Pusan National University Children's Hospital

Clinical and molecular characterization of a newly recognized overgrowth syndrome: interstitial 7q22.1-7q22.3 microdeletion

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INTRODUCTION

- Overgrowth syndromes comprise a group of disorders associated with excessive growth and other features such as facial dysmorphism, developmental delay, neurological problems and an increased risk of neoplasia. The genetic basis for many of these conditions is being increasingly elucidated. Here, we report on a 3-year-old boy who was referred for evaluation of generalized overgrowth.

METHODS

- Array based CGH analysis was performed using commercially available oligonucleotide microarrays containing about 43,000 60-mer probes with an 29 estimated average resolution of about 100-130 Kb (Human Genome CGH Microarray 44B Kit, Agilent Technologies) and microarrays containing 99,000 60-mer probes with an estimate average resolution of 50-65 Kb (Human Genome CGH Microarray 105A Kit, Agilent Technologies).

RESULTS

Brief history

A 3-years-boy is the second child of unrelated healthy parents of normal stature. He was born at term with uneventful. Dysmorphic features included high and prominent forehead, hypertelorism, and small mouth. Other features were noted, including cryptorchidism, retractile testis, and developmental delay. Vigorous appetite was also shown in the patient at 1 year of age. He began to walk unaided at 23 months of age, and could sign one words at 3 years of age. To date, at 3 years, height was 106.1 cm (>97th percentile), weight 26.4 kg (>97th percentile) and head circumference 56 cm (>97th percentile) (Fig1). Bone age is advanced over chronolgical age by 6 months (Fig2). Karyotype was normal. In order to determine putative chromosomal imbalances, microarray array was done, resulting in a *de novo* heterozygous 2.2 Mb deletion in chromosome region 7q22.1-22.3 covering 2,244,033 bp region (Fig3). The deletion was starting from 102,877,293 bp extending to 105,121,326 bp which contain involved 9 genes including PMPCB, DNAJC2, PSMC2, SLC26A5, RELN, ORC5, LHFPL3, KMT2E, and SPRK2 (Table1).

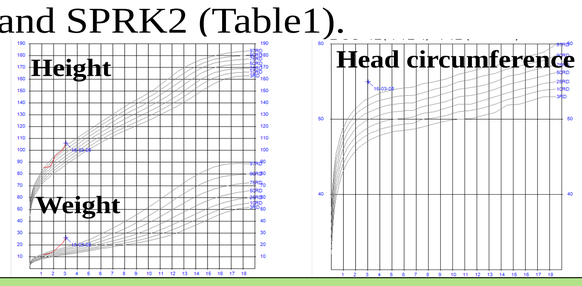

Figure 1.

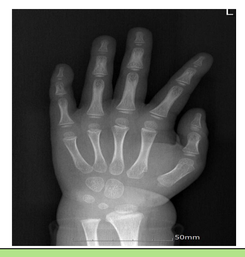

Figure 2.

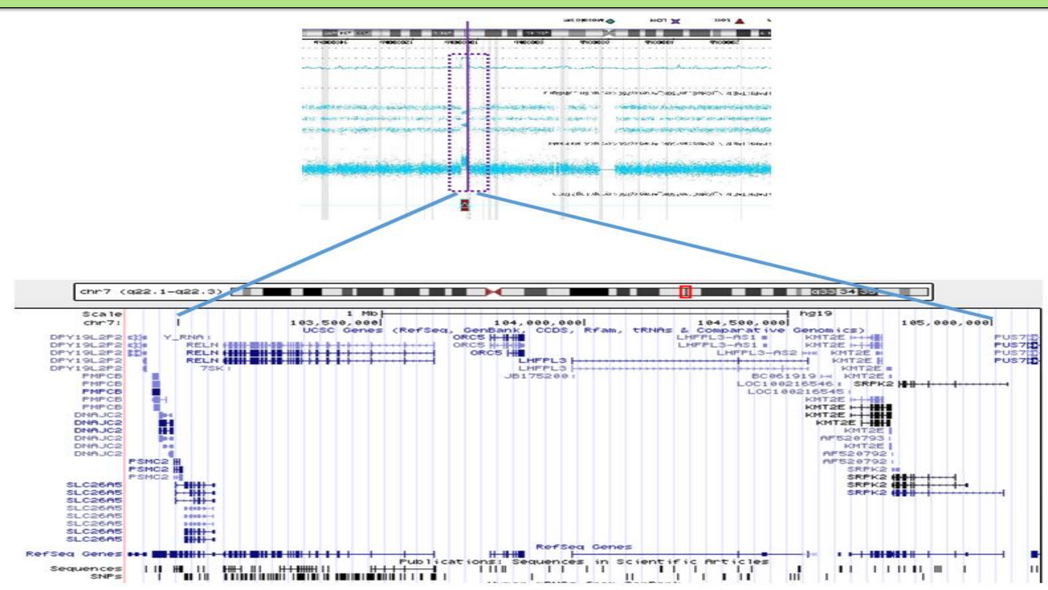

Figure 3. . Array comparative genomic hybridization (aCGH) analysis plot is taken from Agilent's CGH Analytics software and presented at vertical orientation. At the lower, on the chromosome 7 ideogram, the red arrow is indicating the position of the deletion and the affected cytobands. The deleted probes are indicative of a hemizygous deletion with a value of -1.

Table 1 . Gene content of the deleted region. Genes indicated in bold may be involved in the clinical phenotype of the patients

Gene	Description
PMPCB	Peptidase, Mitochondrial processing, beta
DNAJC2	DNA/HSP40 Homolog, Subfamily C, Member2
PSMC2	Proteasome 26S Subunit, ATPase, 2
SLC26A5	Solute Carrier Family 25, Member 5
RELN	Reelin
ORC5	Origin Recognition Complex, Subuit 5, S. Cerevisiae, Homolog OF
LHFPL3	Lipoma HMGIC fusion partner-like 3
KMT2	Histone–lysine N-methyltransferase 2
SPRK2	Serine/threonine-protein kinase 2

DISCUSSION

- A review of the literature identifies 13 publications on 7q22 abnormalities since 1980. Several genes have been proposed as potentially involved in cell cycle control and two such genes are included in the microdeletion reported here: SPRK2, LHFPL3. Computational analysis suggests that LHFPL3 protein belongs to the tetraspanin superfamily of transmembrane proteins that play an important role in the control of cell proliferation, cellular adhesion, and signalling. SRKP2 belongs to the SRPK kinases, a family of cell cycle-regulated protein kinases. Based on its function, RELN is the plausible major contributor to the facial anomalies and neurological findings. In the ''Reeler'' (rl) mouse whose both reln alleles are deleted, impaired motor coordination, tremors and ataxia predominate the phenotype, whereas heterozygous reeler mice, haploinsufficient in reelin expression, exhibit a phenotype that is different from wild-type and rl mouse and that shares behavioral, neurochemical, and neuroanatomical abnormalities. Humans carrying mutant KMT2 alleles have defined a developmental role for the KMT2 family. Recent studies on KMT2 mutations in patients show that these genes are altered in a broad spectrum of cancers as well as hematologic malignancies

CONCLUSION

- This is the first report on generalized overgrowth syndrome having 7q22.1-7q22.3 microdeletion. We should consider performing array-CGH for the diagnosis of unclassified overgrowth syndromes, because some still it may be caused by subtle genomic imbalances and help to identify novel genes involved in growth anomalies.

REFERENCES

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