

be that caloric restriction down regulates the expression of sodium dicarboxylate cotransporter(s) genes thus decreasing the rate of intracellular metabolism and consequently increasing cellular life. These observations suggest that perhaps some obese subjects possibly have gain-of-function mutations in one or another sodium dicarboxylate cotransporter that enhance intracellular intermediary metabolism leading to accumulation of fat, while other individuals (who can

“eat a tone and never gain an ounce”) may have a variant that impedes metabolism. The data also suggest that it may be possible to modify the activity of these cotransporter molecules chemically - opening a portal for treatment of a group of obese subjects.

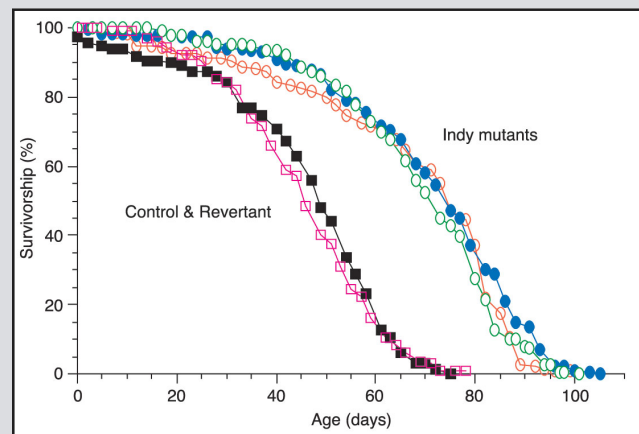
Pennisi E. Old files may hold secrets of aging. *Science* 290:2048, 2000.

Allen Root, MD

Figure

Life-span extension in *Indy* mutants. Survival curves of males heterozygous for three different *Indy* mutations, a precise excision of the P-element from *Indy* 302 (revertant), and an enhancer-trap control are shown. All flies were tested as heterozygotes over a wild-type Canton-S strain. The *Indy* mutants are *Indy*302 (open white circles), *Indy*206 (solid gray circles), and *Indy*159 (strikethrough circles). The excision line (strikethrough squares) is one of four exact excisions (sequence confirmed) of the P element obtained by mobilizing the P element from either the *Indy*302 or *Indy*206 line, using delta 2-3 transposase. The control (solid black squares) is one of four other enhancertrap control lines from the same mutagenesis that generated *Indy*302 and *Indy*206, tested as a heterozygote over Canton-S.

From Rogina B, et al. *Science* 290:2137-2140, 2000.



## Insulin Resistance and Insulin-Like Growth Factors in Children with Intrauterine Growth Retardation

The authors recently proposed that when tissues in utero are chronically depleted of insulin and IGF1, but subsequently exposed after normalization of nutrient supply in postnatal life to increased levels, insulin resistance often develops. Carrying this thesis forward, they postulate that postnatal “catch-up” growth might, therefore, be associated with a higher risk of developing insulin resistance, especially when other risk factors such as genetic predisposition and/or obesity coexist.

To investigate this possibility, 49 children with IUGR (22 boys) with birth weight <10th percentile for gestational age were studied. Children with malformations and/or genetic disorders were excluded. Stature was corrected for mid-parental height. Children were divided into two groups according to their corrected height; specifically, those with corrected height z-score  $\geq 0$  and those  $< 0$ . Insulin resistance was evaluated using OGTT, fasting glucose and insulin levels, and a G/I  $< 6$  to interpret insulin resistance. Thirty-nine percent (19/49) of the children with IUGR had a corrected stature  $> 0$  z-score and 61% had not reached their genetic height, as expressed as MPH z-score. Corrected stature at the age evaluated correlated with birth weight, whereas actual height was related to birth length, MPH

and BMI. Twenty-two percent or 11 of 49 IUGR children had a G/I  $< 6$ . The endocrine variables in children as divided on the basis of G/I  $< 6$  and  $> 6$  are provided in Table 1. All the parameters related to insulin resistance correlated with alanine aminotransferase (ALT) and gamma glutamyltransferase ( $\gamma$ -GT) levels. IGF system parameters were in the normal range and correlated neither with growth nor with insulin sensitivity.

The first aim of the study was to assess the prevalence of insulin resistance in children and adolescents with IUGR. The authors considered that insulin resistance was at a high prevalence since 22% of the children were so classified, and these data are consistent with previous studies reporting impairment in insulin sensitivity in children with IUGR. The second objective was to prove the *catch up growth hypothesis* that catch up growth induces insulin sensitivity. The data in this study suggest that catch up growth is not a risk factor. They further comment that the finding of high prevalence of insulin resistance did not show a significant influence over postnatal growth - is consistent with the intrauterine reprogramming previously postulated by the authors and is consistent with a genetic predispositioning determining both low birth weight and

insulin resistance. The authors also postulate that obesity may be an additional risk factor during childhood. One of the most important findings was the close relationship observed between insulin resistant parameters and liver function tests; this suggests that the liver might be a target organ of the reprogramming process. The authors did not find any indications that the IGF systems (IGF1, IGF1BP-3, etc) are related to the insulin sensitivity status, at least during childhood. The latter data are in accord with those of at least two other authors.

Cianfarani S, et al. *Horm Res* 2001;55(suppl 1):7-10.

**Editorial Comment:** The authors have provided excellent data on a large number of small for gestational age infants. I have not used the term *intrauterine growth retarded children* as in the title of the article, as I believe

that term should be reserved for children who are <3rd percentile. I remain skeptical that one out of every 10 children is *intrauterine growth retarded*, which would be the case if one uses the 10th percentile as cutoff. The article as presented does not indicate to me what percentages of the children born <3rd percentile had insulin resistance. The authors and others are invited to comment to the Editor concerning which criteria are appropriate to use for determination of metabolic alterations in IUGR children, as much confusion now exists among data stated to be that of IUGR.

Regardless of what I consider this limitation, the data are worthwhile and provide interpretations to postulated metabolic alterations in children who are small for gestational age.

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	G/I <6(n = 11)	G/I >6(n = 38)	p	
Age, years	10.3 ± 3.6	8.9 ± 3.3	n.s.	ALT = alanine aminotransferase
Birth weight, kg	2.16 ± 0.35	2.18 ± 0.38	n.s.	AST = aspartate aminotransferase
Birth length, cm	45.4 ± 2.8	45.8 ± 2.8	n.s.	AUC <sub>ins</sub> = area under the curve of insulin during oral glucose tolerance test
Ponderal index, g/cm <sup>3</sup>	0.002 ± 0.002	0.022 ± 0.004	n.s.	BMI = body mass index
BMI, kg/m <sup>2</sup>	18.5 ± 4.0	16.2 ± 3.9	n.s.	HOMA-β-cell = homeostasis model assessment β-cell function
BMI, z-score	1.0 ± 2.6	-0.29 ± 1.8	n.s.	HOMA-IR = HOMA for insulin resistance
Height, z-score	-1.08 ± 1.29	-1.23 ± 1.3	n.s.	IGF = insuline-like growth factor
MPH, z-score	-1.4 ± 0.6	-0.8 ± 0.9	<0.05	IGFBP = IGF binding protein
Corrected stature, z-score	0.36 ± 1.1	-0.36 ± 1.3	n.s.	IUGR = intrauterine growth retardation
Fasting insulin, mU/l	12.4 ± 9.0	8.2 ± 3.3	n.s.	MPH = midparental height
HOMA-IR	3.5 ± 1.0	1.5 ± 0.8	<0.0001	n.s. = not significant.
HOMA-β-CELL	180 ± 139	43 ± 90	<0.01	
AUC <sub>ins</sub> , mU/l	240 ± 113	164 ± 115	n.s.	
Proinsulin, pM	9.6 ± 11.2	5.0 ± 4.4	n.s.	
IGFBP-1, μg/l	83 ± 59	119 ± 50	<0.05	
IGF-I, z-score	0.41 ± 2.8	0.47 ± 3.0	n.s.	
IGF-II, z-score	0.56 ± 0.7	0.62 ± 0.9	n.s.	
IGFBP-3, z-score	0.35 ± 0.7	0.23 ± 1.3	n.s.	
IGF-I/IGFBP3 ratio	61.2 ± 23	63.5 ± 35	n.s.	
AST, U/l	29.1 ± 8.0	27.4 ± 6.7	n.s.	
ALT, U/l	27.4 ± 17.1	16.3 ± 7.2	n.s.	
γ-GT, U/l	15.7 ± 6.6	11.7 ± 3.8	n.s.	

Adapted from Cianfarani S, et al. *Horm Res* 2001;55 (suppl 1):7-10.

## The Molecular Basis of X-Linked Spondyloepiphyseal Dysplasia Tarda

The gene for X-linked form of spondyloepiphyseal dysplasia tarda has been identified as SEDT, a protein that apparently plays a role in endoplasmic reticulum-to-Golgi transport and involves subcellular localization of normal sedlin constructs. The protein is relatively small with 140 amino acids. It is located in the non-X-inactivated part of Xp22. This suggests that female

carriers express sufficient normal gene to avoid the disease.

The present study looked at 36 unrelated cases and attempted to make phenotype/genotype correlations. Mutations could be found in 30 individuals. The 6 individuals in which mutations were not found either lacked a strong family history or convincing physical