family members. Two chromosome variations were found to be segregating in the family. These variations involve chromosomes No. 11 and 21.

One chromosome No. 11 has a paracentric inversion of the long (q) arm. The breakpoints leading to the inversion are in bands 11q21 and 11q23, as recently reported [2]. The inversion [termed *inv(11)*] is present in the father (Fig. 1, II, 4), the probanda (Fig. 1, III, 2), and her normal sister (Fig. 1, III, 3). In all three of these heterozygous individuals, the *inv(11)* appears balanced.

A chromosome No. 21 in the family has little or no short (p) arm material [2]. This 21p- chromosome is a normal cytogenetic marker. It is present in the probanda, her mother (Fig. 1, II, 3), and her maternal grandfather (Fig. 1, I, 1).

DISCUSSION

This article shows the power of longitudinal studies on cancer-prone families. The original report [1] on this family consisted of three cases with neuroblastoma. However, two of the cases were revealed after the probanda was found to have neuroblastoma. Hence all three cases were retrospective, so that bias of reporting was a possibility. The newest case of neuroblastoma (Fig. 1, IV, 1) in this family occurred prospectively—after that involving the probanda.

The prospective occurrence of neuroblastoma tends very strongly to support the concept that this family is really cancer-prone and, specifically, neuroblastoma-prone.

As regards risks, since the probanda was ascertained, three new children have been born into the family: two normal (Fig. 1, III, 3 and 4) sisters and one boy with neuroblastoma (Fig. 1, IV, 1). On the basis of these small numbers, the risk of neuroblastoma in this family appears to be significantly increased above that for the general population.

What are the genetics of neuroblastoma? There are four alternative answers:

1. Neuroblastoma is entirely nongenetic
2. Neuroblastoma is due to a constitutive chromosome abnormality
3. Neuroblastoma is a polygenic phenomenon
4. Neuroblastoma is a single-gene disorder.

In this family the mode of inheritance for neuroblastoma most closely resembles that of an autosomal dominant trait with incomplete penetrance. One testable feature of this concept is that asymptomatic gene carriers [such as III, 5 in Fig. 1] might be found to have "neuroblastoma in situ" with microscopic foci of neuroblastoma in the adrenals, the incidence of neuroblastoma in situ being about 1 in 200 during infancy [3].

The 1975 report [1] on this family indicated that the probanda had "cytogenetic abnormalities derived from each parent." In a subsequent note [2] we observed that these abnormalities were a balanced inversion of chromosome No. 11 and a phenotypically innocuous deletion of the short arm of chromosome No. 21.

Segregation analysis of these two chromosome variants viz-à-viz each other reveals totally independent segregation (Fig. 1), as expected. Further, neither the *inv(11)* or the 21p- marker is segregating consistently with the postulated neuroblastoma gene, since for example the putative asymptomatic carrier (Fig. 1, III, 5) and his affected daughter (Fig. 1, IV, 1) lack both variant chromosomes.

The evidence for the existence of a neuroblastoma gene is still scant and consists

primarily of familial recurrences [4] such as are reported here. The reported families could constitute an impressive table. However, it could be misleading since the denominator, the base population, is unknown.

To our knowledge, the present family is the only one to date with this many cases of neuroblastoma (four affected children). And, more importantly, this family is the only family of which we are aware that has been followed longitudinally and been reported serially. Long-range studies have considerable power, because they are prospective and free from bias of ascertainment.

In cancer genetics, one may occasionally lack conclusive evidence for a specific cancer gene. The situation in some ways is analogous to that concerning the existence of God. As Voltaire wrote in 1770, "Si Dieu n'existait pas, il faudrait l'inventer." (If God did not exist, it would be necessary to invent Him.) Likewise, it is necessary at present to postulate a gene for neuroblastoma. We can conclude that this gene for neuroblastoma cannot be located in or near the marked regions on 11q or 21p.

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