Copy Number Variant (CNV) Detection at Blueprint Genetics

Blueprint Genetics offers high resolution CNV detection. CNV analysis is a powerful diagnostic tool, especially when paired with deep, uniform sequencing.

Our platform's comprehensive, publicly available analytic validation demonstrates the following CNV detection capabilities:

Our CNV sensitivity (as of March 2018)

CNV size	Sensitivity
Single exon deletion	92.3%
Two-exon deletions and duplications	100%
Five-exon deletions and duplications	98.6%
Microdeletion/ microduplica-tion syndromes	100%

What are CNVs?

- A CNV is a type of genetic variant where there is either an extra or missing copy of a stretch of DNA.
- CNVs can also be called deletions or duplications.
- CNVs can range in size from small (several hundred base pairs) to very large (one million base pairs or more).

Why are CNVs important?

- CNVs are becoming increasingly recognized as an important cause of many genetic diseases.
- On average, 5%-10% of disease-causing variants are CNVs. This number can be as high as 35% in some specialties (Truty et al, 2018).
- Small CNVs (≤3 exons) are the hardest to detect, but account for a significant portion of all CNVs (43% based on internal statistics).
- Including high-resolution CNV detection provides a more comprehensive analysis than sequencing alone and maximizes the diagnostic potential for your patient.

Can next-generation sequencing (NGS) reliably detect CNVs?

It has long been thought that NGS technologies are unable to detect small CNVs (eg, ≤3 exons) or very large CNVs (eg, microdeletion or microduplication syndromes).

However, our experience and analytic validation demonstrate that NGS can accurately detect both small and very large CNVs.

These factors include:

- Good sample quality
- Deep and uniform sequencing coverage
- Multiple bioinformatic tools
- Visualization of data and manual review for called CNV events to minimize false positives
- The use of orthogonal confirmation techniques and policies

Case 1: CNV analysis for cardiovascular indications

Patient information

23-year old male with a history of syncope at age 6, cardiac arrest at age 18 and 2 episodes of ventricular fibrillation and syncope with an implantable cardioverter defibrillator (ICD). Cardiac imaging was suspicious for a cardiomyopathy. Previous genetic testing of 11 genes involved in Long QT syndrome and cardiomyopathy was negative.

Genetic testing

A Blueprint Genetics Comprehensive Cardiology Panel (184 genes), including both sequencing and CNV analysis, was ordered.

Diagnostic summary

Sequence analysis did not detect any novel or rare variants that were considered deleterious; however, CNV analysis identified a 243 base pair deletion in *RYR2* encompassing exon 3. The deletion was confirmed with a custom designed qPCR assay and was classified as pathogenic. Parental testing revealed that the *RYR2* c.(168+1_169-1)_(273+1_274-1)del was *de novo*.

Diagnostic implications

This deletion in exon 3 of *RYR2* is a well-described pathogenic variant associated with catecholaminergic polymorphic ventricular tachycardia (CPVT) and/or left ventricular noncompaction (LVNC). This finding may further inform this patient's medical management and surveillance. Each of the patient's children has a 50% chance of inheriting this pathogenic variant.

Case 2: CNV analysis for hereditary hearing loss

Patient information

6-year-old girl with bilateral mild to moderate sensorineural hearing loss. No previous genetic testing was performed.

Genetic testing

A Blueprint Genetics Comprehensive Hearing Loss and Deafness Panel (181 genes), including both sequencing and CNV analysis, was ordered.

Diagnostic summary

Sequence analysis identified a likely pathogenic variant in the *STRC* gene, c.4559C>A, p.(Pro1520His).

CNV analysis identified a deletion c.(4701+1_4702-1)_(4993+1_4994 1)del encompassing exons 25 and 26 of the *STRC* gene. The deletion was confirmed with a custom-designed qPCR assay and is classified as pathogenic. Parental testing revealed the variants are in trans.

Diagnostic implications

Variants in *STRC* are associated with autosomal recessive nonsyndromic hearing loss. Therefore, the etiology of this child's hearing loss was confirmed, and no further investigations are needed. Her parents have a 25% chance to have an affected child in any subsequent pregnancy. Genetic counseling and genetic testing are available to the family.

Blueprint Genetics Take Home

CNVs are an important disease mechanism that should be assessed in all patients with a suspected inherited disorder. Reliable calling of small CNVs from NGS data requires uniform sequencing coverage, careful review for called CNV events to identify likely false-positive findings, and confirmation with other methods for the smallest events. If CNV detection is not included, many patients will not receive a molecular diagnosis.

Blueprint Genetics