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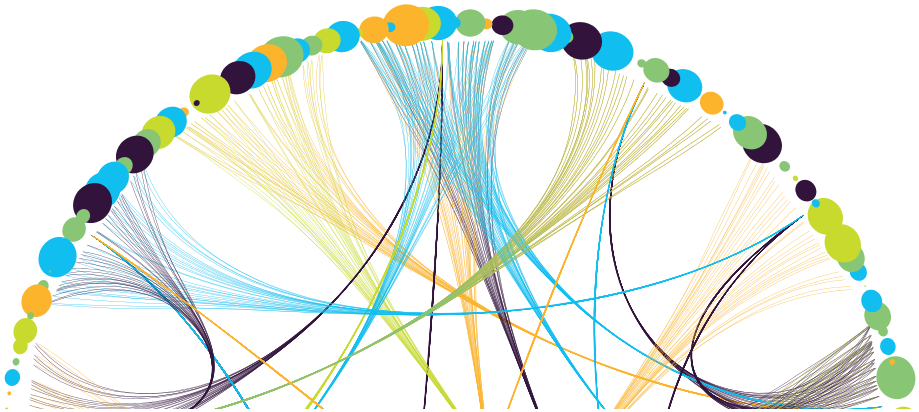
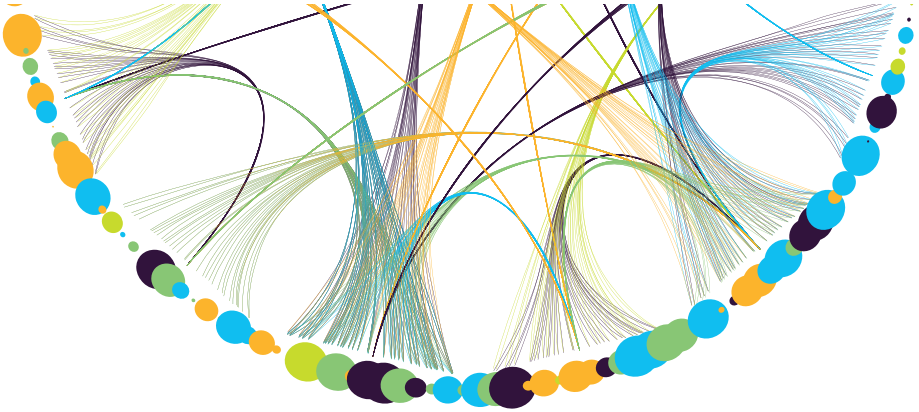
MEDGENOME



CLINICAL EXOME

VERSION 4

Focused Design for Deeper Coverage



- Enhanced CNV detection with additional probes
- Applying advanced machine learning tools for variant identification

- Over 150000 Exomes done till date
- Report reviewed by Clinical Geneticist

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

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About MedGenome Clinical Exome (Ver.4)

As the leader in genetic diagnostics in India, MedGenome is constantly updating its genetic panels based on the latest scientific literature.

The latest Clinical Exome is lighter and refined to provide focused and in-depth coverage of known disease genes. Our custom design offers flexibility to add content not possible in off the shelf exomes.

Clinical Exome Version 4 is a custom focused exome curated in-house by experts at MedGenome and covers 6,670 genes encompassing both nuclear and mitochondrial genes.

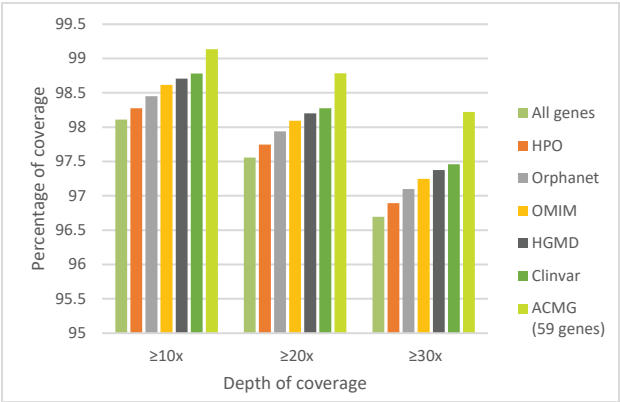
This exome provides better coverage of disease associated genes including coding variants, splice variants, reported deep intronic variants and CNV. It gives very high diagnostic utility at a low cost compared to whole exome sequencing.

Better disease association

"Clinical Exome (Ver.4)" Panel is enriched for disease associated genes (with strong evidence) and genes with limited but emerging evidence from OMIM, Orphanet and other sources.

Improved coverage

The Clinical Exome (Ver. 4) has been designed not only to include variants in coding region, but also known pathogenic noncoding mutations (HGMD, ClinVar) and enhanced coverage for the detection of copy number variants. In genetically heterogeneous diseases, the additional disease associated genes with moderate evidence increases the potential for better diagnosis.



Representative metrics of the coverage of disease associated genes in MedGenome Clinical Exome (Ver.4)

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What are the key features of Clinical Exome (Ver. 4)

✓ **Enhanced coverage of disease associated genes with strong, moderate or supporting evidence in literature and databases**

- 4,468 genes from OMIM (19 Oct-2019 update)
- 2,937 genes from ClinVar (Sep-2019 update)
- 4,860 genes from HGMD (version. 2019.2)
- 3,931 genes from Orphanet (Sep-2019 update)
- 4,217 genes from HPO (Sep-2019 update)
- ACMG (59 genes; incidental finding)

✓ **Coverage of known pathogenic/likely pathogenic mutations**

- Professional HGMD (184,632)
- High confident pathogenic variants from ClinVar (70,703)
- In-house reported novel variants (10,120) from 50,000+ clinical reports

✓ **Coverage of deep intronic and promoter pathogenic mutations based on HGMD (2,170) and ClinVar (13,037)**

✓ **Improved CNV detection**

- Additional probes in the intronic regions in 668 genes previously reported in publications and in-house clinical reports for the Mendelian disorders

✓ **Probes designed based on multiple gene models**

✓ **Coverage of mitochondrial genome (37 genes)**

✓ **Phenotype based analysis, using Varminer, a MedGenome developed proprietary tool**

✓ **Latest analysis pipeline using GRCh38.p13 assembly** validated on NA12878 reference sample and clinical samples

✓ **Proficiency:**
Requisite quality control steps throughout the workflow from the laboratory sample processing till the interpretation ensures consistency, validity and accuracy of results.

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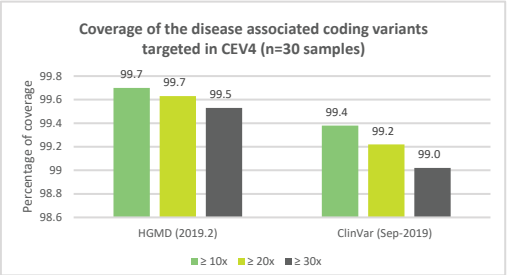
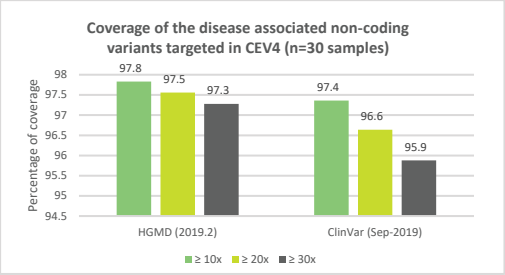
Focused Design for Deeper Coverage Of Disease Variants

Approximately **184,076 + 70,268 coding variants** and **2123 + 12693 noncoding variants** from **HGMD and ClinVar** respectively are covered with a minimum of **10x coverage.**





Coverage of the disease associated variants targeted in Clinical Exome (Ver. 4) (n=30 samples)

Clinical Exome (Ver.4) has baits designed to cover multiple gene annotation sources and multiple transcripts facilitating highly sensitive and accurate variant calling

Gene Models	Number of genes	Number of transcripts
GENCODE V31	**6,653**	**45,980**
Refeq UCSC	**6,583**	**42,619**

How does MedGenome Clinical Exome (Ver. 4) compare with other exomes

Deep-Targeted Coverage of Disease Associated Regions

Clinical Exome (Ver. 4) shows better coverage of the disease annotation sources compared to other exomes, increasing the likelihood of identifying the disease-causing variant. Percent coverage of databases (intersect of baited regions with the databases) is shown in the table below.

Coverage across selected annotation sources (Percentage of databases targeted)

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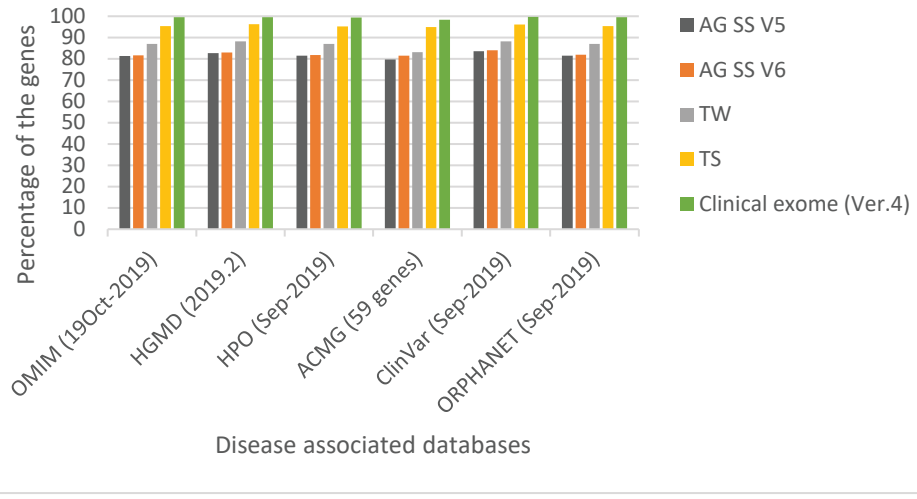

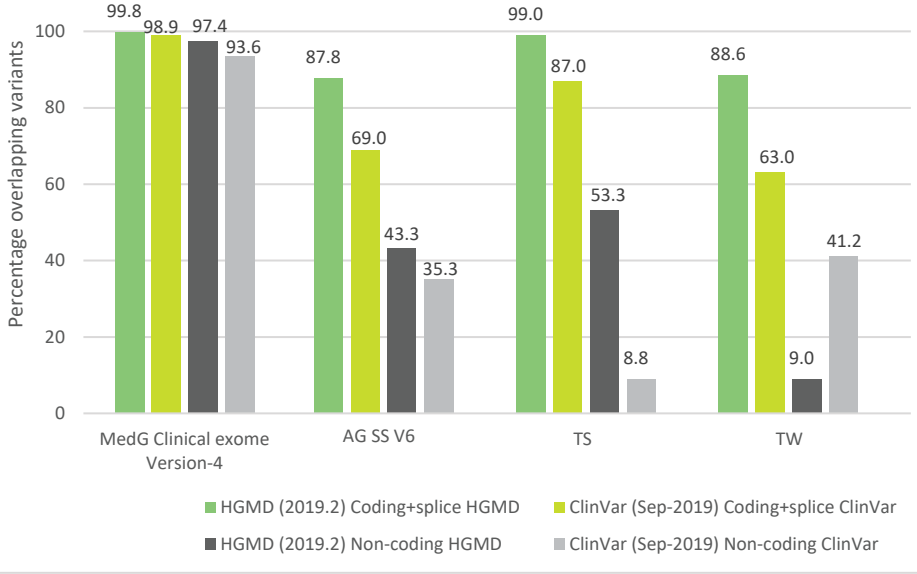

Bed file based coverage comparison of the disease causing coding (n=255,335) and non-coding (n=15,207) variants from HGMD and ClinVar

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Clinical Exome (Ver.4) validation has been done as per global standard

- The sensitivity and precision of the variant calling was determined based on the NA12878 (a reference standard with truth genotypes).
- The analytical sensitivity is >99% for SNPs and 93% for indels
- Repeatability, reproducibility, sensitivity and specificity were tested and were on par with global standards (99% for SNVs and >80% for CNVs).
- CAP (College of American Pathologists) Proficiency Testing score of 100%.

Validation in positive cases with known mutations

- 41 samples with known pathogenic variants in the nuclear genes were validated end to end including analysis and interpretation
- Variant position and zygosity of the 49 pathogenic variants corresponding to 40 genes were concordant
- The 49 pathogenic variants consisted of
  - 29 SNV (Missense/Nonsense/splice variants)
  - 11 Indels (7 deletion, 4 insertion)
  - 9 CNV (7 deletions, 2 duplications)
- The copy number variants (deletions and duplications) corroborated in the positive samples
- Similarly ~99.8% concordance of mitochondrial gene variants in 40 samples

Limitations

- All Clinical Exome orders include Del/Dup analysis of phenotypically significant genes. Single exon deletions or duplications are not routinely detected by this assay, however may occasionally be identified. Deletions and duplications are reported at the exon level. Breakpoint locations are not analyzed.
- Although next generation sequencing technologies and our bioinformatics analysis significantly reduce the contribution of pseudogene sequences or other highly-homologous sequences, these may still occasionally interfere with the technical ability of the assay to identify pathogenic variant alleles in both sequencing and deletion/duplication analyses.
- Due to the inherent limitation of the assay technology translocations, repeat expansions, gross chromosomal rearrangements and methylation cannot be assessed

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FREQUENTLY ASKED QUESTIONS

When should one opt for clinical exome panel for testing?

Clinical exome design is enriched to capture genes involved in Mendelian diseases.
The panel can be used for one or more of the below reasons:

- Clinical finding or family history is suggestive of underlying genetic etiology
- Screening of genetically heterogeneous diseases
- Patient with undiagnosed genetic disease (diagnostic odyssey)
- To facilitate medical intervention and/or treatment
- To confirm the suspected genetic diagnosis

Are all known disease associated genes covered in Clinical Exome (Ver. 4)?

This diagnostic panel encompasses genes based on latest version of several clinical databases (Sep-2019) with 4,468 genes from OMIM, 2,937 genes from ClinVar 4,860 genes from HGMD, 3,931 genes from Orphanet and 4,217 genes from HPO with strong, moderate and additional genes with limited but emerging evidence from HGMD, Orphanet and other sources. However, it has to be noted that new disease associated genes are being reported in literature. Please free to contact our technical support "techsupport@medgenome.com" with the list of genes for any questions that you may have.

Does this panel cover only variants in the coding regions of the genome?

The design also includes coverage of known pathogenic deep intronic mutations based on HGMD (2,170) and ClinVar (13,037).

Can clinical exome be used for detection of novel disease genes, recently reported disease genes or genes with moderate evidence in literature?

Genes with both strong and moderate disease evidence has been covered in the version 4 panel. To confirm the genes of interest, please free to contact our technical support "techsupport@medgenome.com" with the list of genes. And we strongly recommend whole exome sequencing for exploratory research purposes of novel disease gene identification.

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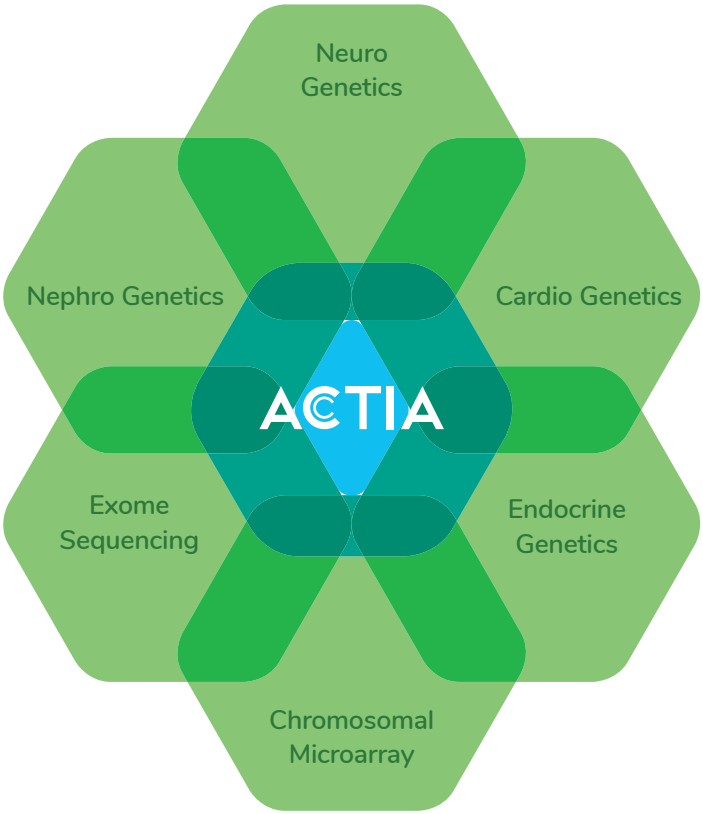

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