Assessment of Structural and Copy Number Variants in Constitutional Samples using Electronic Genome Mapping

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Introduction

The detection and interpretation of structural variants (SVs), including copy number variants (CNVs), is the key function of modern cytogenetic laboratories and is important for diagnosis, clinical management, and genetic counseling. Current cytogenetic laboratory methods such as chromosomal microarray analysis (CMA), fluorescence *in situ* hybridization (FISH), and chromosome banding analysis (CBA) can each provide structural genomic information, but each technique has specific limitations in their ability to resolve certain types or sizes of SVs. Electronic genome mapping (EGM), a solid-state nanochannel-based platform, is a high-resolution technology capable of detecting a broad range of structural genomic variations. We present the concordance of EGM for the detection of SVs in a cohort of constitutional and prenatal samples with findings previously characterized by conventional cytogenetic testing and Optical Genome Mapping (OGM).

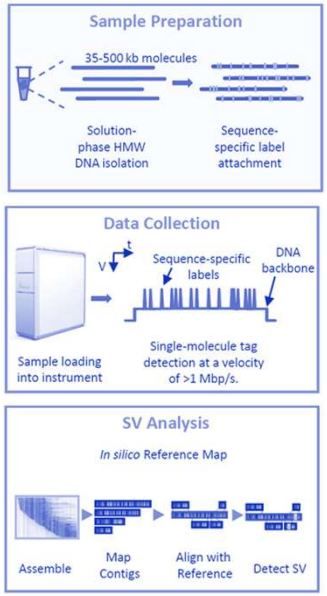

Figure 1. EGM sample processing workflow. Extraction of HMW DNA is labeled at specific sequences (top). Sample is loaded on detector and data collected in OhmX instrument (middle). Molecule data is assembled and SV and CNV events detected (bottom).

Methods

Cohort

Blood specimens referred for follow up of known chromosomal abnormality were analyzed in this study and included samples with genomic findings previously characterized using orthogonal methods such as CMA, quantitative PCR, CBA and OGM. Institutional IRB approval under # SCMM-RND-403.

EGM

DNA was extracted using NEB Monarch® high molecular weight DNA Extraction Kit and processed using a dual-enzyme workflow and the OhmX™ Platform. SVs were identified using Human Chromosome Explorer® (HCE) *de novo* assembly, while copy number alterations were assessed using a CNV analysis pipeline.

OGM

Ultra high molecular weight DNA was extracted and labelled using the Bionano Blood Extraction kit. Labelled DNA was loaded on a nanochannel chip and imaged using a Stratys™ instrument. Genome assembly was performed using the Guided Assembly pipeline and visualized in Access and/or VIA™.

Array

DNA was run on Thermo-Fisher Cytoscan ™ HD Accel assay, processed using Genechip System 3000 and analyzed using Chromosome Analysis Suite software.

Table 1. Concordance of Results Between Array, EGM and OGM

Sample	Event	Region	EGM [GRCh38]	Size in kb	OGM [GRCh38]	Size in kb	Array [GRCh38]	Size in kb	Comment
EGM361	Inversion	6q14.1	6::6(q14.1::q14.3)(77,948,869::86,856,919)	8,908	6::6(q14.1::q14.3)(77,622,617~77,624,243::87,207,318~87,209,933)	9,583	Not Detected	-	Array cannot detect balanced rearrangements (Fig 2C)
	Duplication	6q14.1	6q14.1(77,641,282_77,881,326)x3	240	*6q14.1(77,642,688-77,881,674)x3*	239	6q14.1(78337721_78655840)x3	318	Deletions and duplications flanking inversion is a common mechanism
	Duplication	6q14.3	6q14.3(86,825,273_87,230,273)x3	405	*6q14.3(86,829,785-87,229,762)x3*	400	6q14.3(87565439_87920197)x3	355	Deletions and duplications flanking inversion is a common mechanism
	Loss	15q11.2	15q11.2(22,639,042_23,489,042)x1	850	15q11.2(22,522,095_23,392,094)x1	870	15q11.2(22595659_23102645)x1	507	Size discrepancy due to probe placement in repetitive region
EGM366	Duplication	22q11.1	22q11.1(16,844,635_17,244,635)x3	400	dup(22)(q11.1)(16,948,763_17,204,010)	255	22q11.1(16947158-17235989)x3	289	22q11.1~q11.2 region challenging due to presence of multiple low copy repeats
EGM378	Deletion	13q31.2q31.3	13q31.1q31.3 (82,870,000_90,720,000)x1	7,850	del(13)(q31.1q31.3)(82,950,924~82,954,146::90,499,601~90,502,823)	7,545	13q31.1q31.3(82,947,255_90,503,450)x1	7,556	All techniques highly concordant
	Gain	Xp22.33	-		dup(X)(p22.33)(1,653,916_2,464,217)	810	Xp22.33(1,630,017-2,468,877)x3	839	
EGM349	Gain	9p12p11.1	9p12p11.1(38,810,000_43,213,392)x4	4,400	9p13.1p11.2(38,780,001_41,246,000)x4	2,466	ND - last probe at ~38.9Mb	-	Chromosome 9 heteromorphism (Fig 3D).
	Gain	9q13q21.11	9q13q21.11(61,688,937_68,338,937)x4	6,600	9q12q21.11(60,800,359_68,276,358)x4	7,476	9q13q21.22(63,762,386_68,387,896)x4	4,626	EGM/OGM has better coverage in 9 pericentromere than array (Fig 3A,B,C)
EGM371	Deletion	10q21.1	del(10)(q21.1)(54,850,341_54,939,277)	89	del(10)(q21.1)(54,846,835_54,943,344)	96	10q21.1(54,849,462_54,936,124)x1	87	All techniques highly concordant
EGM381	Deletion	9p21.3	del 9p21.3(22,224,822_22,749,272)	515	Sample unavailable	-	9p21.3(22,219,776_22,739,865)x1	520	EGM and array highly concordant

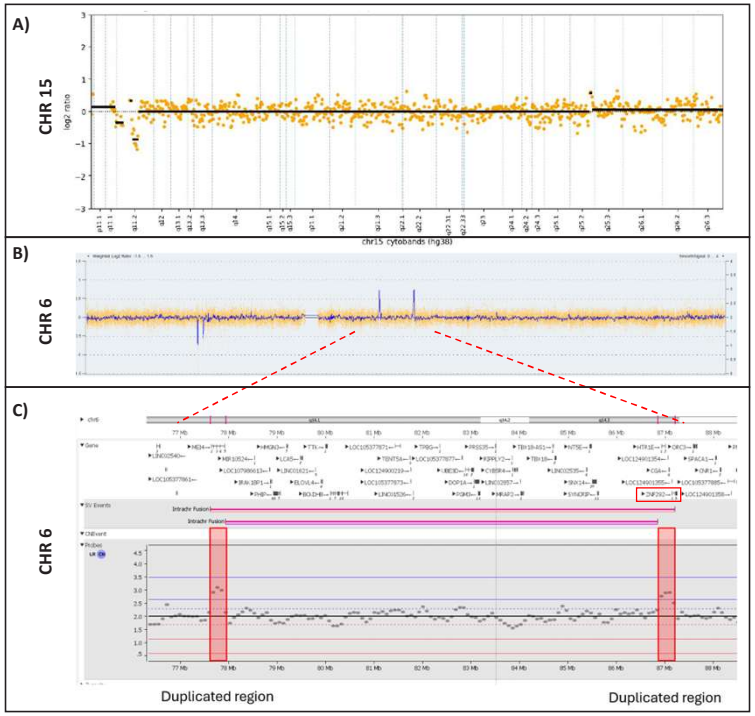

Figure 2. Data for EGM361. A) EGM copy number analysis confirms a deletion on proximal chromosome 15 in the BP1-BP2 region. B) An observation on the array showed two small duplications on chromosome 6. These regions did not meet positive reporting criteria for array. The mechanism (gain) did not match any genes in the region susceptible to triplosensitivity. C) Genome mapping shows that the duplications are actually flanking an intrachromosomal inversion. The distal duplication on chromosome 6 disrupts the coding region of the gene ZNF292 (red box), which has a Pathogenic/Likely Pathogenic ClinGen Score for haploinsufficiency.

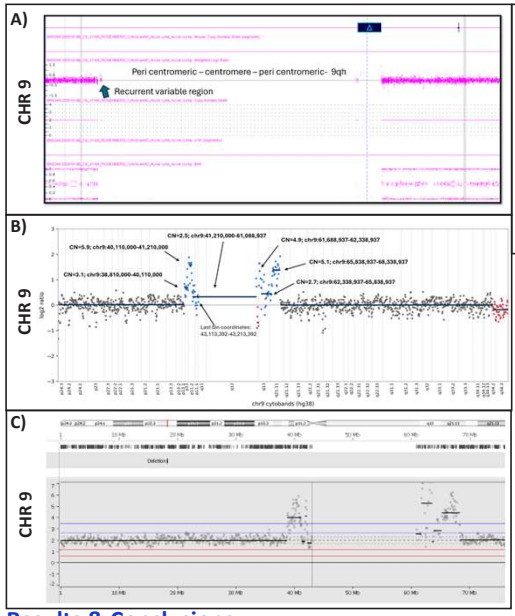

Figure 3. Data for EGM349.
A) CMA data showing a small gain on chromosome 9q13 to 9q21.22. Note low coverage in 9 centromere and 9qh region as expected.
B) EGM copy number plot showing gain of both the 9p and 9q peri-centromeric regions.
C) OGM copy number plot showing nearly identical copy number profile of 9p and 9q gains.
D) CBA showed additional material in the 9q12 to 9q21 bands. This was interpreted as a triplication of this region. OGM/EGM copy number assessments confirm copy number consistent with triplication and also show involvement of 9p12-p11.2 region. Consistent with chromosome 9 duplication variant heteromorphism (Kosyakova et al. 2013).

Results & Conclusions

EGM361 shows a 15q deletion concordantly detected by all platforms. An inversion on 6q was detected only by EGM and OGM flanked by two duplications (confirmed by array). The inversion disrupts a gene, ZNF292, that is relevant to the reason for referral showing benefit of comprehensive high resolution structural analysis. EGM349 shows a 9q variant with gain of the p- and q-arm. Array shows the triplication but has sparser probe coverage (especially in the p-arm) due to the highly repetitive nature of the sequence, but with more coverage in this region for EGM and OGM that provides additional clarity to the karyotype results. EGM, OGM and array results were highly concordant and show EGM to be a promising, emerging technology for integrated genome-wide assessment of SVs in constitutional and prenatal samples.

Reference:

Kosyakova et al. Heteromorphic variants of chromosome 9. Mol Cytogenet. 2013;6(1):14.

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