Genetic mutations, birth lengths, weights, and head circumferences of children with IGF-I receptor defects. Comparison with other congenital defects in the GH/IGF-I axis

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Background

Using new technologies, genetic defects along the GHRH-GH-IGF-I axis have been reported.

"primary" IGF-I deficiencies:

IGF-I gene deletion and IGF-I-Receptor mutation (IGF-I-R)

"secondary" IGF-I deficiency:

GHRH-R mutations, hGH-AI gene deletion (cIGHD)
hGH-R mutations (Laron syndrome LS)
cMPHD mutations including hGH deficiency

Aim

To ascertain body length, (BL) weight (BW) and head circumference, (HC) in neonates with IGF-I-receptor mutations, (IGF-I-R) and compare the findings with those described in neonates with LS, cIGHD and cMPHD

Methods

Search of the literature using PubMed. (1992-2015)
(The IGF-I receptor (IGF-I-R) was identified and cloned in 1989 and 1992).

Subjects

The clinical descriptions of 67 neonates were found in 24 articles.
Not all reports contained all the data looked for. All patients are heterozygotes for the defect as homozygocity is lethal.

Results

In the 67 patients 47 mutations of the IGF-I-R, located on chromosome 15, were found. (Fig 1)
Mean neonatal birth length (BL) available in 26 neonates (10M, 16F) was 44.2±4cm. There was no correlation between BL and type of mutations, (Fig 1) but there was a significant positive correlation between BL and gestational age (GA) (r=0.71;p<0.001) Fig 2. The BL was shorter than in neonates with LS, cIGHD and cMPHD. (Table 1)
Mean neonatal birth weight (BW) in 41 babies was 2388±74gr significantly less than that of neonates with LS, cIGHD, cMPHD, (Table 2).
There was no assosiation between BW and type of mutation, but a significant correlation with GA (r=0.55, p<0.01) (Fig 3).
The BMI available for 25 neonates ranged between 6-13 (norm 10-20)
The distribution of head circumference (HC) as SD of normal in 17 neonates with IGF-I-R mutations is shown in Fig 4.
The height of mothers of IGF-I-R mutations was significantly lower than that of children with "secondary IGF-I deficiency" (Table 3)

fig 1

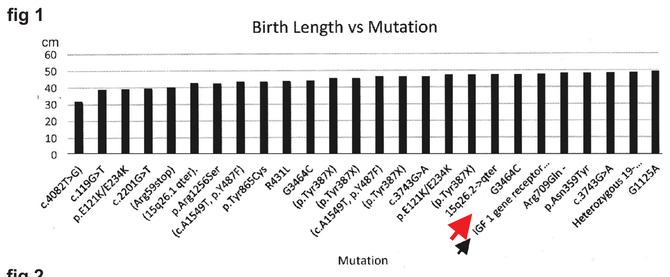

fig 2

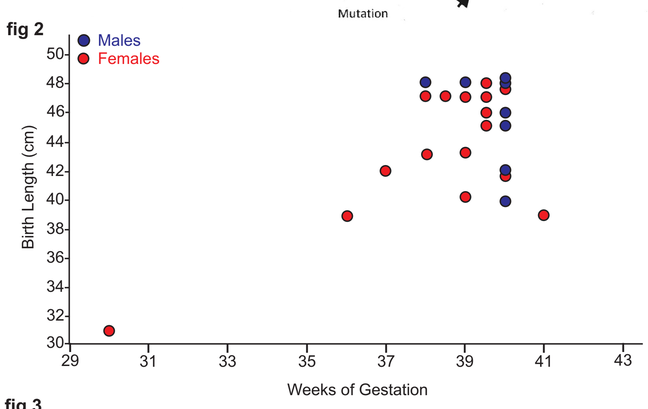

fig 3

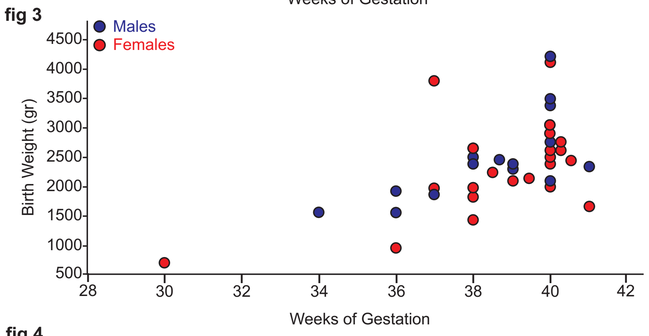

fig 4

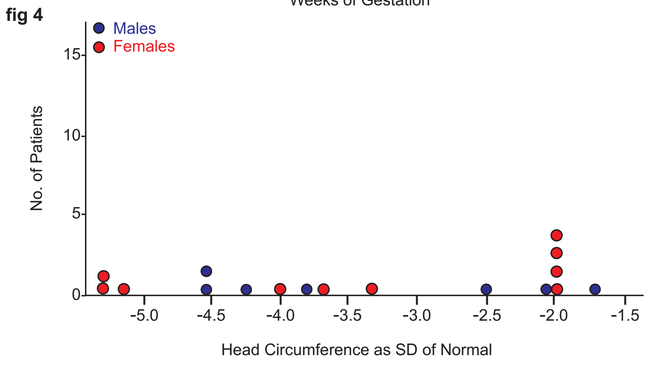

Table 1.
Birth length of neonates with IGF-I-R mutations, Laron syndrome, congenital IGHD and congenital MPHD

Diagnosis		N	Mean ± SD (cm)
IGF-I-R mutation	(1)	26	44.2 ± 4.03
Laron syndrome	(2)	30	1.95 ± 46.3
cIGHD	(3)	11	2.18 ± 48.5
cMPHD	(4)	13	2.72 ± 47.7

1 vs 2: p=0.014 2 vs 3: p=0.004
1 vs 3: p=0.002 2 vs 4: p=0.06
1 vs 4: p=0.008 3 vs 4: p=0.44

Table 2.
Birth weight of neonates with IGF-I-R mutations, Laron syndrome, cIGHD and cMPH

Diagnosis		N	Mean ± SD (gm)
IGF-I-R mutation	(1)	41	2388 ± 743
Laron syndrome	(2)	49	3180 ± 530
cIGHD	(3)	33	3220 ± 450
cMPHD	(4)	39	3000 ± 620

1 vs 2: p=0.001 2 vs 3: p=0.72
1 vs 3: p=0.001 2 vs 4: p=0.15
1 vs 4: p=0.001 3 vs 4: p=0.095

Table 3.
Height of mothers of neonates with IGF-I-R mutations, Laron syndrome, congenital IGHD and congenital MPHD

Diagnosis		N	Mean ± SD (cm)
IGF-I-R mutation	(1)	16	150.5 ± 7.3
Laron syndrome	(2)	41	154.3 ± 6.4
cIGHD	(3)	28	155.9 ± 6.8
cMPHD	(4)	32	155.2 ± 6.1

1 vs 2: p=0.058
1 vs 3: p=0.0181
1vs 4: p=0.023

Conclusions and Discussion

Heterozygote neonates with a variety of IGF-I-R mutations tend to be shorter than neonates with homozygous hGH gene deletions and GH-R defects, (Laron syndrome). They are also not obese as neonates with the above diagnostic entities. The below normal head circumference is further proof for the important role of IGF-I in the intrauterine growth of the brain in addition to that of linear growth.
We speculate that "primary IGF-I deficiency" affects intrauterine growth more severely than "secondary IGF-I deficiency", probably by preventive paracrine and autocrine IGF-I secretion.

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