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Mendlewicz J & Fleiss J L. Linkage studies with X-chromosome markers in bipolar (manic-depressive) and unipolar (depressive) illnesses. *Biol. Psychiat.* 9:261-94, 1974.
[Dept. Medical Genetics, New York State Psychiatric Inst.; Biometrics Research Unit, New York State Dept. Mental Hygiene; and Columbia Univ., New York, NY]

This paper demonstrates that a dominant X-linked gene is involved in the biological transmission of bipolar manic-depressive illness. This was done through the application of linkage methods using chromosome markers in a large sample of families. The paper also emphasizes the notion that depression is heterogeneous from the genetic point of view since X-linked inheritance could not be found in unipolar depressive illness. These findings have now been replicated by our group and other laboratories and have stimulated interest and research in the area of molecular genetics of mental disorders. [The *SCI*® and *SSCI*® indicate that this paper has been cited in over 135 publications.]

Manic-Depression Is Linked to the X Chromosome

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During my medical studies, I was fortunate to work as a research fellow in the medical genetics laboratory at the Free University of Brussels. It was then a great privilege to learn about the methodology of research and the philosophical implications of the new developments in modern genetics and neurobiology. Ever since my childhood, I have been fascinated by the complex interaction between brain and behavior; this led me to do a residency training in psychiatry, with the aim of combining genetics and psychiatry.

This dream started to become a reality when I received a one-year fellowship from the Belgian American Educational Foundation to work in the Department of Medical Genetics at the New York State Psychiatric Institute of Columbia University in New York, where I was to stay from 1969 to 1974.

With the help and support of J.D. Rainer, I then decided to start studying the genetic mode of transmission of manic-depression, because this rather prevalent mental illness was known to cluster in families and to be, to a large extent, of biological origin and to respond to treatment with lithium salts. At the same time, I enrolled in the Department of Human Genetics and Development and was awarded a PhD degree from Columbia University in 1973. I first decided to explore the presence of a major gene on the X chromosome as a possible mode of inheritance in manic-depression, because some sex ratio family and twin studies had shown an excess of females over males and because preliminary linkage studies[1,2] with chromosomal markers were suggestive of X-linkage. Thanks to the collaboration of R.R. Fieve and A. Glassman, who allowed me to study their patients, I was able to collect clinical and genetic data, with M. Cataldo, on a large sample of families of bipolar manic-depressive and unipolar depressive probands. This was also a unique social, cultural, and human experience for me to discover the people and the city of New York, which I have since learned to love as a second hometown. The 1974 paper provided the first unequivocal evidence of linkage between manic-depression and X-chromosome markers such as color blindness, using sophisticated linkage analysis conducted in collaboration with J.L. Fleiss, my coauthor, who has since gained international recognition in biometrics and biostatistics. Our paper also clearly showed that manic-depression is genetically heterogeneous. This article has probably been highly cited because it provided the first demonstration of the presence of a Mendelian inheritance in psychiatric illness, thus leading to new insights into the biological basis of a major mental disorder. This article was given the A.E. Bennett Award, which was presented to me by the American Society of Biological Psychiatry in Boston on my birthday, June 11, 1974. Subsequently, this work has been confirmed and extended by us and other laboratories[3-5] and, more recently, in molecular biology studies using the DNA recombinant method.[6] The significance of this work has further resulted in the attribution of several awards such as the First International Anna Monika Award in 1981, the Assubel Prize for Medicine in 1981, the Award of the Belgian Royal Academy of Medicine in 1983, the Award of the National Academy of Medicine in France in 1986, and the First Lundbeck Prize for Biological Psychiatry in 1987.

It is hoped that these findings will, in the near future, permit the isolation and sequencing of a gene responsible for manic-depression and hold great promises for the diagnosis and etiological treatment of the mentally ill.

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3. **Mendlewicz J.** Adoption study supporting genetic transmission in manic-depressive illness. *Nature* 268:327-9, 1977. (Cited 120 times.)
4. **Mendlewicz J, Linkowski P, Gurroff J J & Van Praag H M.** Color blindness linkage to bipolar manic-depressive illness. New evidence. *Arch. Gen. Psychiat.* 36:1442-7, 1979. (Cited 50 times.)
5. **Baron M, Risch N, Hamburger R, Mandel B, Kushner S, Newman M, Drumer D & Belmaker R H.** Genetic linkage between X-chromosome markers and bipolar affective illness. *Nature* 326:289-92, 1987. (Cited 50 times.)
6. **Mendlewicz J, Simon P, Sevy S, Charon F, Brocas H, Legros S & Vassart G.** Polymorphic DNA marker on X chromosome and manic depression. *Lancet* 1:1230-2, 1987. (Cited 20 times.)

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