Customized copy number analysis of pre and post-natal samples using our Chromosome Analysis Suite software

BOLDLY FORWARD

PH712

2021 S&T Symposium
April 20-22, 2021

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ABSTRACT

Chromosomal copy number variations (CNVs) account for roughly 20% of patients affected with developmental delay, multiple congenital anomalies, and autism spectrum disorder. Accurate interpretation requires methods to consistently evaluate the genomic content of the CNV region while correlating those annotations with clinical relevance. One major challenge for interpretation is deciding on the significance of the aberrations, (*i.e.,* is the aberration associated with a disease or genetic defect). Recently, American College of Medical Genetics and Genomics (ACMG) updated their standards for copy number interpretation. This update aims to produce consistent, evidence-based classification across laboratories. We have implemented similar rules to assist our customers by automatically prioritizing the more relevant CNV(s) in each sample in the latest release of Chromosome Analysis Suite (ChAS).

INTRODUCTION

Chromosomal Microarray (CMA) has been widely used for the detection of genomic imbalances for over a decade and is currently recognized as a first-line test for CNV detection. Our CytoScan™ family of microarrays offers the broadest coverage and highest performance for detecting CNVs. The ChAS software has been a popular and instrumental analysis tool in aiding cytogeneticists with their interpretation of our products.

BUSINESS IMPACT

This new automated prioritization of CN segments will decrease interpretation time for the sample allowing for more samples to be run with no additional resources.

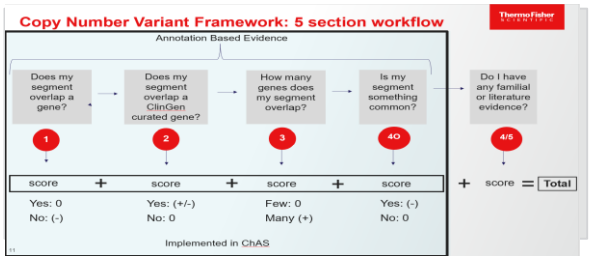
RESULTS

Table 1 ACMG Updates

Major Update	Reason
Establish a quantitative, evidence-based system for variant classification	Reduce discordancy in variant calling across labs
Adoption of the 5 Tier Classification System	Align interpretation recommendations across technologies (SNV)
Separate the variant classification from the clinical interpretation	Is the variant causing the disease in the patient at this time?

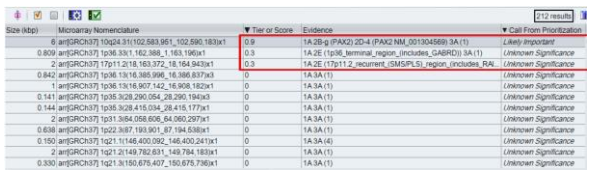
ACMG introduced multiple updates in the 2019 guidelines. The establishment of a quantitative scoring method for each CNV is the basis for our Score-based Segment Prioritization method in ChAS.

Figure 1. Quantitative CNV Classification



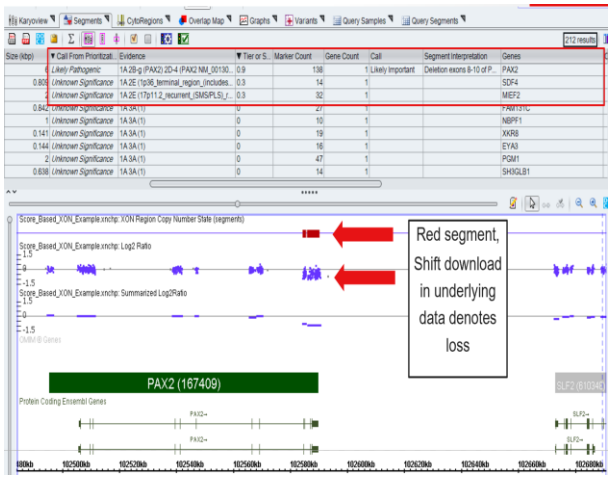
High level ACMG workflow for CNV analysis. A score is provided at each section of the workflow based on the type of evidence overlapping the CN segment. Then a total score is summed for the segment. Higher scores indicate the more likely the CNV is relevant. Workflow within the black outline are implemented in ChAS.

Figure 2. ChAS Segment Table Results



Post-natal sample on CytoScan XON run in ChAS 4.2.1. Score-based Segment Prioritization quickly identifies 3 xon regions (out of 212 total CN segments) overlapping relevant annotations. The score, annotation evidence, and user-defined Call are automatically generated.

Figure 3. ChAS



CONCLUSION

Prior to this new feature, individual segments were manually reviewed looking for relevance of the overlapping genomic content. Score based copy number segment prioritization efficiently sorts the segment(s) overlapping relevant annotations to the top of the table. Upon quick visual investigation, as shown in PAX2 above, the reviewer can determine segments(in red) overlapping the PAX2 are true losses. Comparing the phenotype information from the sample with easy to access OMIM or ClinGen information for this gene from within ChAS, the reviewer decides which segment(s) are relevant in this sample for the report. The prioritization tool instantly identifies 3 segments from 212, which would have taken hours in manual review.

REFERENCES

https://pubmed.ncbi.nlm.nih.gov/31690835/

ACKNOWLEDGMENTS

I would like to thank the GSD Microarray software team. In particular Ed Erwin and Karen Shaw who also had to understand the minute details of the ACMG guidelines.