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Familial Dwarfism with High IR-GH: Report of Two Affected Sibs with Genetic and Epidemiologic Considerations

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Summary. Two sibs with high serum IR-GH dwarfism, born to first-cousin parents are described. Genetic analysis based upon 25 reported informative kindreds indicates that the condition has an autosomal recessive pattern of inheritance. Population evaluation and epidemiology of the affected subjects suggest that mutation rates of the gene determining the disease in non-Jewish populations could be as rare as 3.2×10^{-5}. However, its prevalence must be exceptionally high among endogamous Oriental Jewish groups derived from a common gene pool in historical times.

Introduction

In 1966 Laron et al. reported the first description of patients presenting dwarfism with high serum immunoreactive growth hormone (IR-GH) levels. The familial nature of the disease was demonstrated by Pertzelan et al. (1968) in two highly consanguineous Jewish kindreds. Patients also have low somatomedin generation (Daughaday et al. 1969), usually severe shortness of stature, small external genitalia, retarded bone development (Laron et al. 1966, 1968; Laron and Sarel 1970), and affected males may exhibit slow puberty (Laron et al. 1971a; Collado et al. 1971). Furthermore, the patients have a borderline intelligence (Wechsler IQ = 70) with distinct deficiencies in visuo-motor performance (Frankel and Laron 1968).

Abnormal GH receptor sites were reported in this condition (Jacobs et al. 1976). However, according to Zonana and Rimoin (1979) the primary defect of the disease cannot presently be distinguished between: (a) a metabolic defect in somatomedin generation, (b) defective growth hormone receptor sites, and (c) an abnormal GH molecule which is immunologically normal but has altered biologic activity.

So far, 27 sibships with 39 affected subjects have been described in the literature, 64% being Oriental Jews mainly from Iran, Iraq, Yemen, and Afghanistan. Non-Jewish cases reported have been Arabs (two cases), Spaniards (three patients), a patient in Holland (nationality not reported), a Mexican in the United States, and an American (ancestry not reported) (see Table 1). However, some of these patients could be of Jewish descent (Collado et al. 1971). Most Jewish patients were described by Laron and Pertzelan (Laron et al. 1966, 1968, 1971a; Pertzelan et al. 1968) so that the abnormality should be denominated as Laron-Pertzelan dwarfism (LPD) rather than pituitary dwarfism II (Goodman 1979).

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The purpose of the present report is to describe two affected brothers and to discuss the genetic and epidemiologic background of the disease.

Case Report and Comments

The patients were two white male sibs: CP, 13 years old and JAP, 8 years old (Cases I and II, respectively), possibly of Italian extraction (IV-2 and IV-5 in Fig. 1). They have three normal sibs. No other patient has been reported in this family. The patients' parents were first-cousin (Fig. 1) and 155–160 cm tall. There is no maternal history of drug ingestions or X-ray expsure during pregnancy. Only the two patients and their parents were examined. Growth retardation in both cases was conspicuous during the second year of life and both patients had several hypoglycemic episodes between eight months and seven years of age, which did not recur spontaneously later. Late closure of fontanels was noted in both patients. Birth lengths and weights are unknown and psychomotor development is poorly documented. Learning difficulties were more evident in the younger brother who also had a speech impairment.

At examination Cases I and II (Fig. 2) showed respectively: height: 87.5 and 76 cm; weight: 12.4 and 10.0 kg; span: 83 and 72 cm; lower body segment: 43 and 35 cm; upper/lower body segment ratio: 1.02 and 1.17; head circumference: 49 and 48 cm. Both patients had trunkal obesity, a high-pitched voice, doll-like face, irregular hypoplastic teeth, absence of pubertal development, and small external genitalia. Heights and height velocities were obviously abnormal. IQ evaluated using the Terman-Merrill scale was compatible with mental ages of 10 and 5 years, in Cases I and II, respectively.

Roentgenograms showed the presence of maxillary/mandibular hypoplasia, craniofacial disproportion, retarded bone age, wormian bones in the lambdoid/coronary sutures, a small but normal shaped sella turcica, retarded dental age, and misshapen teeth in both brothers. Case I had a deformed, broad left femoral neck compatible with Legg-Perthes disease.

Results of blood counts and determination of sedimentation rate, serum proteins, mucoproteins, blood urea nitrogen, cholesterol, serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), bilirubin, creatinine, Ca, K, Na, PO_4, Cl_2, alkaline phosphatase activity, and Sabin-Feldman test were all normal; persistent total blood sugar levels of 60–75 mg/ml were seen in both brothers (normal = 70–100 mg/dl, estimated using the Auto-Analyser). In the urine, the values of Ca, K, PO_4, Na, Cl_2, and excretion of 17-hydroxy-

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Table 1. Genetic data concerning previously reported patients with LPD

Sibship no.	Sibship size	Ratio of abnormal to normal sibs	Sex-ratio of affected sibs	Parental consanguinity		Country of registry (national origin)	Reference
				Type	*f*		
1	7	3:4	2:1	Half U-N	1/16	Israel (Yemenite Jew)	1, 2, 3, 4
2	6	2:4	1:1	Half U-N	1/16	Israel (Yemenite Jew)	2, 3, 4
3	2	2:0[b]	1:1	Half 1 1/2C	1/64	Israel (Iraqi Jew)	2, 3, 4
4	2	2:0[b]	0:2	2C	1/64	Israel (Iraqi Jew)	2, 3, 4
5	1	1:0[b]	0:1	2C	1/64	Israel (Iraqi Jew)	2, 3, 4
6	7	2:5	0:2	1C+3C	5/64	Israel (Afghanistan Jew)	2, 4
7	2	2:0[b]	1:1	1C	1/16	Israel (Iraqi Jew)	2, 4
8[a]	2	2:0	1:1	(Affected father)	0	Israel (Iraqi Jew)	2, 4
9	5	1:4	0:1	1C	1/16	Israel (Algerian Jew)	2, 4
10	6	1:5	1:0	1C	1/16	Israel (Iraqi Jew)	2, 4
11	3	1:2[b]	1:0	1C	1/16	Israel (Iranian Jew)	2, 4
12	3	1:2[b]	0:1	Unrelated	0	Israel (Iranian Jew)	2, 4
13	4	1:3	0:1	Unrelated	0	Israel (Iranian Jew)	2, 4
14	9	1:8	1:0	1C	1/16	Israel (Iranian Jew)	4
15	2	1:1	1:0	U-N	1/8	Israel (Iranian Jew)	4
16	4	1:3	0:1	1 1/2C	1/32	Israel (Iranian Jew)	4
17	1	1:0	0:1	Unrelated	0	Israel (S. American Jew)	4
18[a]	?	?	1:0	Unrelated	0	USA (?)	5
19[a]	?	?	1:1	2+2 1/2C	3/128	Lebanon (Arab ?)	6
20	4	2:2	1:1	Unrelated	0	Spain (Spaniard)	7
21	3	1:2	1:0	Unrelated	0	?	8
22	3	1:2	1:0	U-N+1 1/2C	3/32	USA (Persian Jew)	9
23	2	1:1	1:0	1C	1/16	USA (Arab)	10
24	3	2:1	0:2	Unrelated	0	Spain (?)	11
25	1	1:0	1:0	Unrelated	0	Holland (?)	12
26	8	1:7	1:0	Unrelated	0	USA (Mexican)	13
27	2	2:0	1:1	2C	1/64	Spain (Spaniard)	14
28	5	2:3	2:0	1C	1/16	Brazil (Italian ?)	15

[a] Not included in the genetic analysis;

[b] Parents decided no to have more children following birth of the affected child (Laron et al. 1968); *f* = coefficient of inbreeding; U-N = uncle-niece; 1C = first cousin; 1 1/2C = first-cousin once removed; 2C = second cousin; 2 1/2C = second cousin once removed; 3C = third cousin (Morton 1961)

References: 1. Laron et al. 1966; 2. Laron et al. 1968; 3. Pertzelan et al. 1968; 4. Laron et al. 1971a; 5. Merimee et al. 1968; 6. Najjar et al. 1971; 7. Collado et al. 1971; 8. Tanner et al. 1971 and personal communication 1978; 9. New et al. 1972; 10. Elders et al. 1973; 11. Pombo et al. 1973; 12. Van den Brande et al. 1974; 13. Clemons et al. 1976; 14. Alcaniz et al. 1978; 15. Present study

corticoids were normal. Oral chromatin and dermatoglyphics were also normal. The total blood volume in Case II was estimated to be 762 ml. The 17-ketosteroids were normal in both brothers for their age and the protein-bound iodine (PBI), T_4, and ^{131}I radioiodine thyroid uptake were also normal.

The serum somatomedin levels (Phillips et al. 1974) were below 3 units/ml before and 48 h after a human growth hormone (hGH) stimulus (10 IU, IM) in Case II. Basal GH serum levels using a radioimmunoassay method (Morgan 1966) were persistently high, with mean values of 18 and 35 ng/ml in Cases I and II, respectively (normal = 0–5 ng/ml). After both insulin injection (0.05 IU/kg, IV) and sleep (90 min after sleeping), the GH values showed further increments of 100–200% in both. The total blood sugar patterns during oral glucose overload (75 g/kg) were normal but there was a sharp fall and a delayed recovery after insulin injection (0.05 IU/kg, IV) in both brothers. A balance metabolic study performed on Case II with GH revealed no significant variations in the non-proteic nitrogen urinary excretion. Preliminary studies on luteinizing hormone (LH) secretion in this condition were reported elsewhere (Toledo et al. 1981).

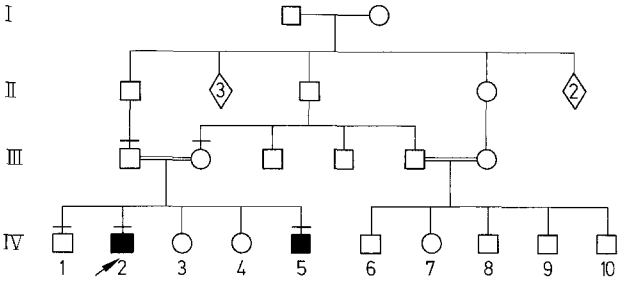

Fig. 1. Pedigree of the patients' kindred. The *arrow* indicates the proband and the bar over symbol indicates subjects clinically examined

The clinical history, physical signs, and endocrine data on both cases agreed with the diagnosis of LPD (Laron et al. 1971a; Scharf and Laron 1972). Thus, other genetic dwarfism could be ruled out (Rimoin et al. 1968). The dysmorphic dwarfs described by Van Gemund et al. (1969) have a non-specific GH unresponsiveness (McKusick 1975; Van den Brande 1978, personal communication). Also, the present patients differ from the

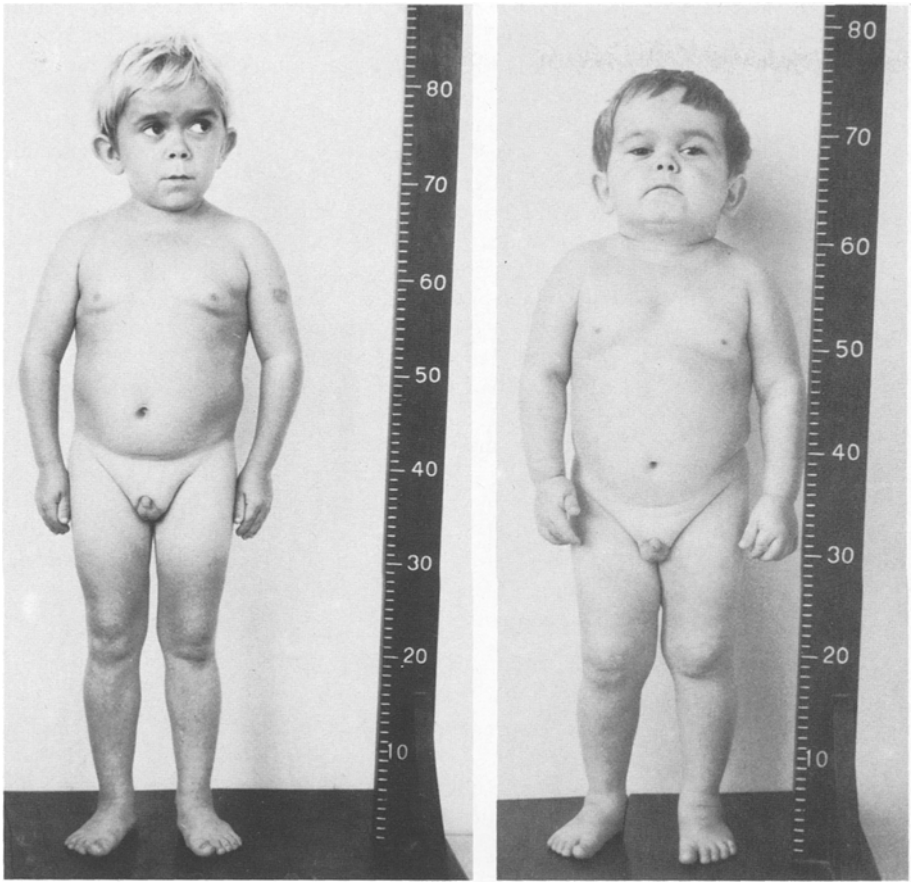

Fig. 2. Patients at 13 and 8 years of age presenting typical signs of the disease

Table 2. Distribution of cousin marriages expressed by their coefficient of inbreeding (f) among Jewish and non-Jewish parents of the affected patients with LPD

Parental ancestry	Number families	Coefficient of inbreeding				
		$f > 1/16$	$f = 1/16$	$f < 1/16$	$f = 0$	Total cousin marriages
Jewish	17	3 (17.6)[a]	7 (41.2)	4 (25.5)	3 (17.6)	14 (82.3)
Non-Jewish	10	1 (10.0)	1 (10.1)	2 (20.0)	6 (60.0)	4 (40.0)
All	27	4 (14.8)	8 (29.6)	6 (22.2)	9 (33.3)	18 (66.6)

[a] Per cent

recently described dwarfs with normal GH serum levels, low somatomedin activity, and normal generation of somatomedin after administration of hGH (Kowarski et al. 1978).

Decreased stature seems to be more often associated with LPD pedigrees than expected. Most of these subjects were parents of the patients, as pointed out by Pertzelan et al. (1968) in five kindreds, and also confirmed in non-Jewish pedigrees (Collado et al. 1971; Van den Brande et al. 1974). Since parents of the patients would be heterozygous for the mutant gene, these findings may represent heterozygote effects. However, this remains to be clarified.

Data concerning the Wechsler Intelligence Scale applied to LPD subjects (Frankel and Laron 1968; Laron et al. 1971b) revealed a borderline (full scale = 71.3) IQ, more marked in performance (IQ = 69.4) than verbal (IQ = 77.4) intelligence. These results agree with the findings of the Bender visuo-motor test which disclosed a definite cognitive deficit in the neuromotor organization of the patients. A similar deficiency of perceptual organization is found in chromosomal aberrations such as Turner's syndrome (Shaffer 1962; Money 1968), whereas hypopituitary dwarfs had normal verbal and performance IQ (Money 1975). Hypoglycemic episodes occurring in LPD during infancy could also contribute to the neuromotor impairment (Laron et al. 1968). The IQs of the present patients were 76.9 and 62.5 respectively, figures similar to the average values reported.

Genetic Analysis

Table 1 presents 27 LPD sibships described in the literature. It does not include some cases quoted by Laron et al. (1971a, Table VII) for the following reasons: Van Gemund et al.'s (1969)

Table 3. Segregation ratios observed in informative LPD sibships classified by size and expected proportions of affected sibs according to different correction methods of ascertainment (explanation in the text)

Sibship size	No. of sibships	No. of affected sibs	Total no. of sibs
1	3	3	3
2	6	10	12
3	5	6	15
4	3	4	12
5	2	3	10
6	2	3	12
7	2	5	14
8	1	1	8
9	1	1	9
Total	25	36	95

No. of sibships with only one affected sib ("singles") = 12
Observed proportion of affected sibs = 36/95 = 0.379
No. of affected sibs corrected by the *a priori* method = 33.2 ± 3.2; $P \cong 95\%$ (corrected frequency estimated as 0.247)
Frequency corrected by the *a posteriori* method = 0.243 ± 0.057; $P \cong 95\%$
Frequency corrected by the "singles" method = 0.262 ± 0.059; $P \cong 85\%$
Frequency corrected by the sib method = 0.157 ± 0.043; $P \cong 3\%$

patient is not regarded as an LPD case as a result of clinical re-examination (Van den Brande 1978, personal communication); four cases (Najjar 1969; Van den Brande et al. 1970; Daughaday and Elders 1970; Fernandes et al. 1970) were afterwards described in detail (Najjar et al. 1971; Collado et al. 1971; Elders et al. 1973; Van den Brande et al. 1974; in the Table 1); and the remaining cases referred to as personal communications were presumably never reported. In addition, the ratio of the affected to normal sibs in sibship no. 1 in Table 1 was discrepantly reported as 3:5 (Laron et al. 1966), 2:5 (Laron et al. 1968), 3:4 (Pertzelan et al. 1968), and 3:6 (Laron et al. 1971a). The ratio 3:4 was taken to be correct on the basis of other genetic references and pedigree examination (Pertzelan et al. 1968). Also inbreeding coefficients (f) were estimated from interpretation of texts and from relationships revealed by pedigrees.

Except for sibship no. 8 in Table 1, all the patients were born to normal parents, who were first-cousin or equivalent to f = 1/16 in 29.6% of the cases. The consanguinity among the parents of the affected subjects was 66.6% (Table 2).

In spite of the availability of data which could give information on recessive inheritance (Table 2), no comprehensive segregation analysis has been carried out. Clinical histories summarized in Table 1 show that among 37 affected subjects (19 males and 18 females) the sex-ratio is close to unity (1.06), as would be expected for autosomal conditions. The sex-ratio of normal sibs could not be estimated because their sex was not given in some investigations.

The observed proportion of affected sibs from 25 informative sibships produced by normal parents was 37.9%. As the families were ascertained through at least one affected child, correction for truncate selection (Morton 1959) or complete ascertainment (Smith 1959) was applied to the data using the *a priori* method (Hogben 1946), by assuming random sampling of the segregating families. Table 3 indicates that the corrected number of affected sibs (33.2 ± 3.2) is not significantly different from the observed one (33) and the corrected ratio of affected sibs is 0.247. The *maximum likehood* ratio calculated by the *a posteriori* method (Haldane 1938), is 0.243 ± 0.057, which is very close to the expected ratio (0.25). Again, assuming complete ascertainment discarding sibships with only one affected sib ("singles") as proposed by Li and Mantel (1968), the corrected proportion of affected sibs was estimated as 0.262 ± 0.059, which is also not significantly different from 0.25.

By considering the ascertainment conditions indicated by clinical histories of the probands, a single selection or single incomplete ascertainment seems to be less probable since many sibships should have included several probands (discussion in Li 1961; Emery 1976). In fact, assuming single incomplete ascertainment, correction using the *sib method* (Fisher 1934) produced an estimate of affected sibs (0.157 ± 0.043) significantly lower than 0.25.

Moreover, multiple selection or multiple incomplete ascertainment (Bailey 1951) with a constant but arbitrary probability of ascertainment is more likely to occur in the sampling of the sibships, but data on LPD are not informative about the probands in the families with more than one affected sib. In conclusion, it seems highly probable that LPD is an autosomal recessive condition.

Epidemiologic and Population Considerations

All the subjects affected with LPD were born to normal parents, except for a patient of sibship no. 8 in Table 3 born to an affected father married to an unrelated normal woman. This situation would not be genetically compatible with recessive inheritance unless the frequency of normal heterozygotes was relatively high in the population.

Most of the patients affected with LPD are Oriental Jews whose parents belonged to highly endogamous communities in Iran, Iraq, and Yemen. According to Goldschmidt et al. (1960), the prevalence of first-cousin marriages was about 14% among 2,505 Oriental-Jewish couples immigrating to Israel.

Group	*No. of couples*	*First-cousin marriages (%)*
Iran	425	15.0
Iraq	1,450	16.4
Yemen	628	8.0
All	2,505	14.2

Cousin marriages are even more frequent among the Jewish parents of the affected subjects (41%) but it is rather low (10%) among non-Jewish parents of the patients (Table 2). These figures allow one to calculate that, according to Dahlberg's (1947) formula[1], the prevalence of the disease among Oriental Jews is as high as 3.6% and the gene frequency is about 20%, a very high value for a gene causing disease. Now, assuming that first-cousin marriages are not higher than 1% in non-Jewish populations (Vogel and Motulsky 1979) the prevalence of affected homozygotes and gene frequency will become 1:32,000 and 1:178, respectively. Thus the disease is expected to be 1,123 times more frequent among Jewish groups and indicates that isolation probably occurred in historical times.

1 $q = \frac{c(1-k)}{16k - 15c - ck}$, where q is the mutant gene frequency; c the proportion of first-cousin marriages in the population; and k the proportion of first-cousin parents bearing affected subjects

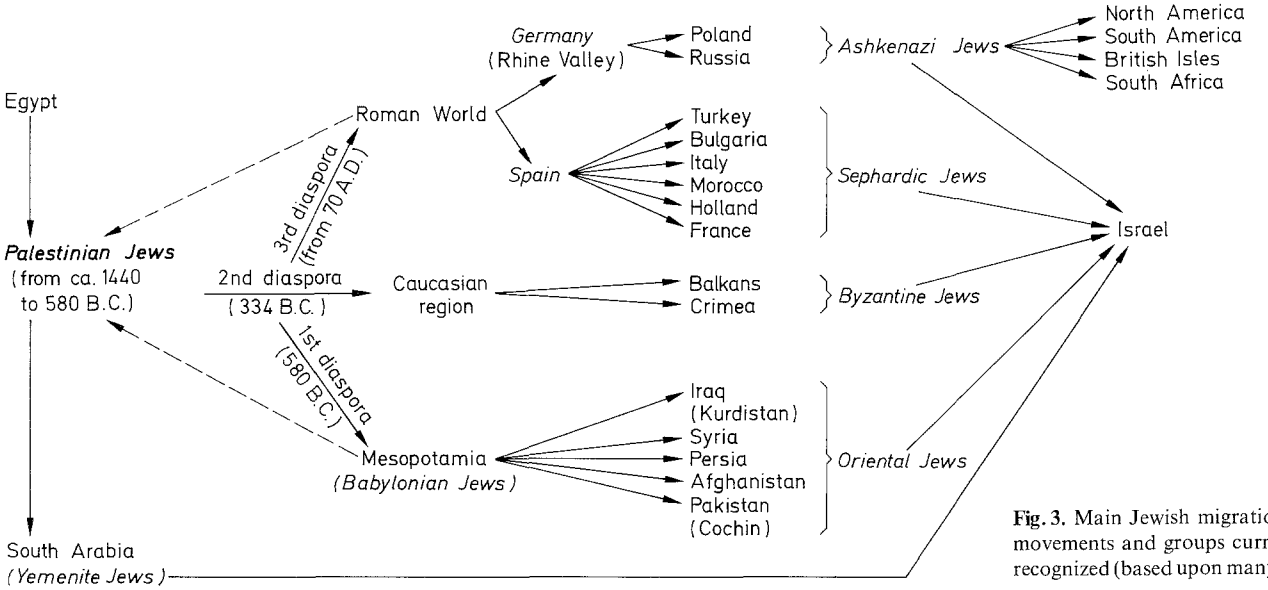

Fig. 3. Main Jewish migration movements and groups currently recognized (based upon many sources)

Too little is known about the relative viability and fitness of the LPD patients to visualize the mutation rate of the genes determining the disease. Most patients were described during childhood or adolescence but no major dysfunction or abnormality was noticed to be associated with the dwarfism (Laron et al. 1971a). Also there are no records of abortions and stillbirths in the case histories of the patients' mothers which would indicate reduced viability in the intrauterine period. The wife of an adult male patient had a stillborn child (Merimee et al. 1968) but this was probably not associated with this disease. Female patients reaching reproductive age were unmarried and childless (Alcañiz et al. 1978), and also dwarf women are known to present great obstetric difficulties. Moreover, severe shortness of stature as well as fairly reduced IQ (Frankel and Laron 1968) could lead to low marriage rates with reduced fertility.

While viability of the affected subjects does not appear to be appreciably impaired, the average number of children per affected individual would be low, suggesting that homozygotes are under some kind of selective pressure. Assuming that the selective coefficient is near to unity, mutation rates of genes determining LPD would be of the same order as the disease prevalence among non-Jewish populations ($\mu = 3.2 \times 10^{-5}$). However, until data on the reproductive performance of the affected subjects are known, the actual mutation rate should be higher than that figure.

The marked prevalence of the disease in a few small isolated groups of newcomers in Israel with exceptionally high rates of consanguineous marriages indicates that the dispersion focus of the mutant genes is located in the original endogamous communities mainly represented by Oriental (Mesopotamic) Jews living in Iran, Iraq, Afghanistan, and in Yemen, but occasionally also among their Arab neighbours.

Figure 3 summarizes the main Jewish migration movements and groups currently recognized on the basis of many sources of information (chiefly Coon 1939). This shows that the first migratory movements of Jews to Yemen had occurred in about 580 B.C. afterwards enlarged by the remnants of the third Jewish migration to the Roman Empire mainly in 70 A.D. (Mourant et al. 1978). Thus, it seems reasonable to place the original mutations to the first Palestinian Jews (Fig. 3) and to retrace the primary gene focus to Babylonian Jews in Mesopotamia, from whom the present Persian, Iraqi, and Afghanistan Jews derive. Mutant LPD genes found in Yemenite Jews would be a relic of the original genetic composition of Palestinian Jews before dispersion, in spite of the Jewish people had outbred extensively with the surrounding Arabs in Yemen, as indicated by their blood-group frequencies (Mourant et al. 1978). The registry of the disease in Afghanistan Jews indicates that Iran was the main area of gene dispersion, so it is likely that the disease is more frequent among Judaeo-Persian speaking people. Founder effects in small isolated endogamous communities living in that region could account for the genetic drift causing the high prevalence of the disease among Oriental Jews.

As a general picture, the Jewish mutant gene associated with LPD should have a few common ancestral *foci* as has been shown for other specific genetic diseases (Mourant et al. 1978), while non-Jewish mutants would be recognized as sporadic affected homozygotes in some consanguineous families (10%, Table 2) or produced by rare random marriages between heterozygotes (90%) for the gene causing LPD. However, this epidemiologic picture remains to be confirmed by extensive sampling data concerning registries of LPD.

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References

Alcañiz JJ, Salto L, Barcelo B (1978) GH secretion in two siblings with Laron's dwarfism: the effects of glucose, arginine, somatostatin, and bromocryptine. J Clin Endocrinol Metab 47:453–456

Bailey NTJ (1951) The estimation of the frequencies of recessive with incomplete multiple selection. Ann Eugen 16:215–222

Clemons RD, Costing G, Kogut MD (1976) Laron dwarfism: growth and immunoreactive insulin following treatment with human growth hormone. J Pediatr 88:427–433

Collado F, Martull MV, Torreblanca J, Fernández A (1971) Enanismo familiar con niveles altos de hormona de crescimento (GH) y falta de respuesta periferica a la hormona de crescimento humana exogena (HGH) y a la testoterona. Bol S Ped Madr 18:7–16

Coon CS (1939) The races of Europe. MacMillan Co., New York, pp 432–444

Dahlberg G (1947) Mathematical methods for population genetics. Karger, Basle, p 127
Daughaday WH, Laron Z, Pertzelan A, Heins JM (1969) Defective sulfation factor generation: a possible etiological link in dwarfism. Trans Assoc Am Physicians 82:129–140
Elders MJ, Garland JT, Daughaday A, Fisher DA, Whitney JE, Hughes ER (1973) Laron's dwarfism: studies on the nature of the defect. J Pediatr 83:253–263
Emery AEH (1976) Methodology in medical genetics. Chapter 5. Churchill Levingstone, Edinburgh
Fisher R (1934) The effect of methods of ascertainment upon the estimation of frequencies. Ann Eugen 6:13–25
Frankel JJ, Laron Z (1968) Psychological aspects of pituitary insufficiency in children and adolescents with special reference to growth hormone. Isr J Med Sci 4:953–961
Goldschmidt E, Ronen A, Ronen I (1960) Changing marriage systems in the Jewish communities of Israel. Ann Hum Genet 24:191–204
Goodman RM (1979) Genetic disorders among the Jewish people. Johns Hopkins Univ Press. Baltimore, pp 184–189
Haldane JBS (1938) The estimation of the frequencies of recessive conditions in man. Ann Eugen (Lond) 8:255–262
Hogben L (1946) An introduction to mathematical genetics. WW Norton, New York, pp 93–97
Jacobs LS, Sneid DS, Garland JT, Laron Z, Daughaday WH (1976) Receptor active growth hormone in Laron dwarfism. J Clin Endocrinol Metab 42:403–406
Kowarski AA, Schnaider J, Ben-Galim E, Weldon WW, Daughaday WH (1978) Growth failure with normal serum IR-GH and low somatomedin activity: somatomedin restoration and growth acceleration after exogenous GH. J Clin Endocrinol Metab 47:461–464
Laron Z, Pertzelan A, Mannheimer S (1966) Genetic pituitary dwarfism with high serum concentration of growth hormone; a new inborn error of metabolism? Isr J Med Sci 2:152–155
Laron Z, Pertzelan A, Karp M (1968) Pituitary dwarfism with high serum levels of growth hormone. Isr J Med Sci 4:883–894
Laron Z, Sarel R (1970) Penis and testicular size in patients with growth hormone insufficiency. Acta Endocrinol (Copenh) 63:625–633
Laron Z, Karp M, Pertzelan A, Kauli R, Keret R, Doron M (1971a) The syndrome of familial dwarfism and high plasma immunoreactive human growth hormone (IR-HGH). In: Growth and growth hormones. Proc 2nd Int Symp, Milan, May 5–7, 1971. Excerpta Medica, Amsterdam, pp 458–482
Laron Z, Pertzelan A, Frankel J (1971b) Growth and development in the syndromes of familial isolated absence of HGH or pituitary dwarfism with high serum concentration of an immunoreactive but biologically inactive HGH. In: Hamburgh M, Barrington EJW (eds) Hormones in development. Appleton-Century-Crofts, New York, pp 373–585
Li CC (1961) Human genetics principles and methods, Chapter 5. McGraw Hill, New York
Li CC, Mantel M (1968) A simple method of estimating the segregation ratio under complete ascertainment. Am J Hum Genet 20:61–81
McKusick A (1975) Mendelian inheritance in man. 4th edn. John Hopkins Univ Press, Baltimore, p 542
Merimee TJ, Hall J, Rabinowitz D, McKusick VA, Rimoin DL (1968) An unusual variety of endocrine dwarfism: subresponsiveness to growth hormone in a sexually mature dwarf. Lancet 2:191–193
Money J (1968) Cognitive deficits in Turner's syndrome. In: Vandenberg SG (ed) Progress in human behavior genetics. Johns Hopkins Univ Press, Baltimore, pp 27–30
Money J (1975) Intellectual functioning in childhood endocrinopathies and related cytogenetic disorders. In: Gardner LI (ed) Endocrine and genetic diseases of childhood and adolescence. 2nd edn. Saunders, Philadelphia, pp 1207–1218
Morgan CR (1966) Human growth hormone immunoassay: two-antibodies method using I-125 tracer. Proc Soc Exp Biol Med 121: 62–64
Morton NE (1959) Genetic tests under incomplete ascertainment. Am J Hum Genet 11:1–16
Morton NE (1961) Morbidity of children from consanguineous marriages. Progr Med Genet 1:261–291
Mourant AE, Kopéc AC, Domaniewska-Sobezak K (1978) The genetics of the jews. Clarendon Press, Oxford, pp 14–17, 23–25, 30–32, 53–56
Najjar SS, Khachadurian AK, Ilbawl MN, Blizzard RM (1971) Dwarfism with elevated levels of plasma growth hormone. N Engl J Med 284:809–812
New MI, Schwartz E, Parks GA, Landey S, Wiedemann E (1972) Pseudohypopituitary dwarfism with normal plasma growth hormone and low serum sulfaction factor. J Pediatr 80:620–626
Pertzelan A, Adam MDA, Laron Z (1968) Genetic aspects of pituitary dwarfism due to absence or biological inactivity of growth hormone. Isr J Med Sci 4:895–900
Phillips LS, Herington AC, Daughaday WH (1974) Somatomedin stimulation of sulfate incorporation in porcine costal cartilage discs. Endocrinology 94:856–863
Pombo JLH, Lozano I, Ruiz-Valdepeñas MP, Arrieta F, Rodrigues-Miñon JL (1973) Enanismo familiar com niveles elavados de STH-immunorreactive. Rec Clin Esp 131:149–152
Rimoin DL, Merimee TJ, Rabinovitz D, McKusick VA (1968) Genetical aspects of clinical endocrinology. Recent Prog Horm Res 24:365–429
Scharf A, Laron Z (1972) Skull changes in pituitary dwarfism and the syndrome of familial dwarfism with plasma immunoreactive growth hormone. Horm Metab Res 4:93–97
Shaffer JW (1962) A specific cognitive deficit observed in gonadal aplasia (Turner's syndrome). J Clin Psychol 18:403–406
Smith CAB (1959) A note on the effects of methods of ascertainment on segregation ratios. Ann Eugen 23:311–323
Tanner JM, Whitehouse RH, Hughes PCR, Vince FP (1971) Effect of human growth hormone treatment for 1 to 7 years on growth of 100 children, with growth hormone deficiency, low birth weight, inherited smallness, Turner's syndrome, and other complaints. Arch Dis Child 46:745–782
Toledo SPA, Pupo AA, Assis LM, Schwartz I, Mattar E (1981) Familial dwarfism, high serum IR-HGH and low somatomedin activity: an approach to pituitary LH secretory reserve. Arq Bras Endocrinol Metab 25:8–14
Van den Brande JL, DuCaju MVL, Visser HKA, Schopman W, Hacheng WHL, Degenhart HJ (1974) Primary somatomedin deficiency. Arch Dis Child 49:297–304
Van Gemund JJ, Angulo MSL, Van Gelderen HH (1969) Familial prenatal dwarfism with elevated serum immuno-reactive growth hormone levels and end-organ unresponsiveness. Maadschr Kindergeneesk 57:372–382
Vogel F, Motulsky AG (1979) Human genetics: Problems and approaches. Springer-Verlag, Berlin, pp 418–423
Zonana J, Rimoin DL (1979) Dwarfism, Laron. In: Bergsma D (ed) Birth defects compendium. 2nd edn. Alan R. Liss, New York, p 352

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