

Copy number variant detection increases diagnostic yield of Mendeliome sequencing

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INTRODUCTION: Although complicated by the fragmented nature of the next-generation targeted resequencing data, copy number variants (CNVs) may be detected by read-depth analysis. Along with whole exome sequencing, sequencing of large panels of disease-associated genes (Mendeliomes) are widely used in clinical practice. The diagnostic utility of CNV detection from Mendeliome sequencing, however, remains underreported.

AIM: To investigate the clinical utility of copy number detection from Mendeliome sequencing data.

METHODS:

1407 patients sequenced by TruSight One panels (Illumina Inc.) targeting 4813 genes.

In addition to regular small-variant analysis CNVs were called using CoNIFER software

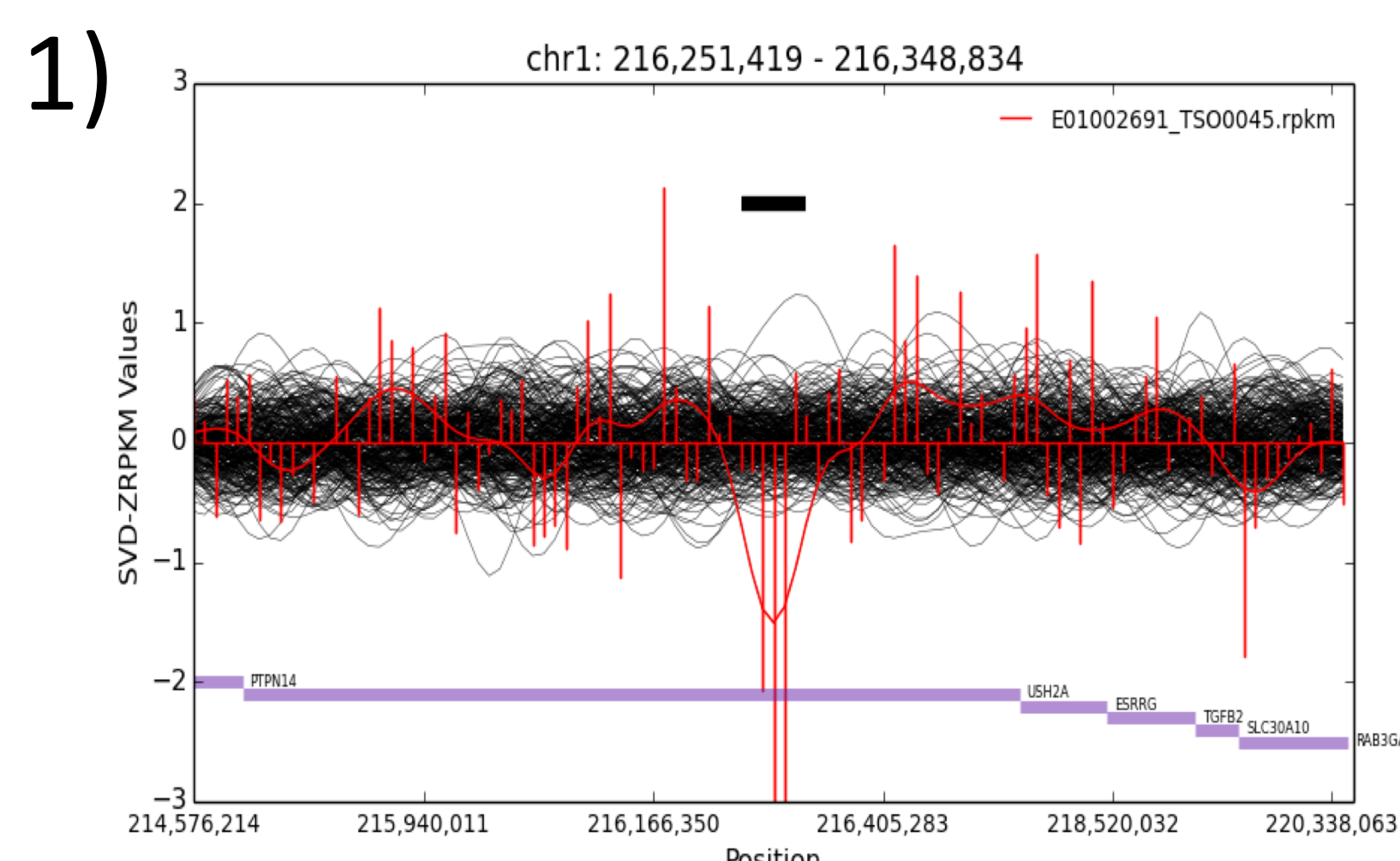
Validation of CNVs using appropriate methods

Analysis of clinical utility and increased diagnostic yield.

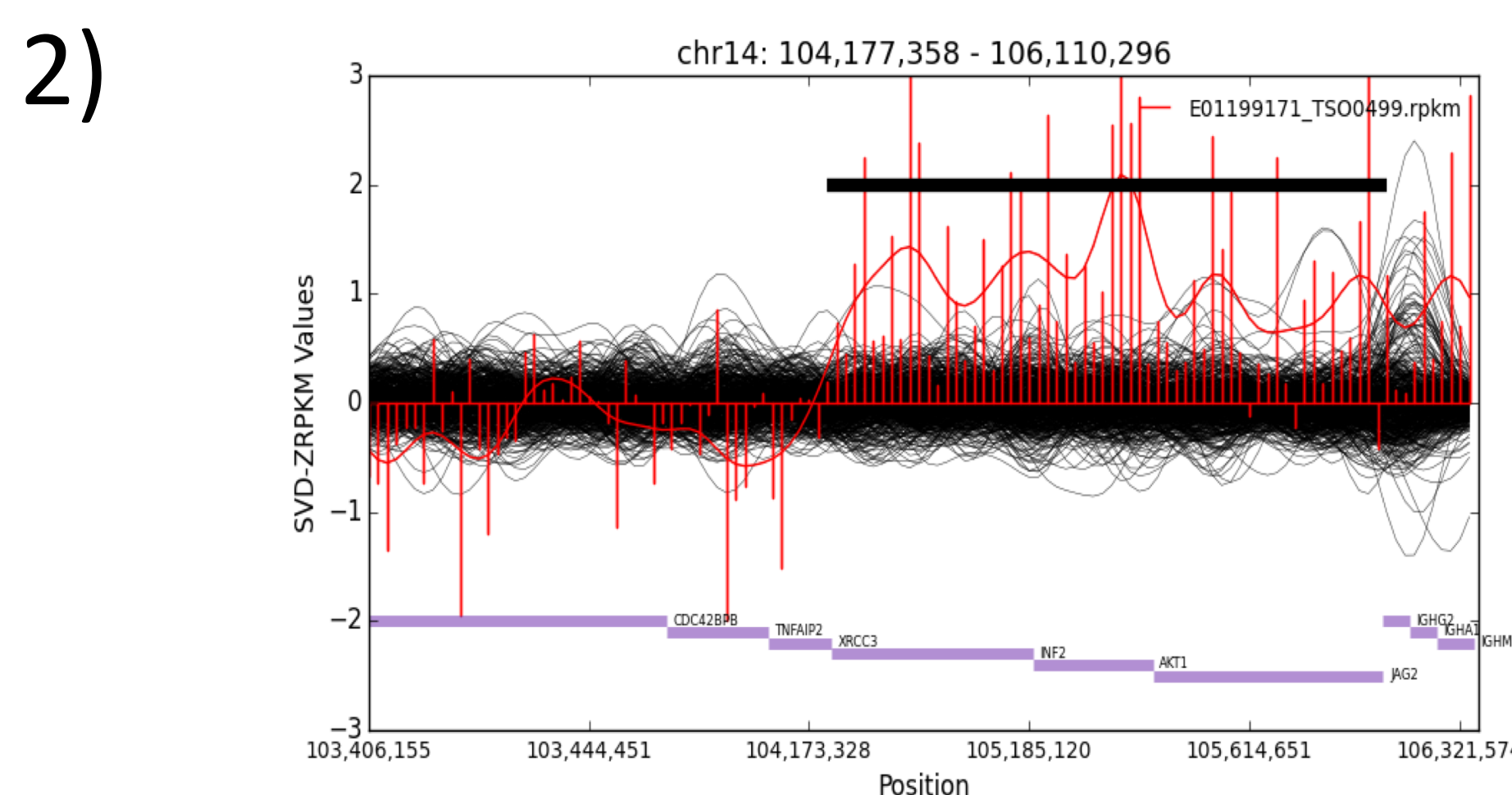
RESULTS:

- Among 1407 patients conclusive genetic diagnosis was made after Mendeliome sequencing in 327 (23.2%), accompanied by additional 10.8% patients in whom variants of unclear clinical significance were reported.
- Rare CNVs were reported for 30 patients.
 - The detected CNVs ranged from single exon to contiguous gene deletions.
 - In additional two cases, X-chromosome aneuploidies were suspected after noticing variant read ratio discrepancies.
- In 18 (1.3%) patients, the CNVs were classified as disease causing, while others remained of unclear significance.
 - In 4/18 cases, the CNV was identified *in trans* with pathogenic small variant.

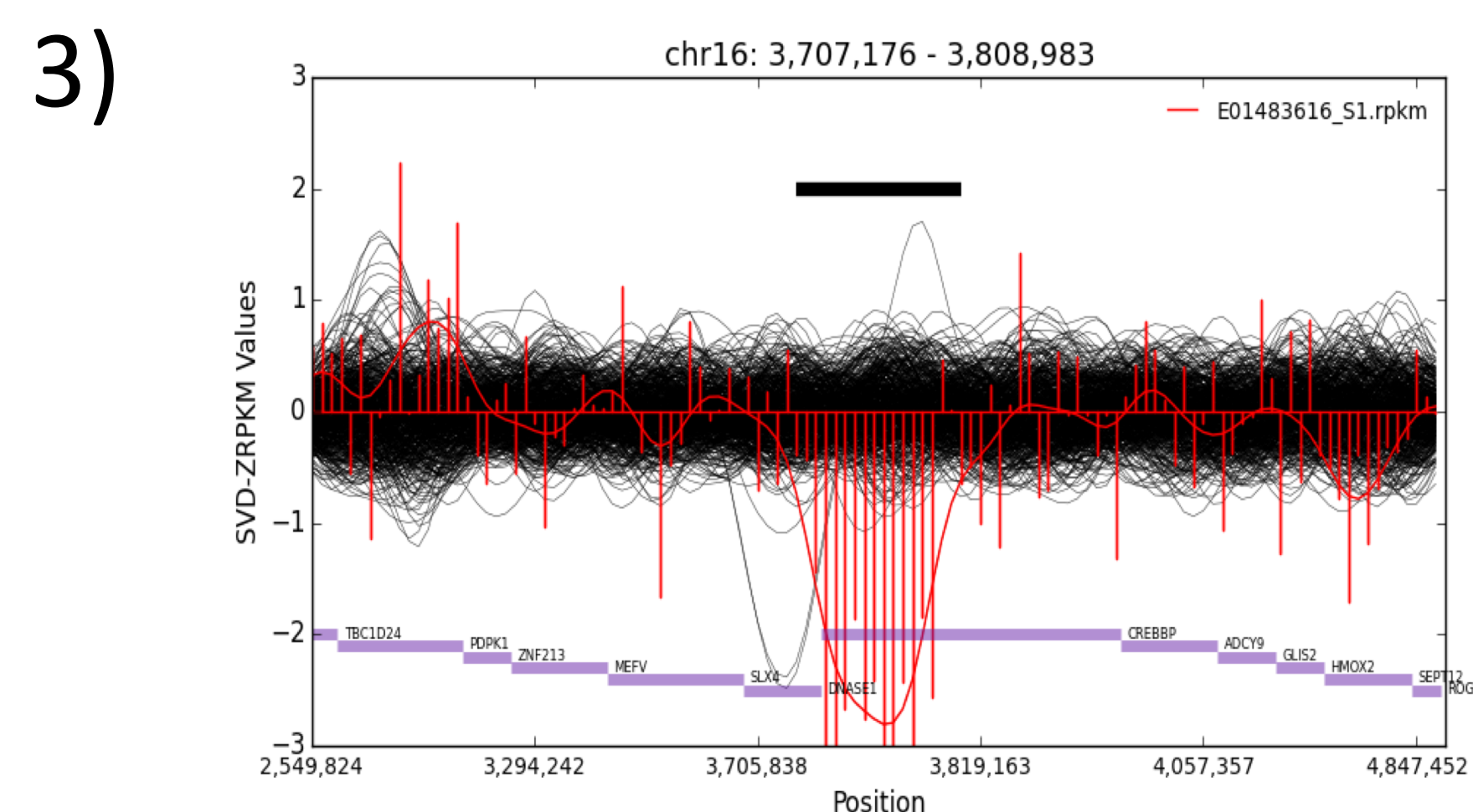
EXAMPLES:



A heterozygous deletion of exons 22-24 in *USH2A* gene. On the second allele heterozygous pathogenic missense mutation was detected.



A distal duplication of chromosome 14, later confirmed to be due to a pathogenic ring chromosome 14.



A partial deletion of *CREBBP* gene (appr. 24kb) causing Rubinstein-Taybi syndrome. Previous chromosomal microarray testing did not reveal this deletion.

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CONCLUSION:

- CNV detection improved diagnostic yield of Mendeliome sequencing by over 1% without increasing costs significantly, and thus should be encouraged in all clinical laboratories.

Authors declare no conflicts of interest.