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Selective Intestinal Malabsorption of Vitamin B12 Displays Recessive Mendelian Inheritance: Assignment of a Locus to Chromosome 10 by Linkage

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Summary

Juvenile megaloblastic anemia caused by selective intestinal malabsorption of vitamin B12 has been considered a distinct condition displaying autosomal recessive inheritance. It appears to have a worldwide distribution, and comparatively high incidences were reported 30 years ago in Finland and Norway. More recently, the Mendelian inheritance of the condition has been questioned because almost no new cases have occurred in these populations. Here we report linkage studies assigning a recessive-gene locus for the disease to chromosome 10 in previously diagnosed multiplex families from Finland and Norway, proving the Mendelian mode of inheritance. The locus is tentatively assigned to the 6-cM interval between markers D10S548 and D10S466, with a multipoint maximum lod score (Z_{max}) of 5.36 near marker D10S1477. By haplotype analysis, the healthy sibs in these families did not appear to constitute any examples of nonpenetrance. We hypothesize that the paucity of new cases in these populations is due either to a dietary effect on the gene penetrance that has changed with time, or to a drop in the birth rate in subpopulations showing enrichment of the mutation, or to both of these causes.

Introduction

Megaloblasic anemia in a child is a rare condition that in all likelihood is heterogeneous. A distinct form was described by Imerslund in Norway under the name "idiopathic chronic megaloblastic anemia in children (Imerslund 1959, 1960). Independently, Gräsbeck et al. detected and studied a series of patients with a similar disease in Finland and determined that the condition was due to selective vitamin B12 malabsorption (Gräsbeck et al. 1960), as originally suggested (Imerslund 1959, 1960). In both series, some but not all patients have proteinuria. The family structures were compatible with autosomal recessive inheritance. McKusick's (1992) catalog lists the disorder under number 261100 and contains the most extensive presently available review of the literature. It appears that the disorder occurs with a low frequency worldwide. As far as we are aware, some 180 cases fitting the description of the disease have been described (Broch et al. 1984). In Finland ~38 cases (Gräsbeck et al. 1960; Anttila and Salmi 1967; Visakorpi and Furuhjelm 1968; Furuhjelm and Nevanlinna 1973; authors' unpublished observations), and in Norway 15 cases (Imerslund 1959, 1960; Imerslund and Bjørnstad 1963; Broch et al. 1984), have been diagnosed. Other countries where the condition has been frequently diagnosed include Israel (18 cases in Jews of Tunisian and Libyan origin) (Ben-Bassat et al. 1969) and Saudi Arabia (3 cases) (Abdelaal and Ahmed 1991).

A hitherto unexplained phenomenon has occurred in Finland and Norway. Within a few years of the initial descriptions of the condition in 1959 and 1960, many cases were diagnosed in both countries, so that there appeared to be relatively high gene frequencies in specific subsets of both populations. In contrast, more recently almost no new cases appear to have been diagnosed in Finland and Norway (see below). This has led to speculation either that the disease perhaps does not exist at all (Norio 1991) or that it does not show Mendelian inheritance.

Many Finnish patients were diagnosed >25 years ago (Gräsbeck et al. 1960; Anttila and Salmi 1967; Visakorpi and Furuhjelm 1968), and by the year 1973 a total of 27 patients had been identified (Furuhjelm and Nevanlinna 1973). Thereafter a few more cases have come to our attention. We note that as few as four patients have been born since 1971, the youngest one

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in 1983. In Norway the youngest patient diagnosed was born in 1982.

In both Finland and Norway most cases have been diagnosed in geographically defined rural regions (Imerslund 1959, 1960; Furuhjelm and Nevanlinna 1973). Given the population structure of these countries, pronounced founder effects of rare disease genes occur in such subpopulations (Gedde-Dahl 1991; de la Chapelle 1993). We would therefore expect new patients to occur in the same districts. We claim that it is unlikely that newly diagnosed patients in Finland and Norway have not come to our attention. Both countries have a centralized hierarchical health-care system that is well organized with regard to child health care. Severe megaloblastic anemia in a child may be recognized at the level of primary care, but patients with such a rare and severe condition will automatically be referred to a secondary or even university-level hospital, for evaluation by a pediatric hematologist. We have scanned the relevant geographical regions and communicated with the relevant physicians in search of new cases, but we found none born after 1983. This should be significant in our small and relatively tightly knit communities.

We reasoned that, if the putative gene could be mapped, this would not only prove the existence of the proposed Mendelian disorder but also would serve as a first step toward the identification of the gene product and its role in intestinal absorption and proteinuria. Here we describe the successful mapping of the gene and the apparent absence of nonpenetrance in multiplex families.

Subjects, Clinical Features, and Methods

Subjects

Of the ~38 patients known to us and who have been diagnosed in Finland, 8 patients have died. Twelve patients belong to six multiplex nuclear families (fig. 1, families 1–6) and were chosen for this study. Consanguinity occurred between families 1 and 2, where one parent from each family were first cousins. More distant genealogical links occurred between families 5 and 6. The panel of patients used in the initial search for linkage consisted of a total of 30 members of these six Finnish families (only 9 of the 14 unaffected sibs were studied at the initial stage).

A total of 15 individuals have been diagnosed in Norway (Imerslund 1959, 1960; Imerslund and Bjørnstad 1963; Broch et al. 1984). Seven of the patients belong to three multiplex nuclear families. We studied these seven patients, one parent, and three unaffected sibs (fig. 1, families 7–9). For uniformity the Norwegian families are not included in the pairwise and multipoint linkage analyses.

Clinical Features

Patients are symptom free at birth but develop signs of megaloblastic anemia within the first 5 (most often within the first 2) years of life (Furuhjelm and Nevanlinna 1973). Usually, recurrent infections, gastrointestinal complaints, pallor, weakness, anorexia, and failure to thrive are the most obvious symptoms (Visakorpi and Furuhjelm 1968; Wulffraat et al. 1994).

Some but not all patients have proteinuria at diagnosis and continue to excrete protein in urine, irrespective of treatment (Gräsbeck et al. 1960; Broch et al. 1984). Even though the pathogenesis is unknown and a specific biomarker does not exist, the diagnostic criteria are straightforward (Gräsbeck et al. 1960; Broch et al. 1984): (1) appearance of megaloblastic anemia within the first 5 years of life, (2) low serum vitamin B12 levels with good hematologic response to parenteral injections of vitamin B12, (3) serum folate not decreased, (4) Schilling tests I and II showing malabsorption of labeled B12 even after the addition of exogenous intrinsic factor, (5) unhampered absorption of other nutrients when vitamin stores are replenished, and (6) exclusion of severe malnutrition or a general malabsorption syndrome.

Data on all patients studied conformed to the above criteria. The clinical features of some of these patients have been described in detail elsewhere: family 4 (Anttila and Salmi 1967) and families 7–9 (cases I, II, and IV–VIII of Imerslund 1959).

Heterozygotes for the disease absorb vitamin B12 well and therefore cannot be identified by clinical tests (Ben-Bassat et al. 1969). If untreated, the disease manifests itself as severe chronic megaloblastic anemia that can be fatal. Therapy is lifelong and consists of intramuscular injections of vitamin B12 at 1–6-mo intervals (Broch et al. 1984). With such therapy, patients remain clinically healthy.

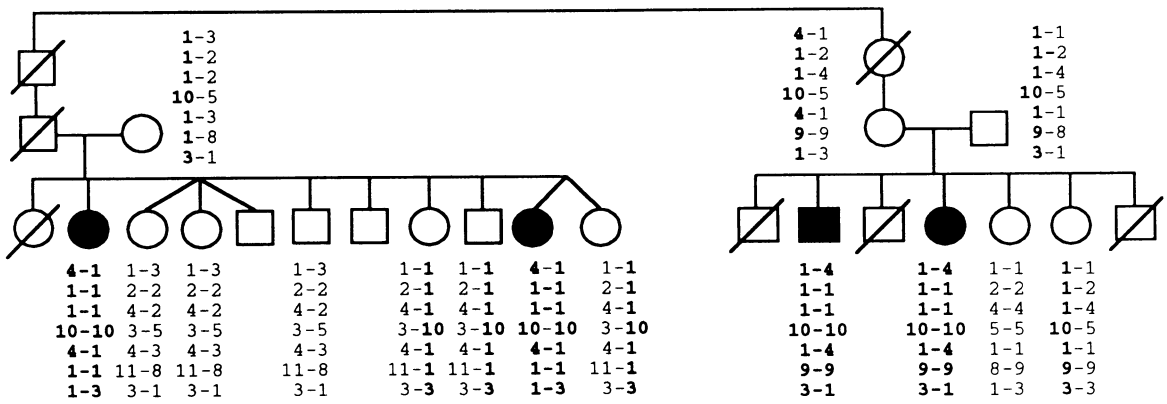
Blood Samples

Venous blood (20–30 ml) was collected from each consenting individual. In a few cases a lymphoblastoid cell line was established for later use. DNA was extracted directly from the leukocytes contained in blood, by standard methods.

Microsatellite Markers

Most markers were from the Généthon or Marshfield collections (Weissenbach et al. 1992; Gyapay et al. 1994; J. Weissenbach, unpublished data). For the initial screening a set of markers located ~20 cM apart was used. Markers were coamplified in 10-μl reaction volumes, by published protocols (Weber and May 1989). Whenever possible, two to six markers were included in each PCR reaction and electrophoretic lane.

Families 1 and 2



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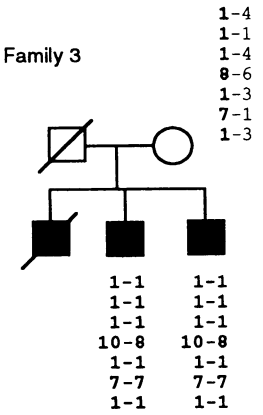

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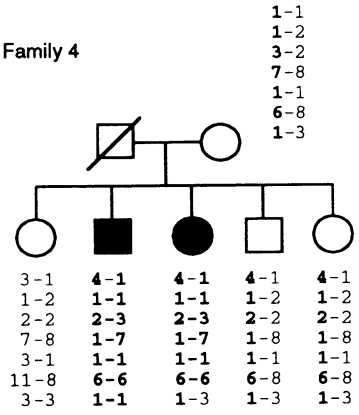

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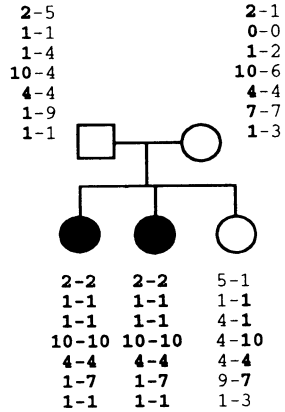
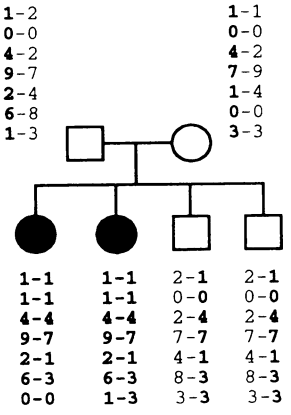


Family 6



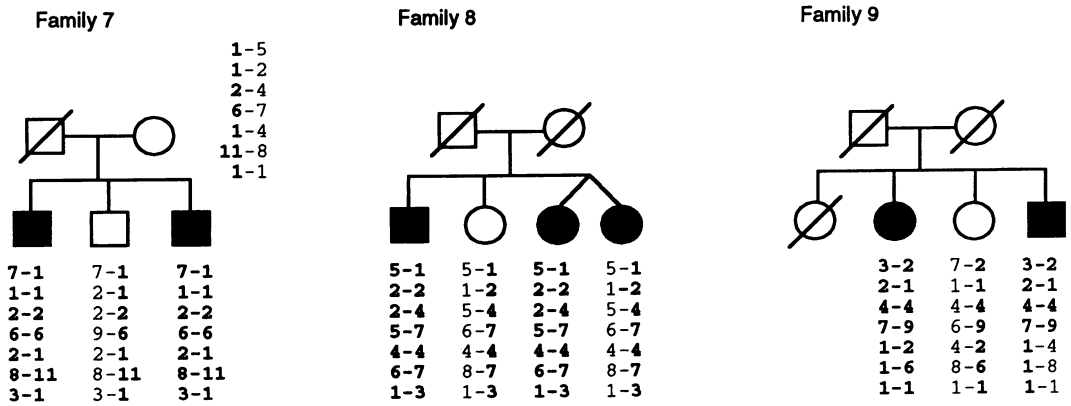


Figure 1 Pedigrees of the six Finnish (1–6) and three Norwegian (7–9) MGA1 multiplex families studied by linkage. Squares denote males; and circles denote females; and an unblackened symbol indicates that the individual is unaffected, and a blackened symbol indicates that the individual is affected. The alleles for D10S466, D10S1475, D10S1476, D10S1477, D10S548, D10S595, and D10S586 (in this order, from top to bottom) are shown for each studied individual; a zero indicates that the allele is not known. Haplotypes were constructed on the basis of the minimum number of recombinations between these markers. The chromosome assumed to carry the disease allele is shown in boldface.

Linkage Analysis

Linkage analyses were performed by computer programs of the LINKAGE program package (Lathrop et al. 1984). The simulation program SLINK (Ott 1989; Weeks et al. 1980) was used to define a minimum number of individuals to be studied in the initial screening. For multipoint analysis, marker genotypes were reduced to three-allele loci. The analysis (LINKMAP) was carried out under the assumption of a fixed order and fixed distances of the seven marker loci. All results were obtained under the assumption of complete penetrance, with sex-average recombination fractions and allele frequencies obtained through the Genome Data Base (Pearson 1991; Pearson et al. 1992; Cuticchia et al. 1993).

Results

Linkage

In the absence of mapped or cloned plausible candidate genes or candidate chromosomal regions, we performed a systematic search for linkage in six Finnish multiplex families, using highly polymorphic DNA markers located at ~20-cM intervals. After 92 markers were tested, probable linkage was observed with D10S191 on chromosome 10. We then expanded the panel of individuals studied for linkage, with five unaffected sibs and with the three Norwegian multiplex families. The observed linkage was confirmed with eight additional markers: D10S570, D10S466, D10S1475, D10S1476, S10S1477, D10S548, D10S595, and D10S586, both in Finnish families and in Norwegian families. The segregation of the alleles in the nine families is shown in figure 1. Pairwise lod scores between the disease locus termed "MGA1" (for *m*egaloblastic *a*nemia *1*) and the marker loci in the Finnish families are shown in table 1. The closest markers with which obligatory recombination was observed were D10S586, on the centromeric, and D10S570, on the telomeric side, defining an interval of ~16 cM.

The data from the three Norwegian families strongly suggest linkage to the same chromosomal region as was shown by the haplotypes (fig. 1, families 7–9). Moreover, the youngest patient in family 9 displays a recombination that places the gene telomeric of marker D10S548.

We do not show numerical pairwise linkage results for the Norwegian families, because the series is small and family 8 does not lend itself to any unambiguous interpretation. The youngest child who is definitely affected has haplotypes identical to those of her unaffected sister; however, with markers from other chromosomes, these two sibs are different (data not shown). Because both parents are dead, we cannot confirm the likely hypothesis that the youngest affected sister shows a crossover placing the MGA1 locus telomeric of marker D10S1475. If a recombination in this region can be confirmed with further nearby markers, the MGA1 interval could be narrowed to between D10S548 and D10S466, i.e., only 6 cM. This tentative localization is shown in figure 2.

The result of an eight-point linkage analysis in the Finnish families is shown in figure 3. The fixed order centromere–D10S586–D10S595–D10S548–D10S1477–D10-S1475– D10S191–D10S570–telomere and sex-specific recombination fractions were assumed to be as reported (.01, .01, .03, .01, .06, and .04) (Gyapay et al. 1994; Weissenbach, unpublished data). A multipoint Z_{max} of

Table 1

Pairwise Lod Scores between MGA1 and Nine Marker Loci in Six Finnish Multiplex Families

Locus	Lod Score at Recombination Fraction of							Z_{max}	θ_{max}	90% Confidence Limits
	.00	.001	.01	.05	.10	.20	.30			
D10S570	$-\infty$	.27	1.21	1.65	1.59	1.14	.59	1.66	.063	$.002 < \theta < .29$
D10S191	3.33	3.33	3.25	2.90	2.46	1.60	.82	3.33	.000	$.000 < \theta < .11$
D10S466	3.72	3.71	3.63	3.26	2.80	1.86	.98	3.72	.000	$.000 < \theta < .11$
D10S1475	3.41	3.40	3.32	2.96	2.51	1.63	.83	3.41	.000	$.000 < \theta < .12$
D10S1476	4.97	4.96	4.83	4.29	3.62	2.32	1.17	4.97	.000	$.000 < \theta < .13$
D10S1477	5.17	5.15	5.02	4.46	3.75	2.38	1.17	5.17	.000	$.000 < \theta < .07$
D10S548	2.17	2.16	2.11	1.87	1.57	.98	.47	2.17	.000	$.000 < \theta < .17$
D10S595	4.39	4.38	4.27	3.81	3.22	2.08	1.05	4.39	.000	$.000 < \theta < .09$
D10S586	$-\infty$	−.35	.59	1.02	1.00	.68	.34	1.04	.065	$.002 < \theta < .5$

5.36 was obtained for a location of MGA1 near marker D10S1477.

Search for Examples of Nonpenetrance

Attempts to construct haplotypes were somewhat hampered by the absence of parental information in several families. The alleles are shown as most likely haplotypes in figure 1. Inspection of these seven-locus haplotypes provides an opportunity to search for likely disease-mutation homozygotes among the healthy sibs of the patients, i.e., sibs with both haplotypes identical to those of the affected individuals. Clearly, no such case occurred among the 14 Finnish and 3 Norwegian sibs, suggesting that nonpenetrance did not occur in these families.

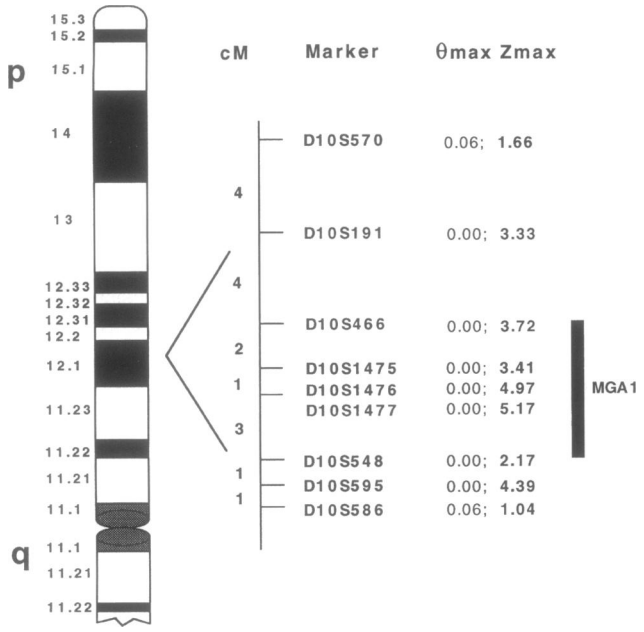


Figure 2 Map detail of chromosome 10, showing tentative physical location of markers linked to MGA1, published and unpublished genetic distances between markers, and pairwise marker–MGA1 maximum-recombination-fraction (θ_{max}) and Z_{max} values in six multiplex Finnish families. The bar on the right depicts the likely localization of MGA1, on the basis of recombinational analysis.

Physical Assignment

Published physical and genetic maps of chromosome 10 were searched for evidence regarding the physical assignment of MGA1 (fig. 2). Taken together, these data place MGA1 in the pericentromeric region of chromosome 10, more probably on the short arm than on the long arm (Cuticchia et al. 1993; Kapsetaki et al. 1994).

Discussion

Our assignment of the disease locus to a <16-cM interval near the centromere of chromosome 10 definitely establishes the regular Mendelian inheritance of the disorder, at least in Finnish and Norwegian families. However, the question of a changing penetrance remains. Here we show that none of the 17 unaffected sibs appears to have a haplotype suggestive of homozygosity for the disease gene. Thus no examples of nonpenetrance appear to have occurred in these families. However, if the observed paucity of newly diagnosed cases is indeed due to a drop in penetrance that is recent, one would not have expected to find it in these families, which were all diagnosed 20–35 years ago.

We shall discuss here four major hypotheses to account for the suggested lack of recently diagnosed cases (table 2). First, the described phenomenon might be due to chance alone. This is unlikely, in view of the comparatively robust numbers shown in table 2. Second, it might be that new cases occur but do not come to our attention, which is unlikely. Third, given that in both coun-

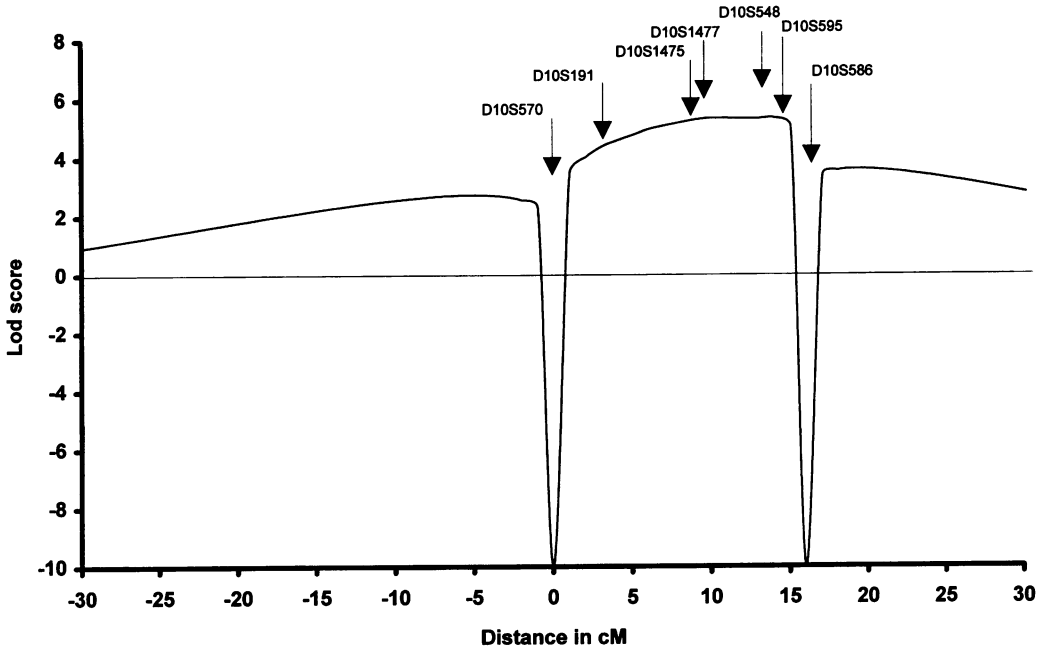


Figure 3 Eight-point linkage analysis in the six Finnish MGA1 pedigrees (1–6), with respect to a fixed genetic map of seven marker loci on chromosome 10. Lod scores were computed by the LINKMAP program. A sex-average map based on the Haldane mapping function is shown. Marker D10S570 was chosen as the starting point (0). The telomere is to the left.

tries most previously diagnosed cases originated in rural subpopulations (in Savo and the northeastern area of Finland and in the southeastern provinces, particularly the region of Valdres, in Norway), the gene frequencies in the main populations of the countries are not necessarily exceptionally high. Since rural isolates are breaking up, and as people from the isolated areas move into the cities, where gene frequencies are lower, the overall gene frequencies drop to levels where homozygosity becomes very rare. For this attractive hypothesis to be correct, a drop in the birth rate of homozygotes will only occur if the number of births in the rural high-incidence areas has dropped significantly during the period of observation. This has indeed occurred in Finland.

Table 2

Number of Affected Individuals, Grouped According to Year of Birth

Year of Birth	Finland	Norway
1931–40	1	1
1941–50	7	9
1951–60	16	2
1961–70	8	1
1971–80	3	1
1981–	1	1

In the provinces of northeastern Finland in which one half of the presently known patients originated, the annual number of births has declined after peaking in the 1950s. In some rural regions the decline is as high as 50%, between the 1950s and present (data not shown). As a whole, however, the figures are not dramatic enough to explain the present paucity of patients. In Norway, on the other hand, in the southeastern part of the country, where most MGA1 patients live, the population has grown and the number of births has increased during the postwar period. Since the population growth is mostly due to immigration from other parts of Norway, a dilution effect on the MGA1 gene could have occurred. We tentatively conclude that in both countries the drop in disease incidence could be due in part to the described changes in population structure—but that these could hardly fully explain the phenomenon. Finally, therefore, we entertain a fourth hypothesis—i.e., that environmental factors influence the penetrance of this gene. Drastic changes have occurred in the dietary habits of both Finns and Norwegians during this same time period. For instance, in the postwar period, when most known patients were born, the diet was far poorer in animal protein (with which cobalamin is associated) than it is today.

In the treatment of pernicious anemia, large oral doses of cobalamin are given, part of which is absorbed by "diffusion" (Chanarin 1979). However, in selective vita-

min B12 malabsorption this mechanism appeared to be hampered (Gräsbeck and Kvist 1967). These observations argue that an altered diet might not explain the present low incidence of the disease.

There has been speculation about an abnormality or lack of the receptor for the intrinsic factor–cobalamin receptor complex, a deficiency due to a disturbance in the intestinal wall. In patients with the disease, there has been no evidence of binding of the intrinsic factor–cobalamin complex by the brush-border fraction of ileal enterocytes, indicating an apparent absence of the brush-border intrinsic factor–cobalamin receptor (Gräsbeck et al. 1960; Kouvonen and Gräsbeck 1979; Seetharam et al. 1981; Burman et al. 1985). An obvious candidate gene for MGA1 is the one encoding the intrinsic factor–cobalamin receptor itself. This molecule has been the object of much interest and has been isolated from human, porcine (Kouvonen and Gräsbeck 1979), and canine (Seetharam et al. 1981) intestine. In addition to ileal mucosa, a high intrinsic factor–cobalamin receptor activity has also been detected in the mammalian kidney (Seetharam et al. 1988; Fyfe et al. 1991*b*) and in concentrated human urine (Guéant et al. 1995). The gene has not been cloned.

The cause of malabsorption might involve defective processing and transport of either the intrinsic factor–cobalamin receptor to the cell surface or the intrinsic factor–cobalamin complex in the cell interior (Seetharam et al. 1991). The defect is believed to disturb the translocation of vitamin B12 from its intrinsic factor–intrinsic factor receptor–bound form in the enterocyte to transcobalamin II subsequently entering the blood stream (Gräsbeck and Kvist 1967; Guéant et al. 1995). However, in the cases reported by MacKenzie et al. (1972) there seemed to be no defect, in the ileal receptors for the complex, between intrinsic factor and B12: the defect appeared to be located between the attachment of the complex to the surface of the ileal cell and the binding to transcobalamin II.

An animal model for this disease may exist. As shown by Fyfe et al. (1989), a recessively inherited mutation produces a phenotype in giant schnauzer dogs that greatly resembles that of the human disorder. These dogs have selective vitamin B12 malabsorption and proteinuria (Fyfe et al. 1989, 1991*a*). The researchers who detected and have studied this mutation in the dog apparently favor the intrinsic factor–cobalamin receptor as a main candidate for the disease gene. If the two diseases prove to have an identical molecular background, the elucidation of the gene in dogs might lead to the resolution of the problem in humans.

The present assignment of a locus for the disorder provides an opportunity to examine whether one or several of the numerous genes that have been mapped to the same region might be plausible candidate genes (Pearson et al. 1991; Pearson et al. 1992; Cuticchia et al. 1993). With ever-increasing numbers of human genes being mapped and cloned, this approach is becoming more and more likely to succeed (Collins 1995). We plan to continue this work by attempting to evaluate some of these genes as candidates for MGA1. If this approach fails, we shall proceed by physical mapping and positional cloning.

Acknowledgments

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References

Abdelaal MA, Ahmed AF (1991) Case report: Imerslund-Gräsbeck syndrome in a Saudi family. Acta Paediatr Scand 80:1109–1112

Anttila R, Salmi HA (1967) Selective malabsorption of vitamin B12 with proteinuria in children. Acta Paediatr Scand 52:238–240

Ben-Bassat I, Feinstein A, Ramot B (1969) Selective vitamin B12 malabsorption with proteinuria in Israel: clinical and genetic aspects. Isr J Med Sci 5:62–68

Broch H, Imerslund O, Monn E, Hovig T, Seip M (1984) Imerslund-Gräsbeck anemia: a long-term follow-up study. Acta Paediatr Scand 73:248–253

Burman JF, Jenkins WJ, Walker-Smith JA, Phillips AD, Sourial NA, Williams CB, Mollin DL (1985) Case report: absent ileal uptake of IF-bound vitamin B12 in vivo in the Imerslund-Gräsbeck syndrome (familial vitamin B12 malabsorption with proteinuria). Gut 26:311–314

Chanarin I (1979) Intrinsic factor. In: Chanarin I (ed) The megaloblastic anaemias, 2d ed. Blackwell Scientific, Oxford, pp 76–92

Collins FC (1995) Positional cloning moves from perditional to traditional. Nat Genet 9:347–350

Cuticchia AJ, Fasman KH, Kingsbury DT, Robbins RJ, Pearson PL (1993) The GDB (TM) Human Genome Base Anno 1993. Nucleic Acids Res 21:3003–3006

de la Chapelle A (1993) Disease gene mapping in isolated human populations: the example of Finland. J Med Genet 30:857–865

Furuhjelm U, Nevanlinna HR (1973) Inheritance of selective malabsorption of vitamin B12. Scand J Haematol 11:27–34

Fyfe JC, Giger U, Hall CA, Jezyk PF, Klumpp SA, Levine JS, Patterson DF (1991*a*) Inherited selective intestinal cobala-

min malabsorption and cobalamin deficiency in dogs. Pediatr Res 29:24–31

Fyfe JC, Jezyk PF, Giger U, Patterson DF (1989) Inherited selective malabsorption of vitamin B12 in Giant Schnauzers. J Am Anim Hosp Assoc 25:533–539

Fyfe JC, Ramanujam KS, Ramaswamy K, Patterson DF, Seetharam B (1991*b*) Defective brush-border expression of intrinsic factor-cobalamin receptor in canine inherited intestinal cobalamin malabsorption. J Biol Chem 226:4489–4494

Gedde-Dahl T Jr (1991) Genetic epidemiology in Norway. Finska Lakaresallsleapets Handlingar 135:199–213

Gräsbeck R, Gordin R, Kantero I, Kuhlbäck B (1960) Selective vitamin B12 malabsorption and proteinuria in young people: a syndrome. Acta Med Scand 167:289–296

Gräsbeck R, Kvist G (1967) Kongenitale spezifische vitamin-B12-malabsorption mit proteinurie. A. Münch Med Wochenschr 109:1936–1944. B. Cah Coll Med Hop Paris 8:935–945

Guéant J-L, Saunier M, Gastin I, Safi A, Lamireau T, Duclos B, Bigard MA, et al (1995) Decreased activity of intestinal and urinary intrinsic factor receptor in Gräsbeck-Imerslund disease. Gastroenterology 108:1622–1628

Gyapay G, Morissette J, Vignal A, Dib C, Fizames C, Millasseau P, Marc S, et al (1994) The 1993–94 Généthon human genetic linkage map. Nat Genet 7:246–339

Imerslund O (1959) Idiopathic chronic megaloblastic anemia in children. Oslo University Press, Boston, Oslo, London

——— (1960) Idiopathic chronic megaloblastic anemia in children. Acta Paediatr Suppl 49(119): 3–65

Imerslund O, Bjørnstad P (1963) Familial vitamin B12 malabsorption. Acta Haematol 30:1–7

Kapsetaki M, Kokkinaki M, Angelicheva D, Lubyova B, Mavraki H, Argyrokastritis A, Vergnaud G, et al (1994) The EUROGEM map of human chromosome 10. Eur J Hum Genet 2:193–252

Kouvonen I, Gräsbeck R (1979) A simplified technique to isolate the porcine and human ileal intrinsic factor receptors and studies on their subunit structures. Biochem Biophys Res Commun 86:358–364

Lathrop GM, Lalouel JM, Julier C, Ott J (1984) Strategies for multilocus linkage analysis in humans. Proc Natl Acad Sci USA 81:3443–3446

MacKenzie IL, Donaldson RM Jr, Trier JS, Mathan VI (1972) Ileal mucosa in familial selective vitamin B12 malabsorption. N Engl J Med 286:1021–1025

McKusick VA (ed) (1992) Mendelian inheritance in man, 10th ed. John Hopkins University Press, Baltimore

Norio R (1991) 25 years of the Finnish disease heritage. Finska Lakaresallsleapets Handlingar 135:186–193

Ott J (1989) Computer-simulation methods in human linkage analysis. Proc Natl Acad Sci USA 86:4175–4178

Pearson PL (1991) The Genome Data Base (GDB)—a human gene mapping repository. Nucleic Acids Res Suppl 19:2237–2239

Pearson PL, Matheson NW, Flescher DC, Robbins RJ (1992) The GDB® (TM) Human Genome Data Base Anno 1992. Nucleic Acids Res Suppl 20:2201–2206

Seetharam B, Alpers DH, Allen RH (1981) Isolation and characterization of the ileal receptor for intrinsic factor-cobalamin. J Biol Chem 256:3785–3790

Seetharam B, Levine JS, Ramasamy M, Alpers DH (1988) Purification, properties, and immunochemical localization of a receptor for intrinsic factor-cobalamin complex in the rat kidney. J Biol Chem 263:4443–4449

Seetharam B, Ramanujam KS, Seetharam S, Li N (1991) Normal and abnormal physiology of intrinsic factor mediated absorption of cobalamin (vitamin B12). Ind J Biochem Biophys 28:324–330

Visakorpi JK, Furuhjelm U (1968) Selective malabsorption of vitamin B12. Mod Probl Pediatr 11:150–160

Weber JL, May PE (1989) Abundant class of human DNA polymorphisms which can be typed using the polymerase chain reaction. Am J Hum Genet 44:388–396

Weeks DE, Ott J, Lathrop GM (1980) SLINK: a general simulation program for linkage analysis. Am J Hum Genet Suppl 47:A204

Weissenbach J, Gyapay G, Dib C, Vignal A, Morissette J, Millasseau P, Vaysseix G, et al (1992) A second-generation linkage map of the human genome. Nature 359:794–801

Wulffraat NM, De Schryver J, Bruin M, Pinxteren-Nagler E, van Dijken PJ (1994) Failure to thrive is an early symptom of the Imerslund Gräsbeck syndrome. Am J Pediatr Hematol Oncol 16:177–180