597

Deletion 2q22.1q22.3: An Emerging Microdeletion Syndrome with Variable Phenotype

Deanna Hutchinson, MS, CGC; Justin Schleede, PhD, FACMG
Center for Molecular Biology and Pathology, Laboratory Corporation of America® Holdings, Research Triangle Park, North Carolina

Integrated GENETICS
LabCorp Specialty Testing Group

I. Introduction

SNP microarray analysis can be a powerful tool for uncovering submicroscopic variants. This technology has allowed for discoveries of new microdeletion syndromes and refinement of their phenotypes. Here we present a case report of a child with an emerging microdeletion syndrome with phenotypic comparison of a prior index case and additional reported overlapping deletions.

II. Methods

- **SNP MICROARRAY METHODOLOGY:** All studies were done utilizing the Affymetrix Cytoscan™ HD platform (Affymetrix® and CytoScan® are Registered Trademarks of Thermo Fisher Scientific.). This array platform contains approximately 2.695 million markers across the entire human genome. There are approximately 743,000 SNPs (single nucleotide polymorphism probes) and 1,953,000 structural non-polymorphic probes (NPCNs). On average there are approximately 0.88 kb between each marker. DNA was extracted utilizing standard methods and 250 ng of total genomic DNA was digested with NspI, ligated to adaptors, and amplified using Titanium Taq with a GeneAmp PCR System 9700. PCR products were purified using AMPure beads and quantified using NanoDrop 8000. Purified DNA was fragmented and biotin labeled and hybridized to the Affymetrix Cytoscan® HD GeneChip. Data was analyzed using Chromosome Analysis Suite. The analysis is based on the GRCh37/hg19 assembly.
- qPCR analysis was performed using the QuantStudio™ 7 Flex Real-Time PCR system (Applied Biosystems™) in conjunction with the VeriQuest Fast SYBR Green qPCR Master Mix (2X) (Thermo Scientific™). All samples were run in triplicate. To determine copy number, primers specific to an amplicon within a CNV identified by microarray analysis were compared to amplicons specific to two housekeeping genes (*RNase1* and *TBP*). Two normal controls, one female and one male, were run for all cases with validated primers. For cases with unvalidated primers, a positive control was included. Genomic copy number determinations for specific CNVs were made as follows: qPCR value of 0=0 copies, from .06 to 1.4=1 copy, 1.6 to 2.4=2 copies, 2.6 to 3.4=3 copies and 3.6 to 4.4=4 copies.

III. Case Report

We present the case of an 11 year-old male of Guatemalan and Honduran ancestry with intellectual disability, motor delays and speech apraxia. The proband was born at term to a G1P1 mother with a normal pregnancy history. There is no reported consanguinity. The proband walked at 2.5 years of age and did not speak until after 2.5 years of age. The proband is non-dysmorphic. His family history is unremarkable for learning disabilities, speech delays, or congenital anomalies. SNP microarray analysis using the Affymetrix Cytoscan™ HD platform revealed a 6.3MB interstitial microdeletion of 2q22.1q22.3 (138,304,293-144,612,279)x1, that includes 5 OMIM genes (*HNMT, NXPH2, LRP1B, KYNU* and *ARHGAP15*). qPCR analysis of the parents targeting the deleted region on 2q22.1 (141,856,867 – 141,856,981) revealed a normal copy number. This is consistent with a *de novo* deletion in the proband.

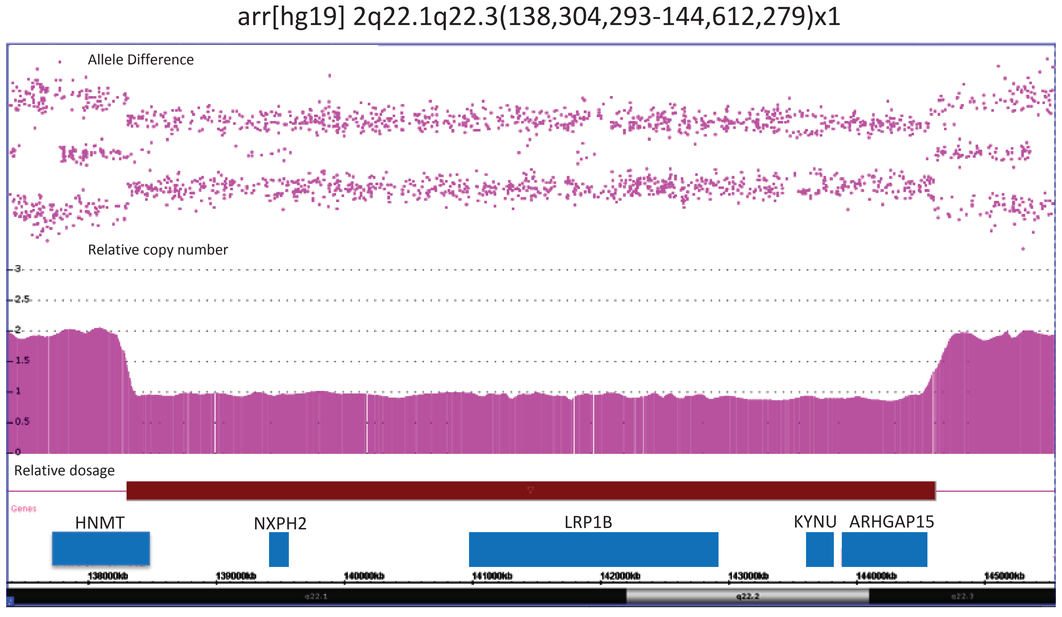


Figure 1: SNP microarray analysis was performed using the Affymetrix Cytoscan™ HD platform and detected a 6.3MB interstitial deletion of 2q22.1q22.3 (138,304,293-144,612,279)x1, that includes 5 OMIM genes (*HNMT*, *NXPH2*, *LRP1B*, *KYNU* and *ARHGAP15*).

Figure 2: qPCR analysis was performed using the QuantStudio™ 7 Flex Real-Time PCR system (Applied Biosystems™) in conjunction with the VeriQuest Fast SYBR Green qPCR Master Mix (2X) (Thermo Scientific™). To determine copy number, primers specific to an amplicon within a CNV identified by microarray analysis were compared to amplicons specific to two housekeeping genes (*RNase1* and *TBP*). Two normal controls, one female and one male, were run for all specimens. Follow up qPCR analysis targeting the deleted region in the proband analysis confirmed the deletion in the proband (**figure 2a**). Paternal (**figure 2b**) and maternal (**figure 2c**) analyses revealed normal copy numbers. FWD and REV qPCR primers were localized to the *LRP1B* gene.

Figure 2a: qPCR analysis on the proband specimen compared to two controls

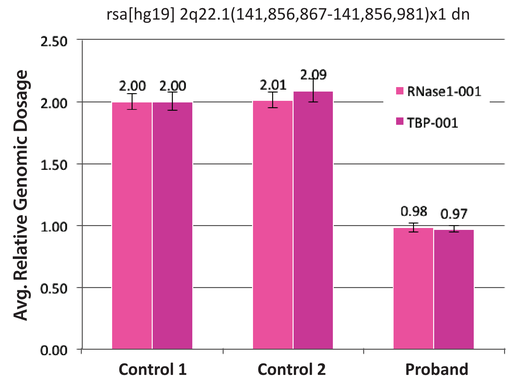


Figure 2b: qPCR analysis on the paternal specimen compared to two controls

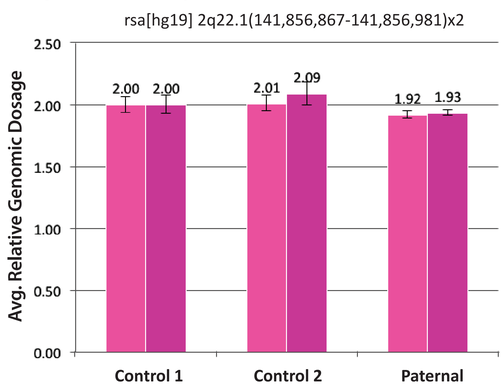
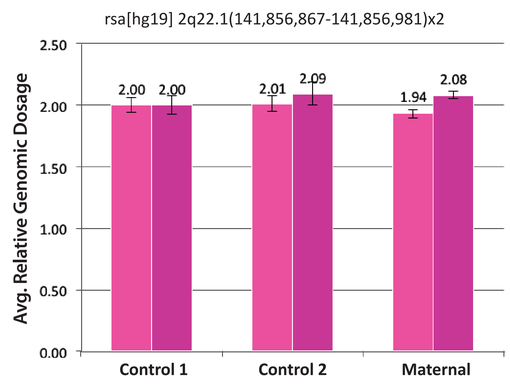


Figure 2c: qPCR analysis on the maternal specimen compared to two controls



IV. Discussion

Interestingly, the molecular break-points of this case are very similar to a prior case report with microdeletion of 2q22.1q22.3 (138,750,000-144,750,000)x1 in which the proband was reported to have intellectual disability, autism spectrum disorder, behavioral disorder, speech delays, omphalocele, cryptorchidism, hypospadias, high blood pressure, scoliosis and dysmorphic features (Mulatinho, et al). Both the current case and the prior case of deletion 2q22.1q22.3 deletion report intellectual disabilities as well as speech delays in the probands. However, the proband reported here does not present with any obvious congenital anomalies or dysmorphic features. These probands have analogous deletion break points, indicating that the variability of the phenotype between these two individuals may be related to other genetic or environmental factors. Hoffer, et al. and Smigiel, et al. also report patients with overlapping deletions to ours. Both also report developmental disabilities in additional to dysmorphic features and other anomalies. Therefore, it is proposed that microdeletions of the 2q22.1q22.3 region likely result in intellectual disabilities and may have variable penetrance for congenital anomalies and/or dysmorphic features, indicating an emerging microdeletion syndrome.

Table 1. Case comparison of overlapping deletions

Patient	Cytogenetic location of deletion	Gender	Breakpoints	Size of deletion	OMIM genes included in region	Phenotype
Our case	2q22.1q22.3	Male	138,304,293-144,612,279	6.3 MB	*HNMT*, *NXPH2*, *LRP1B*, *KYNU*, *ARHGAP15*	Intellectual disability, motor delays, speech apraxia
Mulatinho, et al.	2q22.1q22.3	Male	138,750,000-144,750,000	6 MB	*HNMT*, *NXPH2*, *LRP1B*, *KYNU*, *ARHGAP15*, *GTDC1*	Omphalocele, cryptorchidism, hypospadias, intellectual disabilities, mild dysmorphic features, scoliosis, global developmental delay and behavioral disorder, autism spectrum disorder.
Hoffer, et al.	2q22.1q22.3	Female	139,813,180-145,063,389	5.3 MB	*LRP1B*, *KYNU*, *ARHGAP15*, *GTDC1*	Severe psychomotor retardation, dysmorphic features and microcephaly
Smigiel, et al.	2q22.2q22.3	Female	143,468,147-147,106,860	3.6 MB	*KYNU*, *ARHGAP15*, *GTDC1*, *ZEB2*	Mowat Wilson syndrome, multiple anomalies, dysmorphic features, Hirschsprung disease, delayed psychomotor development, microcephaly, hypotonia

V. References

Mulatinho MV, et al., Severe intellectual disability, omphalocele, hypospadia and high blood pressure associated to a deletion at 2q22.1q22.3: case report. *Mol Cytogenet*. 2012 Jun 11; 5(1):30. PubMed PMID: 22686481.

Smigiel R, et al., Severe clinical course of Hirschsprung disease in a Mowat-Wilson syndrome patient. *J Appl Genet*. 2010; 51(1):111-3. PubMed PMID: 20145308

Hoffer MJ, et al., A 6Mb deletion in band 2q22 due to a complex chromosome rearrangement associated with severe psychomotor retardation, microcephaly and distinctive dysmorphic facial features. *Eur J Med Genet*. 2007 Mar-Apr; 50(2):149-54. Epub 2006 Dec 8. PubMed PMID: 17223398.

LabCorp

Integrated Genetics is a brand used by Esoterix Genetic Laboratories, LLC, a wholly owned subsidiary of Laboratory Corporation of America® Holdings
Poster presented at the *ACMG Annual Clinical Genetics Meeting*; 2019 April 3-5; Seattle, WA.