

# Genome-wide profiling of congenital insulin-like growth factor-1 deficient patients: translational implications in cancer prevention and metabolism

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## Abstract

Laron syndrome (LS) is a rare genetic disorder identified in the 1950s by Professor Zvi Laron. LS results from mutation of the growth hormone receptor (*GH-R*) gene, leading to congenital insulin-like growth factor-1 (IGF1) deficiency and dwarfism. Recent epidemiological studies have shown that LS patients do not develop cancer, emphasizing the crucial role of the IGF1 axis in cancer biology. Genome-wide profiling of LS patients conducted in our laboratory led to the identification of genes and signaling pathways that are over- or under-represented in LS compared to healthy controls of the same age range and ethnic group. Differentially expressed genes may be responsible for the association between lifetime low IGF1 values and protection from cancer. This *experiment of nature* may provide invaluable information that might translate into novel therapeutic approaches in modern oncology.

## Introduction

The processes of growth, differentiation and cell death are tightly regulated by multiple cellular and secreted factors that, in a highly orchestrated manner, regulate the time- and tissue-specific expression of a wide array of genes. Disruption of this genetic program may lead to a pathological phenotype, including tumor formation. The vast amount of information that has been generated in recent years following the elucidation of the human genome, combined

with the almost daily integration of new data emanating from *state-of-the-art* technologies, are changing our notions and dogmas about biological processes. In the area of cancer research, in particular, genomic and proteomic approaches, among other sophisticated platforms, are having a huge impact on our understanding of both basic and clinical questions. Biological processes are now amenable for integrative examination at multiple levels of analysis, ranging from molecular to organismal levels. The present review article focuses on the growth hormone (GH)/insulin-like growth factor-1 (IGF1) axis, an important endocrine network with key roles in physiological and pathological states.

## The growth hormone-insulin-like growth factor-1 endocrine axis

The GH/IGF1 axis has a fundamental role in growth and development throughout life.<sup>1</sup> As originally postulated by Salmon and Daughaday in the mid-1950s, GH actions are mediated by a liver-produced peptide initially termed *somatomedin* and, subsequently, IGF1.<sup>2</sup> IGF1 is also produced by extra-hepatic tissues and circulates as a ternary complex with IGF-binding protein-3 (IGFBP3) and an acid-labile subunit (ALS).<sup>3,4</sup> At the cellular level, IGF1 functions as a progression factor that is required by the cell to traverse the cell cycle.

IGF1 and closely related IGF2 ligands activate a common receptor, the IGF-1 receptor (IGF1R), which signals mitogenic, antiapoptotic and pro-survival activities<sup>5-8</sup> (Figure 1). The IGF1R is a heterotetrameric cell-surface tyrosine kinase receptor coupled to several intracellular second messenger pathways, including the *ras-raf*-MAPK and PI3K signaling cascades.<sup>9</sup> IGF1R is vital for cell survival, as illustrated by the lethal phenotype of mice in which the *IGF1R* gene was disrupted by homologous recombination.<sup>10</sup> IGF1R is evolutionarily related to the insulin receptor (InsR) and is regarded as a key player in malignancy. Transformed cells display augmented numbers of IGF1R on their cell surface as well as increased levels of IGF1R mRNA, suggesting that up-regulation of the *IGF1R* gene constitutes a common paradigm in most types of cancer.<sup>11,12</sup> The role of the InsR in cancer biology is still a controversial topic, albeit a number of studies have established that the InsR-A isoform mediates mitogenic actions in breast and other cancers.<sup>13</sup>

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## Congenital insulin-like growth factor-1 deficiencies: the Laron syndrome case

Growth retardation in infants is multifactorial, although a large portion of the cases remains *idiopathic* because no genetic (or other) defect could be identified.<sup>14,15</sup> Prenatal IGF1 expression is GH-independent, though it becomes reliant on GH secretion shortly before birth and remains GH-dependent during postnatal life. *Congenital IGF1 deficiency* is characterized by low serum IGF1 but normal to elevated GH production. These conditions may result from: i) GH releasing hormone-receptor (*GHRH-R*) defect; ii) *GH* gene deletion (isolated GH deficiency, IGHD); iii) GH receptor (*GH-R*) gene deficiency (Laron syndrome, LS); and iv) *IGF1* gene deletion. Additional conditions leading to congenital IGF1 deficiency are defects of post-GH-R signaling (e.g., STAT5b defects) and *ALS* mutations.<sup>16-19</sup>

Laron syndrome is a type of dwarfism caused by molecular defects (usually dele-

tions or mutations) of the *GH-R* gene, or post-receptor pathways, leading to congenital IGF1 deficiency.<sup>20</sup> This genetic (autosomal recessive with full penetrance) entity was identified by Prof. Zvi Laron in the late 1950s in three siblings of Yemenite origin and reported in 1966.<sup>21</sup> The typical features of classical LS are short stature (-4 to -10 SDS below the median normal height), typical face, obesity, high basal serum GH and low IGF1, unresponsive to the administration of exogenous GH.<sup>22</sup> The recognition that an inherited mutant *GH-R* gene is the etiological factor behind LS was reported in 1984.<sup>23,24</sup> Several *GH-R* defects were identified, including exon deletions and nonsense, frame shift, and missense mutations.<sup>25</sup> The majority of the mutations are in the extracellular domain of the receptor while a number of mutations were mapped to the transmembrane and cytoplasmic domains<sup>26-28</sup> (Figure 2).

(mostly heterozygotes) 18 cases of cancer were reported (8.3%). In addition, five malignancies were reported among 86 siblings (5.8%). It is important to emphasize that despite the fact that the total number of patients in these studies was small, these differences were highly significant in statistical terms. Furthermore, the observations regarding cancer protection are supported by animal experiments using the *GH-R*/*GH*-binding protein (BP) KO (*Laron*) mouse model.<sup>36</sup>

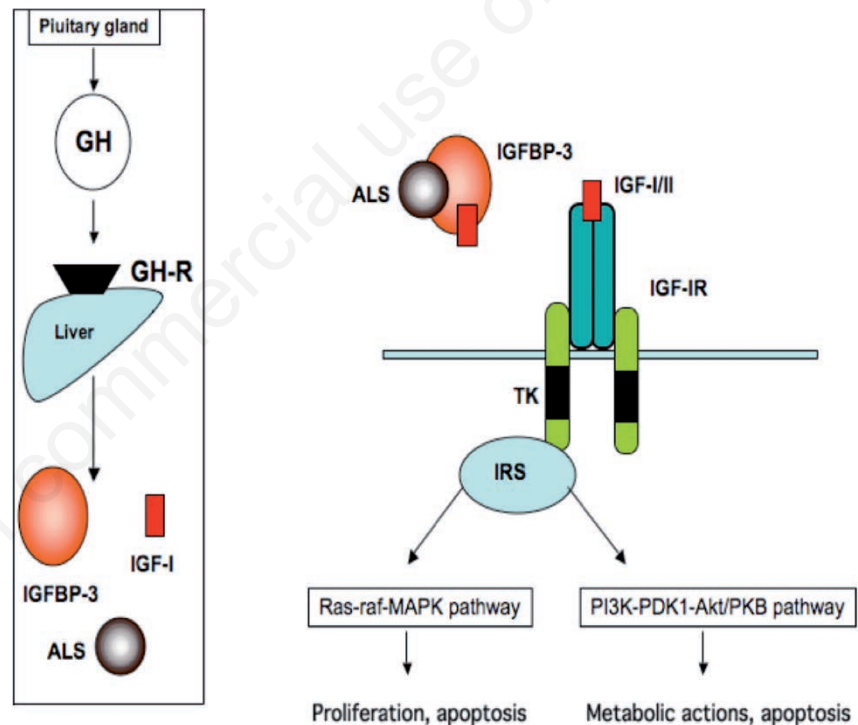
The finding that congenital IGF1 deficient patients do not develop cancer is of major clinical and scientific value. The interpretation of epidemiological data is

consistent with the notion that the *GH*/*IGF1* axis has a fundamental role in predisposing progenitor and somatic cells to malignant transformation. Conversely, congenital IGF1 deficiency might confer protection against future development of cancer. We envision a scenario in which life-long lack of exposure to IGF1 in LS patients activates apoptotic, autophagic and cancer-protecting pathways at the organism level. Studies aimed at identifying some of these protective mechanisms will be described in the next section. Of notice, similar results concerning cancer protection were reported by Guevara Aguirre and collaborators in an Ecuadorian cohort of LS patients.<sup>37</sup>

### Laron syndrome patients are protected from cancer development

Epidemiological studies have indicated that individuals with increased circulating IGF1 levels, as well as those with insulin resistance and obesity, are at an increased risk for multiple types of cancer.<sup>29-33</sup> Nevertheless, it is not clear whether IGF1 plays, by endocrine, paracrine or autocrine mechanisms, a role in the *etiology* or only in the *progression* of neoplasms. Of basic and translational importance, it is relevant to explore whether individuals with reduced serum IGF1 values have a low cancer incidence.

In recent epidemiological studies including 538 congenital IGF1 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, prevalence of malignancy was assessed by responding to a questionnaire.<sup>34,35</sup> None of the 230 LS patients (up to the age of 85) included in this cohort developed cancer and only one out of the 116 IGHD patients had a tumor (Table 1). Among 218 first-degree family members



**Figure 1.** The growth hormone (GH)/insulin-like growth factor-1 (IGF1) signaling pathway. IGF1 and IGF2 bind to the extracellular domain of the IGF1 receptor (IGF1R) and induce autophosphorylation of its tyrosine kinase (TK) domain. The bioavailability of the ligands is controlled by a family of IGF-binding proteins (IGFBP). IGFBP3, the most abundant BP in serum, circulates as a ternary complex with the ligand and an acid-labile subunit (ALS). Inset: activation of liver GH-receptor (GH-R) by GH leads to biosynthesis of IGF1, IGFBP3 and ALS. The *GH-R* gene is mutated in Laron syndrome.

**Table 1.** Prevalence of malignancy in Laron syndrome patients.

Laron syndrome patients			First degree family members			Siblings only		
N	Malignancies	%	N	Malignancies	%	N	Malignancies	%
230	0	0.0	218	18	8.3	86	5	5.8

## Genome-wide profiling of Laron syndrome patients

In order to identify differentially expressed genes that might be linked to cancer protection in LS patients, our laboratory has recently conducted a genome-wide profiling based on our collection at the National Laboratory for the Genetics of Israeli Populations (Tel Aviv University, Israel).<sup>38</sup> Specifically, RNA was obtained from Epstein-Bar virus-immortalized lymphoblastoids derived from four female LS patients and four controls of the same age range (LS,  $44.25 \pm 6.08$  yr; controls,  $51.75 \pm 11.3$  yr; mean  $\pm$  SD; P value=0.29) and same ethnic origin (Iraq, Iran, Yemen). One-way ANOVA was performed using Partek Genomics Suite to create a list of differentially expressed genes. A cluster analysis of differentially expressed genes is depicted in Figure 3A. Thirty-nine annotated genes that were differentially expressed in LS compared to healthy controls were identified (with a P value of  $<0.05$  and fold-change difference cutoff  $>|2|$ ). As shown in Figure 3B, Principal Component Analysis (PCA) revealed a good discrimination between experimental groups. Bioinformatic analyses aimed to identify genes and pathways that are under- or over-represented in LS are presented in the next section.

## Functional analyses

Functional analyses were conducted to identify co-expressed genes sharing the same pathways. Analyses provide evidence for a number of shared pathways, including cell adhesion, G-protein signaling pathway, cell migration and motility, immune response, Jak-STAT signaling, apoptosis, metabolic pathways, *etc.* (Figure 3C). This differential expression may, potentially, explain the evasion of LS patients from cancer. Of relevance, bioinformatic analyses detected markedly reduced levels of gene transcripts associated with oncogenic transformation and cell cycle progression. These genes include, among others, cyclin A1, cyclin D1, serpin B2, versican and zinc finger protein Sp1. Taken together, data are consistent with the concept that life-long lack of exposure to circulating IGF1 in LS patients might lead to downregulation of genes with a positive impact on proliferation and mitogenesis. It is reasonable to assume that IGF1 exposure activates epigenetic and transcription pathways critical for gene expression. Lack of exposure to physiological IGF1 levels in LS patients abro-

gates these signaling pathways, with important consequences in terms of cancer avoidance.

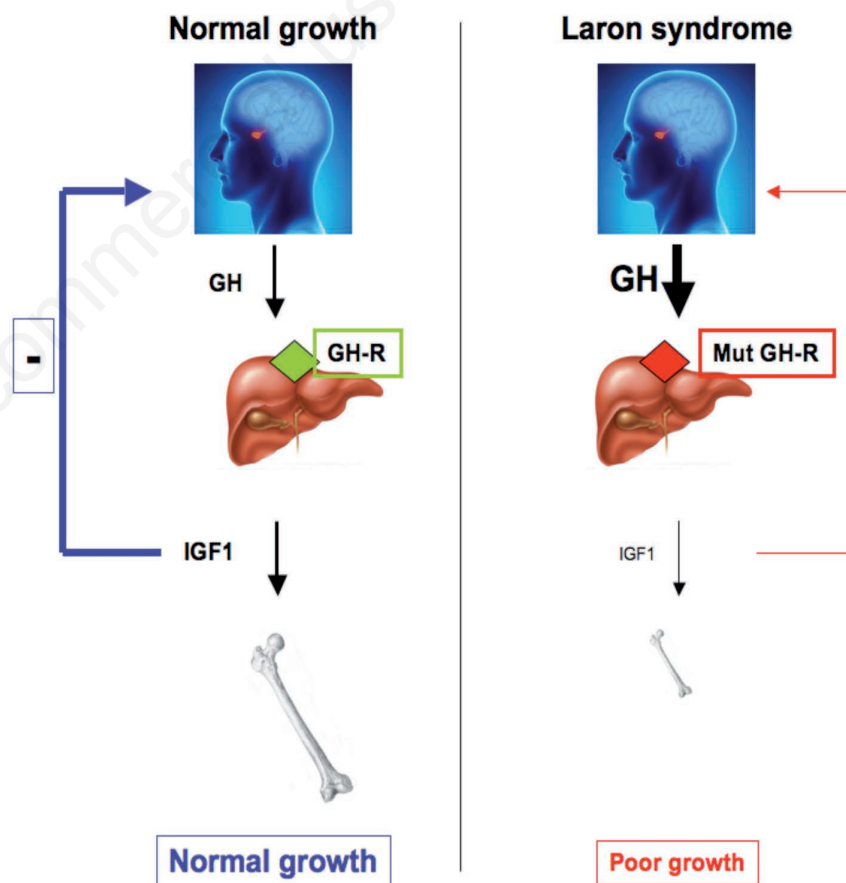
## Identification of novel metabolic genes in Laron syndrome patients

Of particular interest, genome-wide profiling revealed enhanced expression of genes associated with protection from toxic xenobiotic substances and metabolites in LS-derived lymphoblastoid cells. These genes include, among others: i) uridine diphosphate (UDP) glycosyl transferase gene family (*UGT2B15*, *UGT2B17*; fold-change=12.4); ii) ZYG-11 family member A (*ZYG11A*; fold change=4.2); iii) ribosomal modification protein RimK family

member B (*RIMKLB*; fold change=3.7); and iv) thioredoxin-interacting protein (*TXNIP*; fold-change=2.35). These genes have not been previously linked to the IGF1-insulin signaling pathway.

## Uridine diphosphate-glycosyl transferase gene family

The UDP-glycosyl transferase gene family (*UGP*) plays a major role in the conjugation and subsequent elimination of potentially toxic xenobiotic and endogenous compounds. This protein displays activity towards several classes of xenobiotic substrates, including simple phenolic compounds, flavonoids, anthraquinones and certain drugs and their hydroxylated metabolites. Genomic analyses provided evidence that the levels of *UGT2B15/UGT2B17* mRNAs were  $\sim 12$ -fold higher in LS than in control cells. These results were validated by qPCR. Data



**Figure 2. Schematic representation of the growth hormone (GH)/insulin-like growth factor-1 (IGF1) axis in Laron syndrome.** Hypophyseal-derived GH stimulates IGF1 production by the liver, with ensuing bone elongation and longitudinal growth (left panel). *GH-receptor (GH-R)* mutations in Laron syndrome lead to congenital IGF1 deficiency, usually linked to poor growth. In addition, abrogation of IGF1 production leads to inadequate negative feedback at the pituitary gland, leading to high circulating GH levels.

is consistent with the finding that survival of LS cells following oxidative damage was several-fold higher than controls. Combined, results imply that increased *UGT2B15/UGT2B17* levels in LS might confer upon these cells a protective effect against oxidative and, potentially, genotoxic damage. If substantiated by functional assays, this finding may provide valuable insight into the physiological basis for reduced cancer in LS.

### ZYG-11 family member A

ZYG-11 family member A (*ZYG11A*) acts as a target recruitment in an E3 ubiquitin ligase complex. The *ZYG11A* protein is composed of 759 amino acids, includes a leucine-rich repeat and has been postulated to be involved in the ubiquitin-like (Ubl)

conjugation pathway. Over-representation of *ZYG11A* in LS (4.2-fold change) may lead to hyper activation of the Ubl conjugation pathway, with ensuing ubiquitination and degradation of toxic waste compounds.

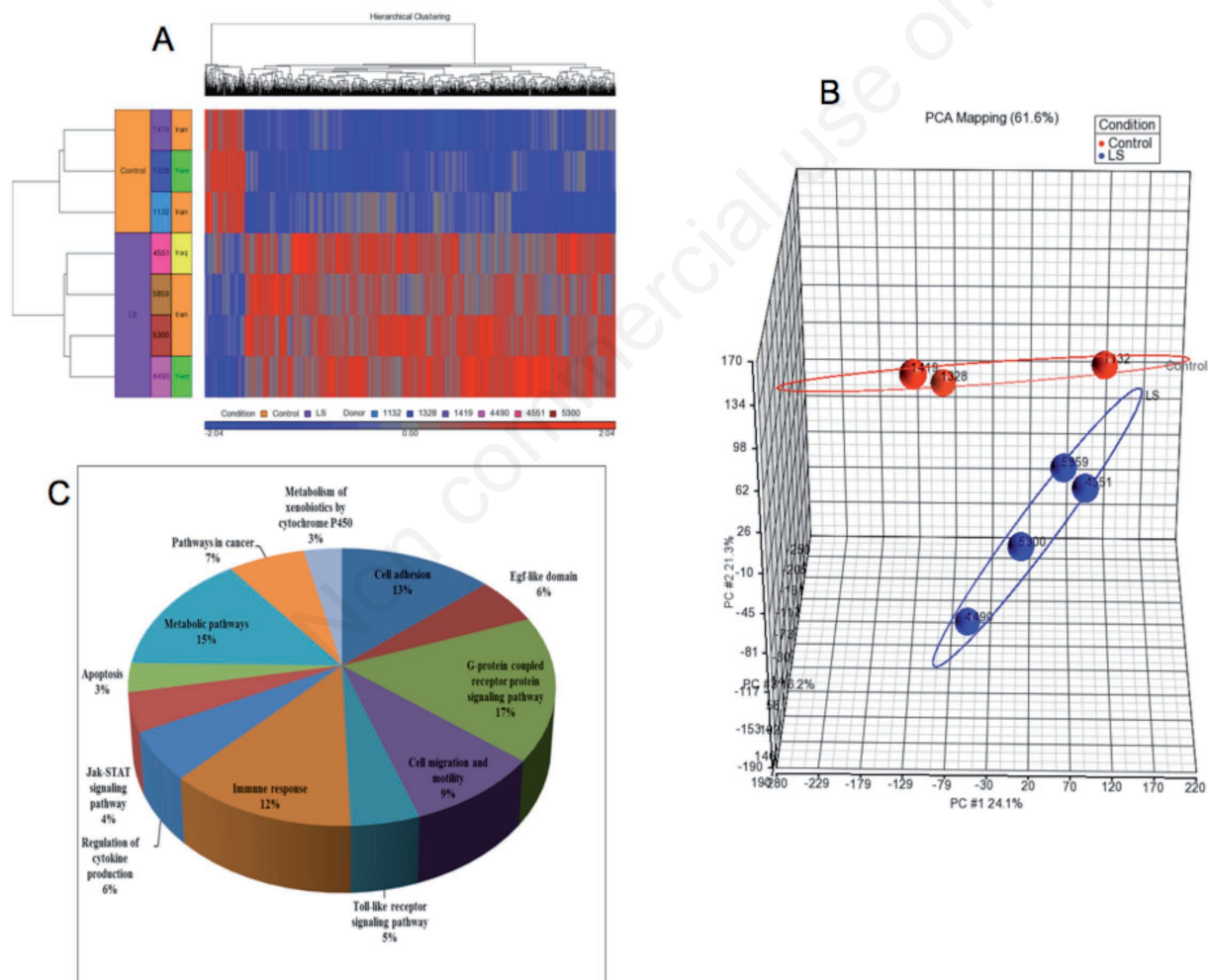
### Ribosomal modification protein

#### RimK family member B

Ribosomal modification protein RimK family member B (*RIMKLB*) is involved in cellular protein modification and metabolic processes. It is mainly localized in the cytoplasm, where it displays catalytic and ligase activity. *RIMKLB* exhibits also metal ion binding activity. Overexpression of this gene in LS (3.7-fold change) may be linked to more efficient catalytic processes, and might be linked to autophagic and apoptotic mechanisms.

### Thioredoxin-interacting protein

Thioredoxin-interacting protein (*TXNIP*) acts as an oxidative stress mediator by inhibiting thioredoxin activity or by limiting its bioactivity.<sup>39</sup> *TXNIP* inhibits the proteosomal degradation of *DDIT4* and, thereby, contributes to the inhibition of the mTOR complex. *TXNIP* belongs to the arrestin family and is downregulated in response to oxidative stress. *TXNIP* has also been reported to function as a tumor suppressor gene that is commonly silenced by genetic or epigenetic mechanisms in cancer cells.<sup>40</sup> As mentioned above, genome wide analyses demonstrated that the *TXNIP* gene was markedly upregulated in LS patients in comparison to healthy control subjects. Considering the fact that *IGF1* is upregulated in most types of cancer, we



**Figure 3.** Genome-wide profiling of Laron syndrome (LS) patients. A) Cluster analysis of differentially expressed genes in lymphoblasts derived from LS patients and healthy controls of the same age range and ethnic origin. The figure depicts a cluster of 39 differentially expressed genes ( $FC > 2$  or  $< -2$  and  $P < 0.05$ ). Up-regulated genes are shown in red, and down-regulated genes are shown in blue ( $FC$ , fold change). B) Principal component analysis (PCA) display of four LS and three control arrays used in the experiment. Blue circles: LS patients; red circles: controls. PCA revealed a good discrimination between both experimental groups. C) Pie chart of gene functions. The sections represent the percentage of genes associated with each function.

hypothesize that the *TXNIP* gene may be under inhibitory regulation by IGF1. *TXNIP*, in turn, may act by protecting LS patients from cancer.

## Conclusions

The finding that congenital IGF1 deficient patients do not develop cancer (up to the age of 85) is of an *exceptional* clinical and scientific value. The interpretation of epidemiological data is consistent with the notion that homozygous congenital IGF1 deficiency, or deficiency in early childhood, may confer protection against future development of cancer. This *experiment of nature* emphasizes the central role of the IGF1 hormonal axis in cancer and justifies the rational use of available post-genomic technologies in order to elucidate in an unbiased fashion the molecular basis that underlies the evasion of LS patients from cancer. The studies described in this *Translational Medicine Reports* review identified mechanisms and factors responsible for the association between lifetime low IGF1 levels and protection from cancer.

The results of genome-wide profiling described here shed light on potential genetic changes associated with evasion of congenital IGF1 deficient patients from malignant transformation and may have a major translational impact in oncology. In summary, by *mining* genomic data from LS patients, a rare condition associated with cancer protection, we might be able to generate clinically relevant novel information and to translate this information into new prophylactic and anticancer tools in oncology. The analyses described here emphasize the power of post-genomic platforms in modern medical research.

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