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SHORT REPORT

Mucolipidosis type IV: the origin of the disease in the Ashkenazi Jewish population

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Mucolipidosis type IV (MLIV) is a neurodegenerative lysosomal storage disease in which most of the patients diagnosed hitherto are Ashkenazi Jews. The basic metabolic defect causing this disease is still unknown and the relevant gene has not yet been mapped or cloned. Seventeen Israel Ashkenazi families with MLIV patients had been interviewed to study their family origin. Although the families immigrated to Israel from various European countries they all could trace their roots three to four generations back to northern Poland or the immediate neighbouring country, Lithuania. Furthermore, there are only one or two ultraorthodox families among the 70–80 Ashkenazi families with MLIV patients worldwide, a marked underrepresentation of this group which constitutes at least 10% of the Ashkenazi population. This data indicate that MLIV mutation occurred only around the 18th and 19th centuries, after the major expansion of this population, in a founder in this defined European region belonging to a more modern, secular family.

Keywords: mucolipidosis type IV; Ashkenazi Jews; origin; founder

Mucolipidosis type IV (MLIV) is an autosomal recessive lysosomal storage disorder first described in 1974.[1] The disease is characterised by psychomotor retardation and ophthalmological abnormalities including cornea opacity, retina degeneration and strabismus.[2] Marked heterogeneity in the clinical symptoms was noted, even among siblings. The disease was classified as a mucolipidosis based on electron microscopy observations which demonstrated lysosomal storage of lipids together with water soluble substances in cells of every tissue and organ of these patients.[3] The accumulating compounds were subsequently identified as mono and polysialo gangliosides, phospholipids and acid mucopolysaccharides. Recently Chen *et al*[4] demonstrated that membrane sorting and/or late steps in endocytosis is abnormal in MLIV fibroblasts resulting in their lysosomal accumulation. The basic metabolic defect causing this phenomenon has not yet been identified and the relevant gene has not yet been mapped or cloned.

Patients from over 70 families, worldwide, had been diagnosed by us, comprising the vast majority of MLIV diagnosed patients hitherto. Of these, over 90% are Ashkenazi Jews, thus classifying MLIV as one of the genetic disorders occurring in relatively high frequency in this population.[5] The precise frequency of MLIV in the Ashkenazi population cannot yet be estimated since there is no accurate diagnostic procedure for heterozygotes identification, and it is suspected that undiagnosed patients exist due to difficulties in diagnosing this

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disease which is represented by mental and motor retardation with no specific symptoms. Thus, the incidence of MLIV among the Ashkenazi Jews is probably not reflected by the patients diagnosed hitherto.

In the attempts to map the MLIV gene we interviewed 17 Israeli families with MLIV patients, all Ashkenazi Jews, to determine their family origin (all the families had one affected child). From these families we obtained information of 61 branches at least for the last three to four generations. The countries of origin of these branches before immigration to Israel is as follows: Poland 23 branches, Lithuania 14, Germany 10, Russia 5, Austria 4, Czechoslovakia 3, Hungary 1 and Rumania 1. Although these families originated in various European countries almost all of them could trace their roots to northern Poland or to its closest neighbour – Lithuania (Figure 1). This is true of the families with severe or mildly affected patients.

Jews emigrated to central Europe as early as the beginning of the Middle Ages, mostly northward to Germany (hence their name: Ashkenaz means German in Hebrew)[6] via southern Europe, primarily Italy. At later periods, during the 13th and 14th centuries, many of these Jews emigrated from Germany eastwards and by the 17th century the bulk of Jewish settlement was in the region of northern Poland–Lithuania–Byelorussia. There was a marked increase in the Ashkenazi Jewish population in this region from some 50 000 in the 15th century to 250 000 in the 17th century and over 8 million in the early 20th century, before World War II, covering an expanded area in eastern Europe and the Balkans. Only in later periods, during the 19th and 20th centuries did Jews emigrate from this region to other European countries and in much larger numbers to North America.

Figure 1 *Map of central northern Europe. The hatched area indicates the region of origin of the MLIV families.*

Of the 70 Ashkenazi MLIV families, worldwide, only one or two are ultraorthodox (Haredim in Hebrew), and only one of which is Israeli, whereas in Israel the ultraorthodox are estimated to be approximately 10–15% of Ashkenazi Jews. (The ultraorthodox Ashkenazim at present are mostly from families who kept the same disciplined religious practices for generations.) When other frequent disorders in this population are examined, including Tay-Sachs, cystic fibrosis, familial disautonomy and Gaucher diseases, all of which are diagnosed at our centre, the proportion of patients from ultraorthodox families is at least the expected 10–15% of the Ashkenazi patients.

Two points therefore characterise MLIV in the Ashkenazi population: origin from a defined region in Europe, and the disproportionately under-representation of ultraorthodox families. This leads us to conclude that the MLIV mutation may have originated in a founder comparatively recently, later than the other known Jewish disorders, mentioned above. This conclusion is based on the fact that the MLIV families originated mostly or entirely from the region where Ashkenazi Jews had been concentrated for five centuries. If the MLIV mutation had occurred earlier we would have expected a broader distribution among the subgroups comprising the present population, ie at least seven to ten ultraorthodox MLIV families. The MLIV mutation might therefore have occurred in a founder only around the 18th to 19th centuries after the major expansion of this population. We might assume that the founder(s) belonged to a family who kept more modern and secular practices and this cultural pattern has been largely kept up by these families until the present; a relatively high proportion of these families emigrated from Poland and Lithuania to Germany during the 19th century.

It should be emphasised that the areas of origin in Europe for most of the other frequent disorders among Ashkenazi Jews has not been defined, but there are indications that Tay-Sachs originated centuries ago in central Europe (Austria, Hungary, Czechoslovakia)[7] and idiopathic torsion dystonia originated in Lithuania and Byelorussia.[8]

The relatively late occurrence of the MLIV mutation will explain the apparently lower frequency of this disease in the Ashkenazi population compared with the other disorders mentioned.[5] The marked heterogeneity in the clinical manifestation among MLIV patients

(including the patients in the present study), primarily in the degree of mental and motor retardation and the degree of cornea opacity, might therefore stem from unknown effectors such as unrelated genes which might influence the degree of temporal lysosomal storage and/or environmental influences (nutrition etc.) and not by different MLIV-causing genes or allelic mutations. A similar broad spectrum of severity is known among Gaucher type 1 patients, homozygotes of the N370S mutation in glucocerebrosidase; some are asymptomatic, others present very mild clinical manifestations, whilst a few manifest more severe symptoms.[9] The cause of this variability is mostly obscure.

Research into MLIV is focused at present on attempts to map the MLIV gene. If a common founder is indeed the origin for at least the majority of Ashkenazi families this will facilitate the search for the MLIV gene, since linkage disequilibrium of polymorphic markers in the region of the MLIV gene is anticipated among these patients. The identification of the MLIV gene will finally answer this question.

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References

1 Berman ER, Livni N, Shapira E, Merin S, Levij IS: Congenital cornea clouding with abnormal systemic storage bodies: A new variant of Mucolipidosis. *J Pediatr* 1974; **84**: 519–526.
2 Amir N, Zlotogora J, Bach G: Mucolipidosis type IV: Clinical and natural history. *Pediatrics* 1987; **79**: 953–959.
3 Bach G, Zeigler M, Bargal R: Mucolipidosis type IV. In: Desnick RJ (ed.). *Advances in Jewish Genetic Diseases*. Oxford University Press: New York, 1999, (in press).
4 Chen C-S, Bach G, Pagano RE: Abnormal transport along the lysosomal pathway in Mucolipidosis type IV disease. *Proc Natl Acad Sci USA* 1998; **95**: 6373–6378.
5 Motulsky AG: Jewish diseases and origin. *Nat Genet* 1995; **9**: 99–101.
6 DellaPergola S: Major demographic trends of world Jewry: The last hundred years. In: Bonne-Tamir B, Adam B (eds). *Genetic Diversity Among the Jews*. Oxford University Press: New York, 1992, pp 3–30.
7 Petersen GM, Rotter JI, Cantor RM *et al*: The Tay-Sachs disease gene in North American Jewish population: Geographic variations and origin. *Am J Hum Genet* 1983; **35**: 1258–1269.
8 Rich N, de Leon D, Ozelius L *et al*: Genetic analysis of idiopathic torsion dystonia in Ashkenazi Jews and their recent decent from small founder population. *Nat Genet* 1995; **9**: 152–159.
9 Beutler E, Grabowsky GA: Gaucher disease. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds). *The metabolic and molecular bases of inherited disease*. McGraw Hill: New York, 1995, pp 2641–2670.