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Copy Number Variants in Patients with Congenital Hypopituitarism Associated with Complex Phenotypes

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Introduction

The aetiology of congenital hypopituitarism (CH) is unknown in the majority of patients. In our cohort of 200 patients, it was possible to establish the genetic cause in only 6.5% of the patients. Copy number variants (CNVs) have been implicated as the cause of genetic syndromes with previously unknown aetiology.

Objectives

To study the presence of CNVs and its relevance in patients with CH of unknown cause associated with complex phenotypes.

Patients and Methods

35 patients were selected for whole-genome array-CGH screening in a customized platform of 180K (Oxford Gene Technologies). The most frequent complex phenotypes and the well-defined genetic syndromes are showed below:

- 35 patients with Hypopituitarism
  - Septo optic dysplasia n=10
  - Developmental delay/ intellectual disability n=6
  - Midline cranio-facial malformation n=4
  - Trichorhinophalangeal syndrome n=1
  - Rubinstein-Taybi syndrome n=1
  - Joubert syndrome n=1
  - PHACE syndrome n=1

Results

In this cohort of 35 patients with syndromic hypopituitarism, 15 (43%) presented with copy number variants.

- 15 Patients with CNVs (43%)
  - 13 with variants of uncertain clinical significance (VUS)
  - 2 with pathogenic CNVs

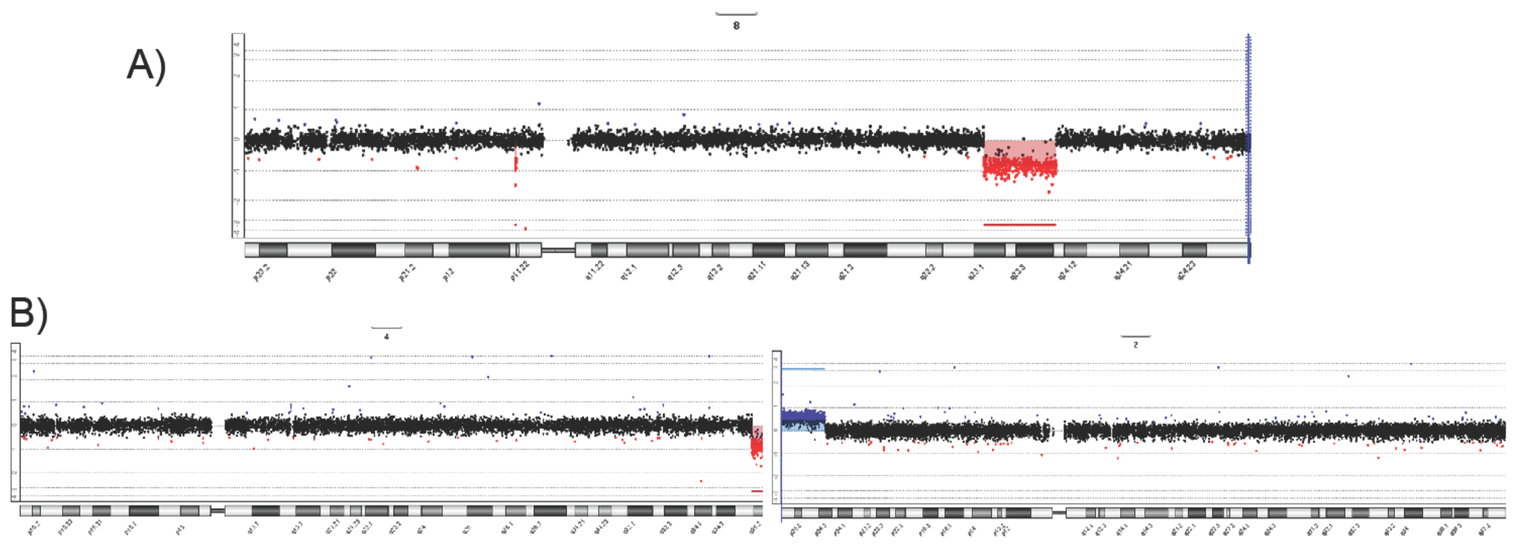

Figure 1 – A) A deletion CNV on chromossome 8q23.1-q24.11 in patient 1. B) Two CNVs in patient 2: one deletion on chromossome 4q35.1-q35.2 and one duplication on chromossome 2p25.3-p24.3.

Table 1 – Phenotype of patients with pathogenic CNVs

Patients	Sex	Hormonal Deficiencies	Brain MRI	Associated Syndrome
1	Male	GH, TSH	Normal	Trichorhinophalangeal
2	Male	GH, LH/FSH	Small anterior pituitary, ectopic posterior pituitary	Rubinstein-Taybi

Table 2 – Characteristics of pathogenic CNVs

Patients	CNV	Size (Mb)	Inheritance	Protein coding genes
1	arr[GRCh37] 8q23.1-q24.11x1	10,5	De novo	20 deleted
2	arr[GRCh37] 4q35.1-q35.2x1 arr[GRCh37] 2p25.3-p24.3x3	4 14,7	De novo	11 deleted 49 duplicated

Conclusions

Copy number variants unveiled the genetic aetiology of syndromic congenital hypopituitarismo in two patients. Variants of uncertain clinical significance may also be implicated in the aetiology of CH but further studies are necessary to establish the role of each CNV.

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