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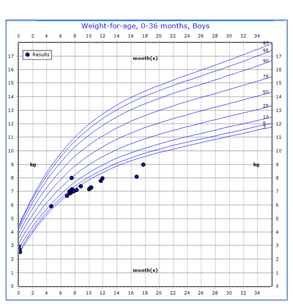
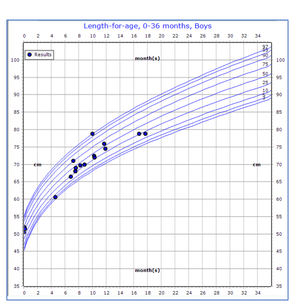
Introduction

A 7-month-old male (cmh004661-01) with a history of developmental delay, plagiocephaly, hypotonia, chronic cough/congestion was admitted for abnormal movements. Prolonged EEG revealed epileptiform discharges consistent with focal epilepsy and epileptic spasms. Genetic testing revealed a complex structurally rearranged chromosome 15 which contains two inverted duplicated chromosome 15s joined together at one end, resulting in partial hexasomy for 15q.

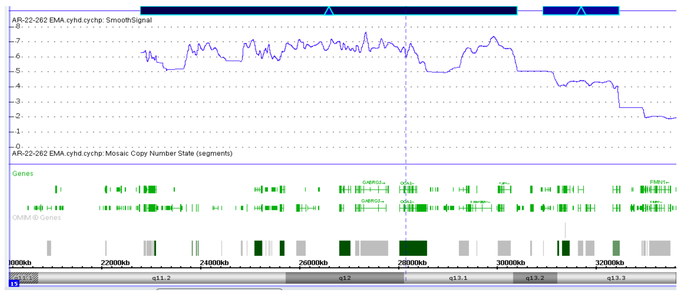
Case Presentation

CMH004661-01 was born to a G2P2 33-year-old mother following an uncomplicated pregnancy at 40 weeks 2 days gestation. At birth he was 6lbs 8oz, 20in long, and APGARs were 3/5/9 at 1/5/10 minutes. At delivery he was limp, pale and had poor tone with minimal crying and respiratory depression. He was admitted for additional neurologic examination due to persistent seizure-like activity, however an EEG was negative, and he was discharged without medication. A newborn hearing screen was failed, and follow-up confirmatory testing confirmed mixed hearing loss with right greater than left. At 7-months-of age he was readmitted for seizure activity. Repeat EEG was indicative of subclinical seizures and epileptic spasms. At 11-months-of age he was noted to have developmental delay, hypotonia, and required bilateral hearing aids. He was unable to sit unsupported but did have head control and was able to roll over and grab objects with both hands. Currently at 19-months-of age he is dependent for standing and weight bearing activities. Imaging studies to date have been negative, including MRI, echocardiogram, and renal ultrasound. Seizures are well controlled with medication. His weight is less than the 3rd %ile, and length is at the 25th %ile.



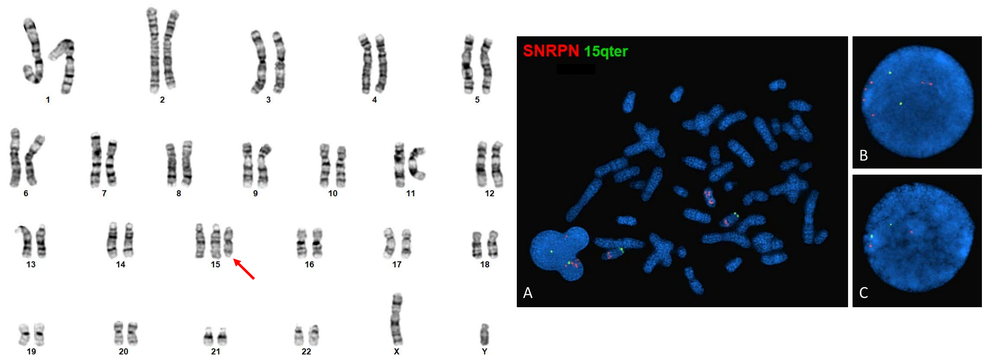


Microarray



Microarray testing was ordered at 7 months and showed six copies of an ~7.6 Mb segment between the common breakpoints BP1 and BP4, followed by four copies of an ~1.5 Mb segment between BP4 and BP5 in proximal 15q from 15q11.2 to 15q13.3.

Karyotype and FISH Analyses



Chromosome analysis demonstrated a male karyotype with 47 chromosomes including an extra tricentric chromosome. A) Metaphase FISH analysis found two enhanced SNRPN (15q11.2) signals consistent with a total of four copies of SNRPN in this additional derivative chromosome, indicating the chromosome 15 is composed of two inverted duplicated 15s linked each other at the ends as a way of mirror image. B) Interphase FISH analysis shows six copies of SNRPN (15q11.2) in 92% of nuclei and C) two copies of SNRPN in 8% of nuclei. Parental chromosomes were normal, confirming de novo inheritance.

Acknowledgements

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MLPA

Probe Name	PWS Deletion Control	cmh004661-01
BP1-BP2 region	1.00	**2.65**
NIPA1	1.03	**2.68**
MKRN3	0.54	**2.64**
MAGEL2	0.53	**2.73**
MAGEL2	0.51	**2.63**
NDN	0.51	**2.60**
SNRPN exon u1B	0.53	**2.86**
SNRPN exon u1B	0.53	**2.64**
SNRPN intron u2	0.55	**2.77**
SNRPN intron u2	0.51	**2.66**
SNRPN xU5 (AS-SRO)	0.52	**2.61**
SNRPN xU5 (AS-SRO)	0.58	**3.13**
SNRPN CpG promotor (50%)	0.53	**2.50**
SNRPN CpG 50%)	0.53	**2.65**
SNRPN CpG (50%)_	0.52	**2.56**
SNRPN CpG int1 (50%)	0.51	**2.62**
ref2q12 digestion control (0%)	1.02	1.04
Results		
^Type I del	1.01	2.67
Type II del	0.58	2.59
Mat. Methylation	0.96	0.82
Digest Controls	0.00	0.00

MLPA analysis of 15q11.2q13.1 for Prader-Willi (PWS) suggested maternal inheritance, and was concordant with the gain identified by cytogenetic studies.

Conclusions

Although supernumerary marker chromosome (SMC) 15 itself is common, occurring in ~1/30,000 births, individuals with a tricentric der(15), resulting in partial hexasomy 15q are rarely reported. Complimentary techniques including microarray, MLPA, FISH, and G-banding were used to resolve the structure of the SMC 15. In the future, novel technologies, such as optical mapping, may also be beneficial in the resolution of complex structural variants.

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