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REVIEW ARTICLE (INVITED)

Laron syndrome – A historical perspective

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Abstract
Laron Syndrome (LS) [OMIm#262500], or primary GH insensitivity, was first described in 1966 in consanguineous Jewish families from Yemen. LS is characterized by a typical phenotype that includes dwarfism, obesity and hypogenitalism. The disease is caused by deletions or mutations of the GH-receptor gene, causing high serum GH and low IGF-I serum levels. We studied 75 patients from childhood to adult age. After early hypoglycemia due to the progressive obesity, patients tend to develop glucose intolerance and diabetes. The treatment is by recombinant IGF-I, which improves the height and restores some of the metabolic parameters. An unexpected finding was that patients homozygous for *GH-R* defects are protected from malignancy lifelong, not so heterozygotes or double heterozygote subjects. We estimate that there are at least 500 patients worldwide, unfortunately only few treated.

Keywords Laron syndrome · Growth hormone insensitivity · Dwarfism · IGF-I · Obesity · Glucose intolerance · Diabetes · Hyperandrogenism · Cancer protection

1 Definition

Laron syndrome (LS), or primary growth hormone (GH) insensitivity (OMIM#262500), is an autosomal recessive disease caused by molecular defects in the GH receptor (*GH-R*) gene, leading to GH resistance.

2 Discovery

In 1958, three children belonging to a consanguineous Jewish family of immigrants from Yemen were referred to our clinic because of dwarfism and a history of hypoglycemia (Fig. 1). They had a typical head configuration: a protruding forehead, small face, sparse hair, obesity and hypogenitalism (Fig. 2). Overall, they resembled children with congenital isolated GH deficiency (IGHD) [1]. However, daily GH administration gave inconclusive metabolic responses and no growth stimulation [2]. Using the recently developed specific radioimmunoassay for human GH (hGH) [3, 4] we found that these patients had high basal levels of serum hGH [5, 6], which rose even more during sleep [7]. This observation led us to recognize that we have discovered a new autosomal recessive disease related to GH production and/or action [6, 8]. After our original publications, reports from other countries followed [9–12]. The disease was initially termed Laron type dwarfism [12] and, subsequently, Laron Syndrome (LS). So far we identified 175 publications on this disease, some of them reporting several patients.

Initially, we considered two possible mechanistic explanations for this new disease: (a) an abnormal (biologically inactive) hGH molecule, or (b) a state of resistance to hGH action [2]. Investigations lasting 20 years led to an irrefutable conclusion, as detailed below.

Serum immune and radio-receptor studies comparing the patients serum hGH with that from healthy subjects showed an identical behavior [13, 14], indicating a normal structure of the GH molecule in LS patients. This assumption was confirmed by hGH gene analysis [15]. Also, the regulation of GH secretion and suppression was normal [16].

Proof of the GH insensitivity was provided by the lack of IGF-I response to the administration of exogenous hGH, in

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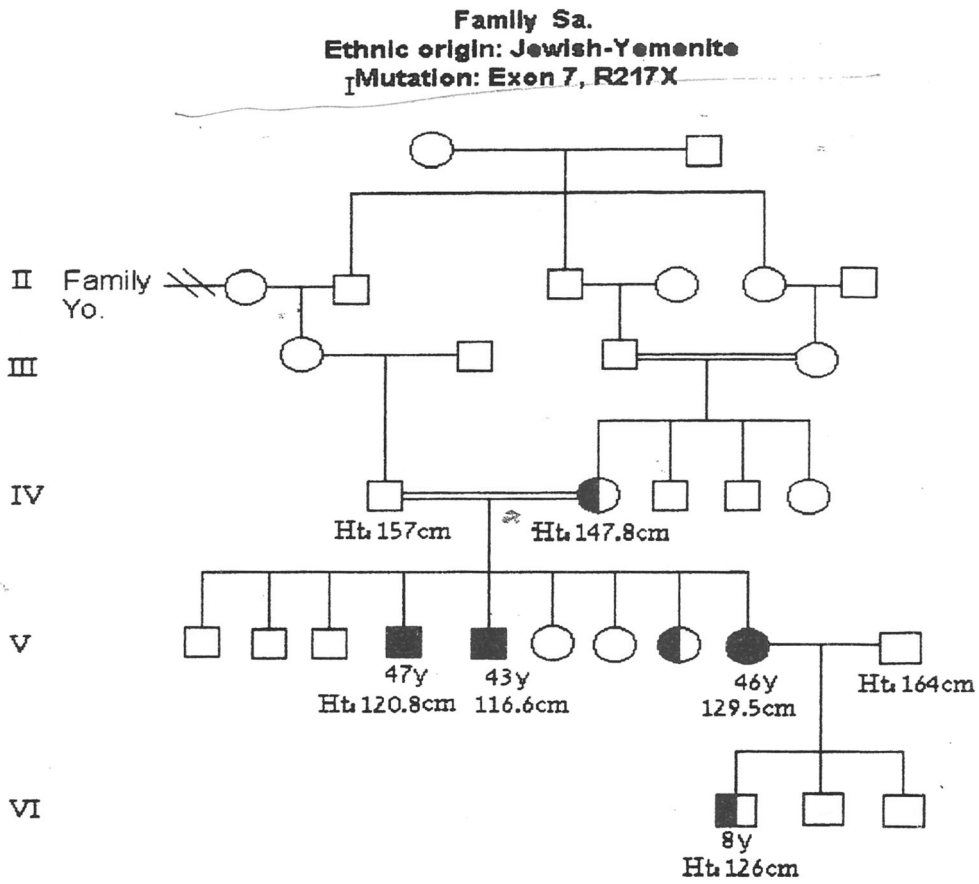

Fig. 1 Pedigree of a consanguineous Jewish-Yemenite family with Laron. Syndrome (Exon 7: R217x mutation). Black symbols indicate LS patients. Half-black symbols indicate heterozygous carriers. Reproduced with permission from Shevah O, Laron Z, Pediat Endocrinol. Rev 2006:3 (Suppl 3):489-497

contradistinction to patients with GH deficiency and normal subjects [17, 18]. This observation led to the initiation of the IGF-I stimulation test as a screening tool for LS.

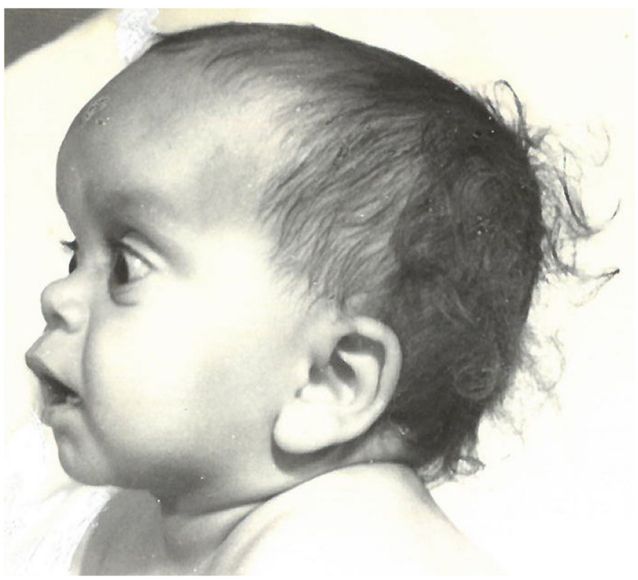

Fig. 2 Lateral view of a 3 year old boy with Laron Syndrome, showing the typical. facial features; frontal bossing, spanse hair, saddle nose, small chin

Final evidence for GH insensitivity as the critical defect in this condition was generated by performing liver biopsies of two LS patients. These experiments showed that ^{125}I-labeled hGH did not bind *in vitro* to liver membranes, in contrast to membranes derived from healthy subjects (obtained at renal transplantation) [19]. Peripheral unresponsiveness to GH was also demonstrated *in vitro* in erythrocyte progenitor cells [20, 21].

3 Etiology

Laron Syndrome is a fully penetrant autosomal recessive disease [8] caused by exon deletions [22, 23] or mutations of the GH receptor gene [24]. The majority of the mutations detected to date are in the extracellular domain-encoding exons [25–28] and a few are in the transmembrane [29, 30] or intracellular domains [31, 32]. So far, over 70 mutations have been described. Only homozygous and double heterozygous patients for these defects express the LS phenotype [33, 34].

The discovery in the Island of Flores of a thousand year-old female skeleton (named LB1) resembling that of LS patients led to the hypothesis that the founder gene for LS originated in Indonesia [35, 36]. According to this hypothesis, the mutation migrated along the Spices route to South Asia [12, 37–40] and the Mediterranean basin [41–45] and, a few centuries later,

from Spain and Portugal to Central [46] and South America [47–51], probably carried by Jews fleeing the Spanish Inquisition [52].

4 Our cohort

We have studied 75 patients with LS. The majority were referred below age 10 and included seven infants. Table 1 shows the present age of our cohort. The long-term and close follow-up of these patients, many from early childhood into late adult age, enabled us to study the genetic, endocrine, metabolic, biochemical and clinical features of this unique disease, characterized by a dissociation between the GH and IGF-I secretion and activity.

5 Diagnosis of LS

In clinically suspected patients, a non-responsive IGF-I stimulation test provides the first evidence of hGH insensitivity. The definite proof is by the molecular analysis of the *GH-R* gene. [53].

6 Clinical aspects

Gestation is usually normal. Neonates are short (42–46 cm) [1]. Hypoglycemia is very frequent [54] during infancy. The clinical characteristics of LS are summarized in Table 2. Part of the infants have a delayed motor development. If originating from the Middle East they have blue sclerae.

Special charts have been constructed by follow-up of untreated children [55]. Their growth deficit ranges from −4 to −10 SDS below the median height for sex and age (58). The body sections are not proportional. Specifically, the upper/lower body ratio is high, denoting short limbs compared to the rest of the body. The final height ranges between 116 and 142 cm in males and between 108 and 136 cm in females, resembling that of the Ecuadorian cohort [48]. The hands and feet are small for age [56] and so are the genitalia and the internal organs (a morphological defect referred as organomicria).

Due to underdevelopment of the facial bones [57, 58] there is a protruding forehead (Fig. 2). The hair is sparse and silky and exhibits an abnormal structure and morphology, as evidenced by electron microscopy [59]. The size of the ocular globe is below normal for age [60]. Finally, the teeth are crowded and tend to break due to frequent caries [61]. Part of the adult patients have cochlear hearing loss [62].

Obesity is evident already at birth, infancy Fig. 3a and prepuberty (Fig. 3b) puberty (Fig. 3c) and it is usually accompanied by hyperlipidemia [63]. It increases progressively reaching 40–50% of body composition in adults [64], in the presence of non-alcoholic fatty liver [65]. The serum adiponectin is high compared to simple obesity of the same degree [66]. Due to obesity, the infantile hypoglycemia turns with age into glucose intolerance [67] and even diabetes (Table 3) with its typical complications, including nephropathy and retinopathy in some patients [68]. An additional adverse effect of the obesity is sleep apnea [69]. Bariatric surgery in one patient resulted in a weight reduction from 80 to 40 kg (unpublished) denoting a normal adipose tissue response to its physiological regulatory mechanism. The genitalia in both sexes are below normal size [70, 71]. Puberty is often delayed, particularly in boys [72], but full sexual development is eventually achieved in both sexes.

With two exceptions, all adults have sexual relations. Ten of our LS patients are married and nine have normal children. In one consanguineous couple with one affected child, pregestational diagnosis (PGD) prevented the implantation of an affected embryo in a subsequent pregnancy.

LS patients have a reduced width of the cardiac muscle and a low cardiac output [73]. The underdeveloped muscular system causes reduced muscular strength and endurance [74]. In addition, pulmonary function tests revealed a reduced exercise capacity [75].

Table 1 Present age of our patients with Laron syndrome

Age yrs	Females	Males	Total
<10	4	1	5
10–20	4	4	8
20–30	7	9	16
30–40	4	5	9
40–50	3	6	9
50–60	10	8	18
60+	7	3	10
Total	39	36	75
			2020

Table 2 Characteristics of Laron syndrome

Dwarfism
Small cranium
Sparse hair (in early childhood)
Crowded and defective teeth
Acromicria
Organomicria
Obesity
Small genitalia
Hypoglycemia (in infancy)
High serum hGH
Low and hGH unresponsive IGF-I

Table 3 Laron Syndrome patients with Type 2 diabetes mellitus

n	Sex	Age at referral	Abnormal OGTT age (yrs)	Diabetes age (yrs)	Present age (yrs)
1	M	4 days	?	56	57
2*	M	5 m	12–26	39	49
3	M	6 m	14–16	37	40
4	M	1y	7	37	53
5	M	3y	16	60	61
6	F	3y	14–39	58	61
7	M	7y	15–26	58	62
8	M	9y	?	52	53
9*	M	36y	39	39	75
					2020

*Deceased

X-ray, CT and MRI studies revealed a small base of the skull with underdeveloped paranasal sinuses and mastoids. Part of the LS patients have diffuse parenchymal loss of the brain [76] and spinal stenosis, which leads to neurological symptomatology [77]. DEXA and MRI studies of the spine and femur showed normal volumetric bone density [78] and structure.

Repeated psychological testing showed that LS patients exhibit a wide spectrum of intellectual capacities, ranging from normal to mental retardation [79] The impact of these intellectual aptitudes affect education, occupation and quality of life. Six of our patients have an academic degree.

Finally, five of our patients have died: an infant from encephalitis, two from coronary heart disease, one during status epilepticus and the eldest patient aged 76 in a road accident.

7 Treatment

The only treatment for LS is recombinant IGF-I, available since 1986 [80]. We have treated 23 children for many years [81, 82] and four adults for one year [83]. One bolus injection of IGF-I reduced the serum levels of growth hormone-

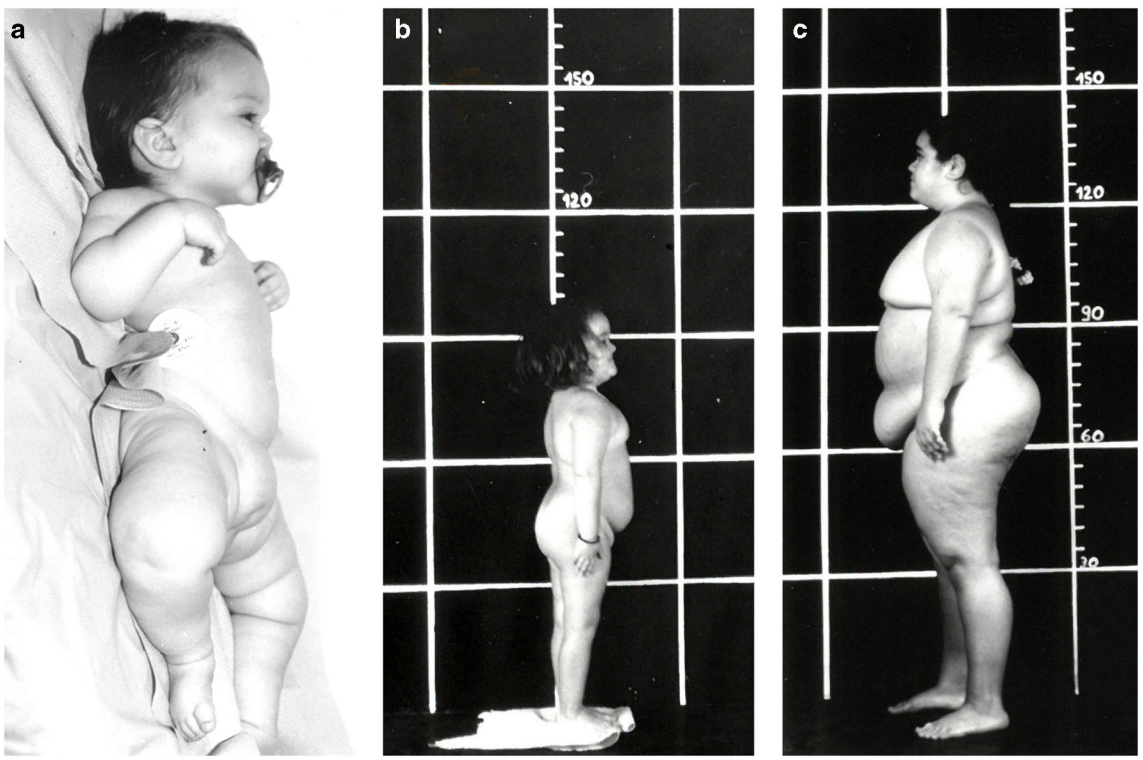

Fig. 3 Shows the progressive obesity in patients with Laron Syndrome. **a**. a 1½ year old girl. **b**. a 6 year old girl. **c**. a 15 year old girl

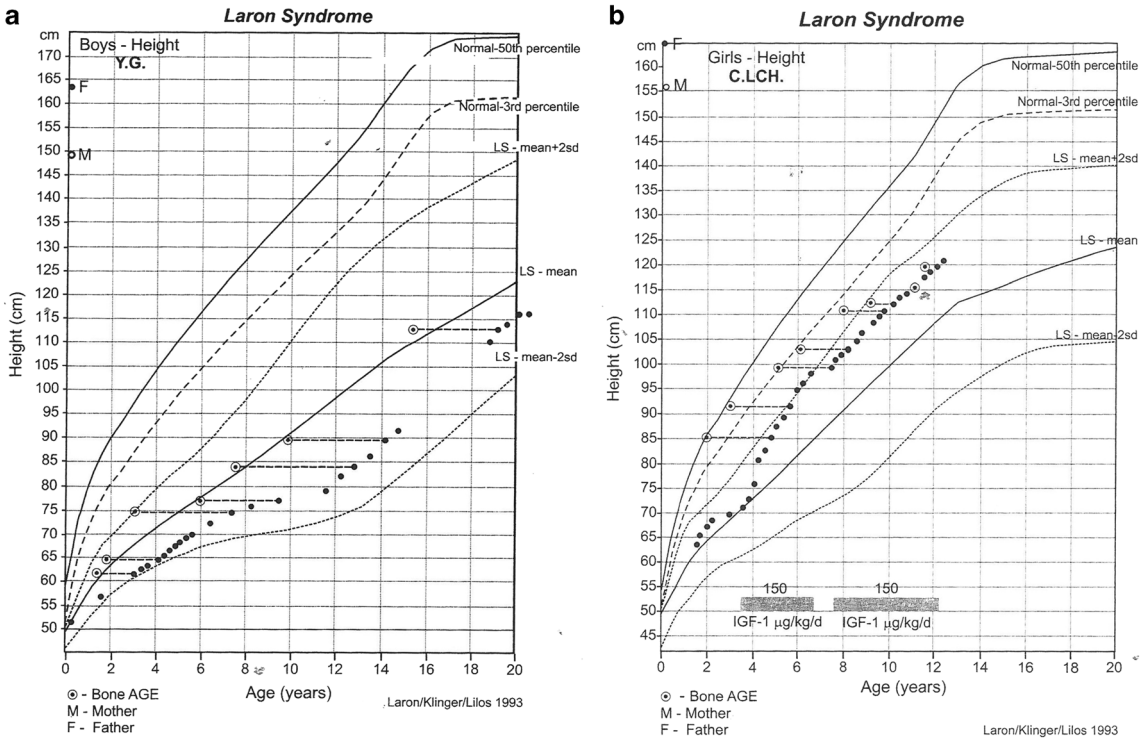

Fig. 4 **a**. Growth of an untreated boy with Laron Syndrome. **b**. Growth of a girl with Laron Syndrome before and after the initiation of IGF-I treatment. Plotted on the specific Laron growth charts (36)

releasing hormone (GHRH), GH and glucose (82). Long-term treatment using a single daily dose of 150–220 μg/kg body weight, given with the largest meal, resulted in a fast catch-up growth in the head circumference (from a mean of −3.3 ± 0.9 to +0.87 ± 1.8 SD) denoting brain growth [81] and a slower catch-up in linear growth when compared to that observed in GH-treated GH deficient children (Fig. 4b). In the first year of treatment the growth velocity of LS children is 8 cm/yr compared to 10–12 cm/yr on GH deficient children [82, 83]. For comparison Fig. 4a presents the growth of an untreated boy with LS. Only one of our LS children reached close to normal height.

After a decrease in body adiposity and lipidemia in the first months of IGF-I treatment, a progressive increase in obesity occurs [84]. The treatment of adult patients with doses of 50–150 μg/kg for 1 year resulted in beneficial metabolic effects during this period [85].

IGF-I treatment reduced blood lipotropin [86], affected the protein metabolism [87] and increased erythropoiesis and blood hemoglobin [88]. IGF-I also increased serum androgen concentrations [89].

The most common adverse effect observed during the IGF-I treatment was the marked obesity alluded to above. In one patient we reported acne and widening of the nose wings [90]. Other authors using two daily doses reported other adverse effects such as hypoglycemia, transitory papilledema, headache, swelling of lymphoid glands and spleen, etc. [91].

One important observation made during the long-term follow-up into adult age was that homozygous LS patients were protected from developing malignancies [92]. On the other hand, heterozygote individuals for the *GH-R* gene defect were not protected [93] (Table 4). This topic is elaborated in the next section.

8 Cancer

Epidemiological studies have indicated that individuals with high circulating IGF-I levels, as well as those with insulin resistance and/or obesity, are at an increased risk for multiple types of cancer [94]. Nevertheless, it is not

Table 4 Prevalence of malignancies in patients with Laron Syndrome and their first degree relatives

Subjects	n	Malignancies	P+
Homozygote Laron syndrome	230	0*	
Heterozygote 1st degree family members	218	8.3%	<0.001
Siblings only	86	5.8%	0.005

Adapted from Steuerman et al. Eur J Endocrinol 2011;164:485–489

*Basel cell carcinoma in one double heterozygote LS patient

+ Comparison between the prevalence of malignancy in relatives with that in LS patients

clear whether IGF-I plays, by endocrine, paracrine or autocrine mechanisms, a role in the *etiology* or only in the *progression* of neoplasms. The impact of low IGF-I dosages on cancer prevalence has not been previously investigated in a systematic manner.

9 Epidemiological analysis of cancer prevalence in LS

Recent epidemiological studies, including 538 congenital IGF-I deficient patients [230 LS patients, 116 IGHD patients, 79 patients with *GHRH-R* defects, and 113 patients with congenital multiple pituitary hormone deficiency (cMPHD)] and 752 of their first-degree family members, assessed prevalence of malignancy in these conditions. *None* of the 230 LS patients (up to the age of 85) developed cancer and only one out of the 116 IGHD patients had a tumor [93]. Among the first-degree family members (mostly heterozygotes) 30 cases of cancer were reported. In addition, 31 malignancies were reported among 131 further relatives. Similarly, in a study conducted in Ecuador, Guevara-Aguirre and colleagues reported that tumors were not a main cause of death among LS patients who died before 1988 and there was no proof of cancer among 99 LS patients since 1988 [95]. Of notice, observations regarding protection from cancer are supported by animal studies using the GHR/GH-binding protein (BP) KO ('Laron') mouse model [96, 97].

The interpretation of epidemiological data is in accordance with the concept that the somatotropic axis has a critical role in predisposing progenitor and somatic cells to transformation. Long-term IGF-I deficiency, on the other hand, might confer protection against impending development of a tumor.

10 Identification of genes associated with cancer protection in LS

Genome-wide profiling analyses were recently conducted to identify genes and signaling pathways that are differentially represented in LS and that might help explain cancer evasion in this condition [98]. Analyses were conducted using a collection of Epstein-Barr virus-immortalized lymphoblastoid cell lines derived from LS patients, relatives and normal controls of the same ethnic group (Yemen, Iraq, Iran). LS-derived cell lines are available at the National Laboratory for the Genetics of Israeli Populations (Tel Aviv University).

Cluster analyses identified 39 annotated genes that were differentially expressed in LS patients compared to controls (Fig. 5a). Functional analyses generated information regarding the signaling pathways in which differences between patients and healthy controls were identified. Under- or over-represented pathways in LS included genes involved in cell adhesion, G protein signaling, cell migration and motility, immune response, Jak-STAT signaling, apoptosis, metabolic pathways, etc. (Fig. 5b). Of interest, LS cells expressed decreased levels of gene transcripts associated with cell cycle progression and oncogenic transformation. These genes include, among others, cyclin A1, cyclin D1, serpin B2, versican, etc. (Table 5). Taken together, data is consistent with the concept that life-long lack of exposure to circulating IGF-I in LS patients might lead to downregulation of genes with a positive impact on proliferation and mitogenesis [99, 100].

11 Cell cycle, apoptosis and proliferation analyses in LS cells

Consistent with the differential expression of oncogenic and tumor suppressor genes in LS we have recently shown in proliferation assays that the viability of LS cells was reduced by 50% in comparison to control cells. In terms of apoptosis, flow cytometry assays revealed that the proportion of apoptotic cells was 40% higher in LS than in control cells. Finally, cell cycle analyses provided evidence that under - or over-expression of a number of key cell cycle genes translated into an altered cell cycle dynamics. Taken together, reduced proliferation along with enhanced apoptosis may, probably, explain at a cellular level the protection from cancer observed in LS patients.

12 LS cells respond differently to oxidative and glucose stresses: The role of TXNIP

Thioredoxin-interacting protein (TXNIP) plays a critical role in cellular redox control by thioredoxin. TXNIP serves as a glucose and oxidative stress sensor, being commonly silenced by genetic or epigenetic events in cancer cells. We have recently shown that levels of TXNIP are several-fold higher in LS-derived lymphoblastoid cells than in healthy control cells [100]. Consistently, IGF-I treatment led to reduction in TXNIP levels. In addition, oxidative and glucose stresses led to a marked increase in TXNIP expression. Supplementation of IGF-I attenuated TXNIP levels, suggesting that IGF-I exerts its antiapoptotic effect via inhibition of *TXNIP* [101]. Augmented *TXNIP* expression in LS may account for cancer protection in this condition. Additional genes that are differentially expressed in LS cells are currently being investigated for their potential involvement in cancer evasion.

13 Conclusions

The dissociation between GH and IGF-I actions in Laron syndrome has provided new insights on the patho-physiology of

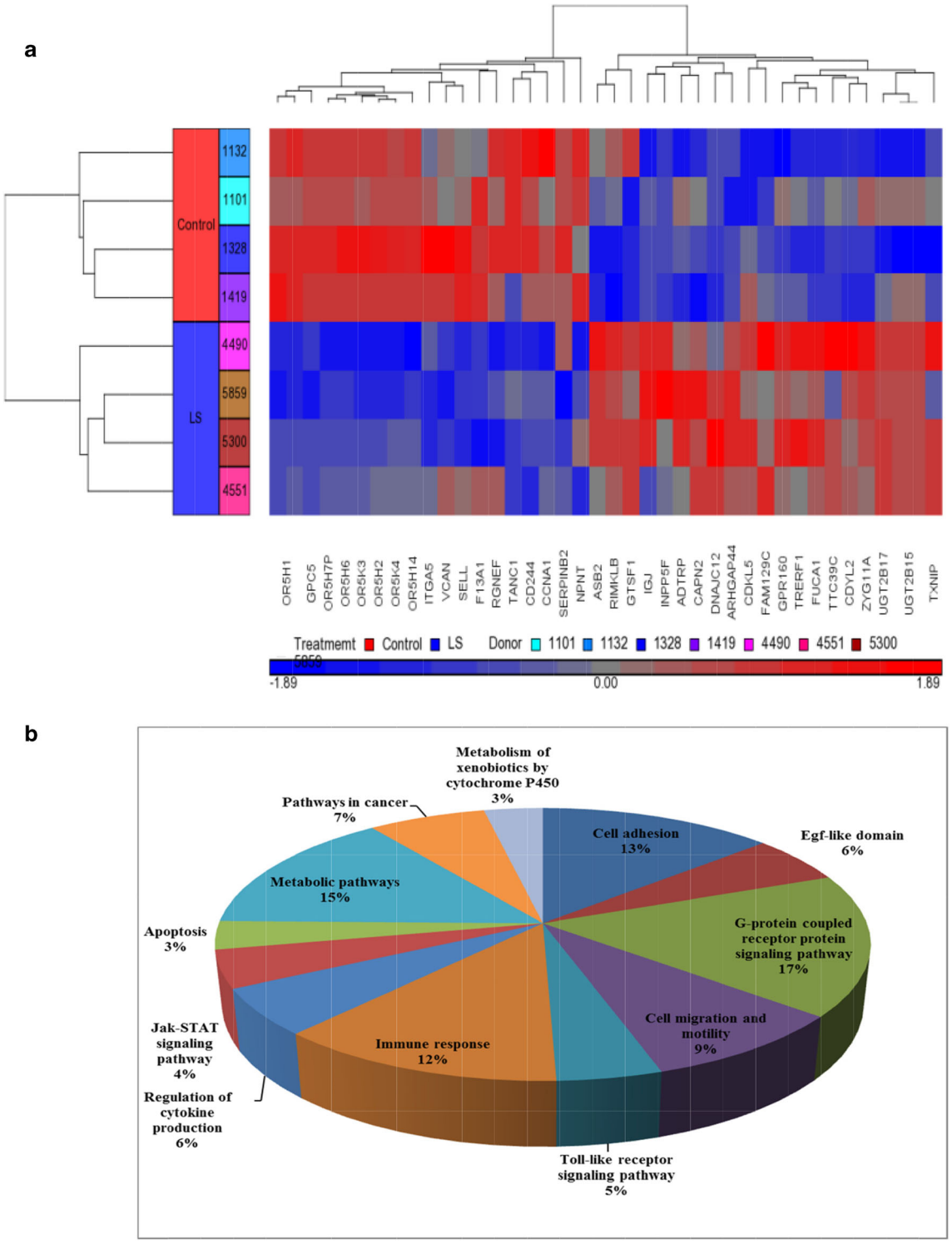

Fig. 5 Genome-wide profiling of LS patients. **a** Total RNA was prepared from four LS-derived Epstein-Barr virusimmortalized lymphoblastoid cell lines and four gender-, age range- and ethnic origin-matched controls. Genomic analyses were conducted using Affymetrix CheneChip arrays, which offer whole transcript coverage. Bioinformatics analyses were conducted using Partek Genomics Suite software. The figure depicts a cluster of 39 genes that are differentially expressed in LS patients compared to controls. Up-regulated genes are shown in red, and down-regulated genes are shown in blue. Gene names are denoted in the x-axis, **b** Pie chart of gene functions. The sections represent the percentage of genes associated with each biological function

Table 5 Selected differentially regulated genes in LS patients

	Biological role
Genes downregulated in LS	
Cyclin A1	Cell cycle
AKT3	Apoptosis
Versican	Extracellular matrix proteoglycan
Olfactory receptor	Detection of odor molecules.
Nephronectin	Cell adhesion
Serpin B2	Apoptosis and proliferation
Genes upregulated in LS	
UDP glucuronosyltransferase 2 family	Elimination of xenobiotic substances
G protein coupled receptor	Signaling
Thioredoxin interacting protein	Metabolic regulation
ZYG11A	Cell cycle regulator
CAPN2	Extracellular matrix disassembly

congenital IGF-I deficiency. Furthermore, research on LS over more than 50 years has generated invaluable information on the biological impact of this endocrine axis on the skeletal, protein, lipid and carbohydrate systems. Of special basic and translational interest is the fact that congenital IGF-I deficiency protects from malignancy throughout the entire lifespan. Extensive details on this syndrome have been published in Laron, Kopchick JJ: Laron Syndrome from Man to Mouse Heidelberg, New York, Springer 2011 pp. 531.

Compliance with ethical standards The study was approved by the Hospital Ethics Committee.

Conflict of interest Zvi Laron has nothing to declare. Haim Werner has nothing to declare.

Declarations Not applicable.

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