Alissa Interpret case study: UMC Utrecht Genetics

One plus one equals three

Combined analysis of CNVs and SNVs in genomic diagnostics

What will you learn

This case study shows how the University Medical Center (UMC) Utrecht Genetics Department built a foundation to efficiently transition to whole genome sequencing with combined CNV and SNV analysis on the same data set and is:

- Evolving to a single software platform for its assessment of genetic abnormalities detected by two tests — one array test and another for whole exome sequencing – previously analyzed using Cartagenia Bench Lab CNV and Cartagenia Bench Lab NGS, respectively.
- Deploying Alissa Interpret, the next evolution of Cartagenia Bench, for analysis of CNVs and SNVs in a single workflow and achieved better detection of recessive disorders, and quicker response time to urgencies and severe phenotypes.

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Introduction

In many genomic diagnostics laboratories both array-testing and Whole Exome Sequencing (WES) are currently offered in case of prenatal multiple congenital anomalies and/or intellectual disability (MCA/ID). Since 2005, the University Medical Center (UMC) Utrecht Genetics lab has offered comparative genomic hybridization (CGH) and single-nucleotide polymorphism (SNP) array-based testing, detecting copy-number variations (CNVs) and regions of homozygosity (ROH). Annually, approximately 1,500 arrays on prenatal MCA/ID patients are performed. WES, detecting single-nucleotide variants (SNVs), small deletions and duplications and indels, was introduced at the UMC Utrecht diagnostic department in 2014.

Array-CGH/SNP-array tests detect pathogenic CNV's in on average 10-15% of MCA/ID cases and the diagnostic yield of WES analysis is estimated to be 30-40%. Hence, a combined analysis of CNVs and SNVs is an effective approach to increase the diagnostic yield of genomic testing for diagnostic applications in MCA/ID and beyond. This is corroborated by several cases in literature in which a combination of a CNV and a SNV gave rise to detection of a recessive disorder.

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The University Medical Center Utrecht Genetics is currently transitioning towards Whole Genome Sequencing (WGS), which allows for a combined CNV/SNV analysis on the same data. While this is in the research phase, performing both WES and array-based testing continues to be needed for combined CNV/SNV analysis in case of MCA/ID. Depending on the severity of the phenotype and/or the urgency, both tests are initiated either simultaneously or subsequently.

Diagnostic flow of CNV and SNV analysis at the UMC Utrecht Genetics

Historically, array-based techniques were embedded in the cytogenetic domain of genome diagnostics and WES in the molecular domain. This entailed that analysis and interpretation of the obtained CNV and SNV data mostly was performed by different laboratory specialists (see **Figures 1 and 2**) and required separate analysis and assessment programs. At UMCU Genetics Department, up until now assessment of the variants identified using these two tests would be performed using two software platforms - Cartagenia Bench Lab NGS and Bench Lab CNV.

To be effective at combining CNV and SNV analysis, merging both worlds into a single workflow is required. To accomplish this, cytogenetic and molecular lab specialists need to work (even) more closely together, which is strongly facilitated by having the CNV and SNV assessment take place in a single analysis environment.

The next evolution of Cartagenia combines CNV and NGS assessment

Agilent's new Alissa Interpret software integrates two previous Cartagenia Bench Lab modules, Bench Lab CNV and Bench Lab NGS, combining their features to allow for an integrated interpretation of CNVs and SNVs. From Alissa Interpret v5.1 onwards, array data and WES data can be added to a single patient, enabling efficient classification and curation of both molecular and structural variants in a single workflow on a single software platform.

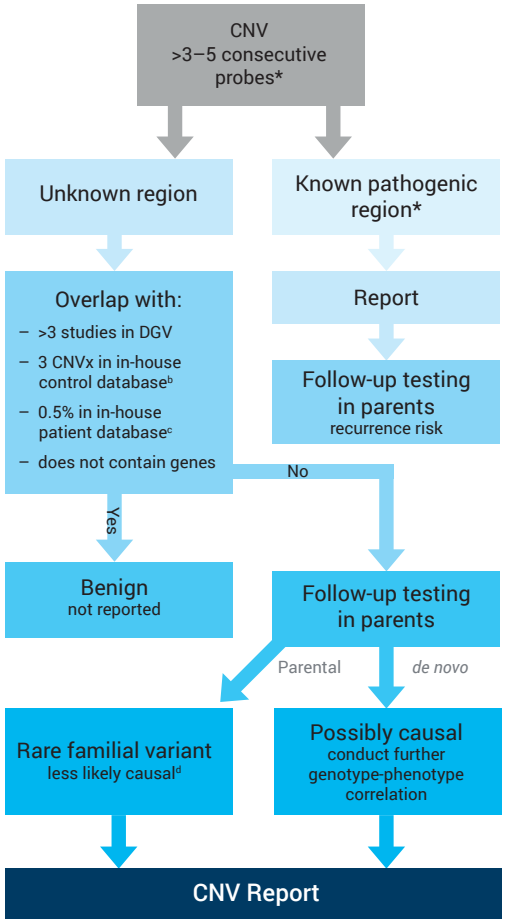

Figure 1 CNV workflow

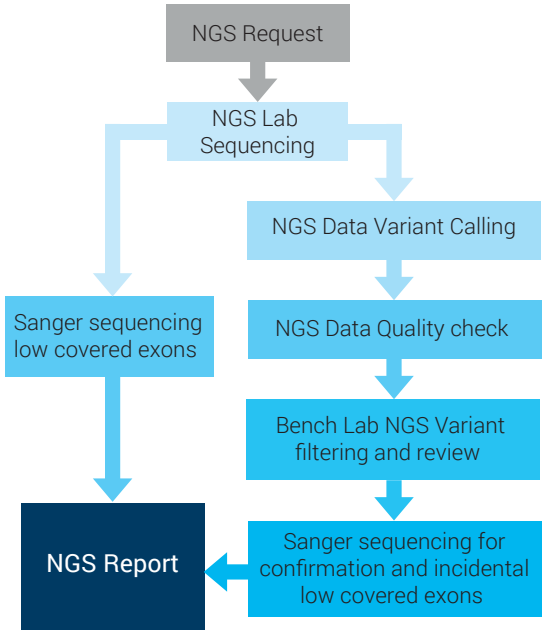

Figure 2 NGS workflow

Combined CNV and SNV analysis answers the clinical question

The additive effect of such a combined analysis is highlighted by a recent prenatal case submitted to the UMC Utrecht diagnostic laboratory. Based on skeletal anomalies detected by ultra sound, prenatal SNP-array assessment on amniocytes was requested .

The SNP-array analysis unveiled a deletion ~144 kb, encompassing two protein coding genes; *EGFLAM* and *LIFR*. As shown in **Figure 3**, the LIFR gene proved to be of special interest due to its association with skeletal abnormalities and being linked to the autosomal recessive Stuve-Wiedemann syndrome (OMIM#601559), matching the prenatal phenotype.

Simultaneously performed SNP-array analysis of the parents showed that the father also carried the deletion. Because of the advanced stage of the pregnancy, WES analysis was performed as soon as possible, revealing a nonsense mutation on the maternal allele of the LIFR gene. **Figure 4** displays how variants from both tests were combined in a single variant assessment workflow using the Alissa Interpret platform, greatly facilitating detection of the recessive disorder.

The diagnosis based on these results enabled physicians to counsel the parents to make a well-informed decision.

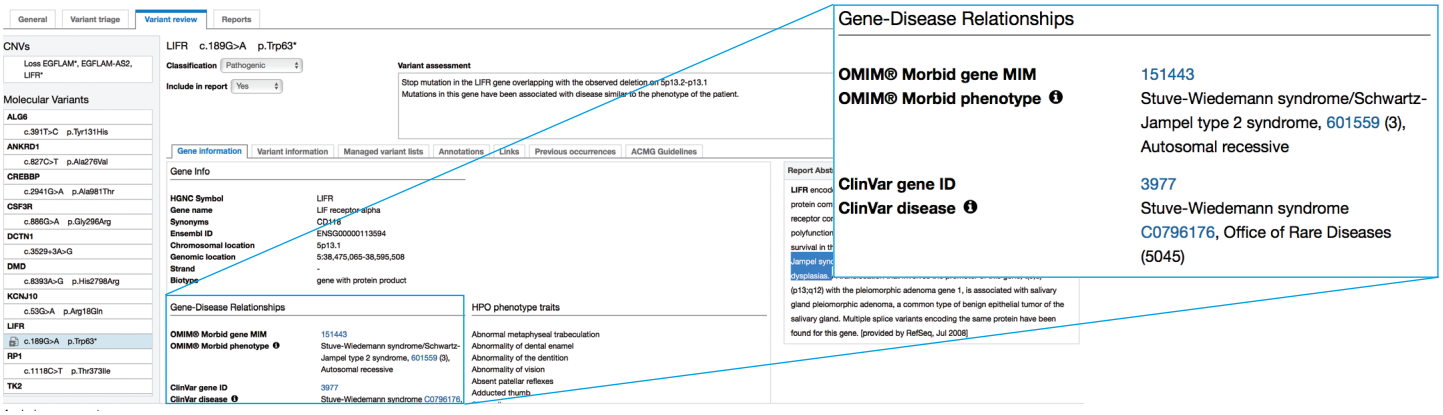

Figure 3. The evidence needed for confident classification of the LIFR gene abnormalities detected using SNP array and WES was provided on Alissa Interpret's variant review tab, presenting extensive gene information including gene-disease relationships, linked HPO phenotype traits and in depth variant annotations.

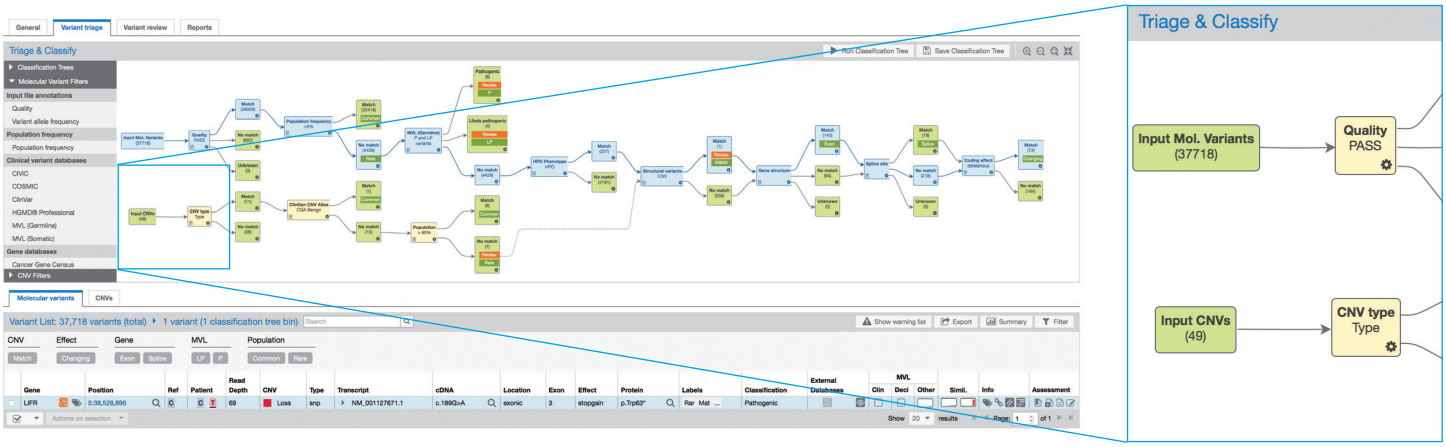

Figure 4. Molecular and structural variants from WES and CGH were assessed and classified together using a single variant triage workflow in Alissa Interpret.

Conclusion

Sometimes, one plus one equals three: This case study shows how the powerful combined CNV/SNV assessment features of Alissa Interpret allow genetics labs to tap into the additive effect of combined WES and array testing in their routine diagnostics. With the introduction of WGS in routine diagnostics, such combined analysis will become even more imperative.

Learn more

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