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Biop-C: a novel Hi-C based approach for PGT-SR

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Motivation and Aim: A high incidence of chromosomal abnormalities in early human embryos can affect their viability, implantation, and also cause abortion and congenital diseases [1]. Couples who turn to IVF have the opportunity to test embryos before implantation. Current PGT methods detect aneuploidy, CNV and unbalanced translocations (due to altered copy number of regions included in translocation), but there is no effective approach which is able to differentiate between balanced and normal embryos. Implantation of balanced embryo should result in birth of phenotypically normal child, who will encounter the same reproduction problems. Possibility of differentiation balanced embryos is also very important in case of X-autosomal translocation, because the phenotype of balanced carriers is unpredictable due to random X inactivation [2]. Hi-C can detect all types of chromosomal abnormalities, including balanced translocations. The aim of our work is optimization of Hi-C protocol for preimplantation genetic testing.

Methods and Algorithms: After culturing of human embryos for 5–6 days biopsy for standard PGT-A and vitrification was performed. Based on the patients informed consent, the embryos were thawed and re-biopsied. The trophectoderm biopsy and the embryo were fixed in a 2 % paraformaldehyde solution and then analyzed using the Biop-C protocol (modified protocol for single nuclei [3]).

Results: We evaluated the possibility of Biop-C to detect different types of chromosomal abnormalities in trophectoderm biopsy samples. Using our method, we prepared Hi-C libraries out of 115 embryos and biopsy samples. For 30 samples (10 trophectoderm biopsy samples and 20 embryos) there were sufficient sequencing depth (more than 1 million read pairs) and known PGT status. Ploidy concordance was 90 % for biopsy samples and 85 % for embryos. We were able to detect all CNV associated with unbalanced translocations analyzing both coverages and Hi-C maps. Biop-C analysis also revealed 4 balanced translocations, one of them Robertsonian (Fig. 1), which are consistent with parent's karyotypes.

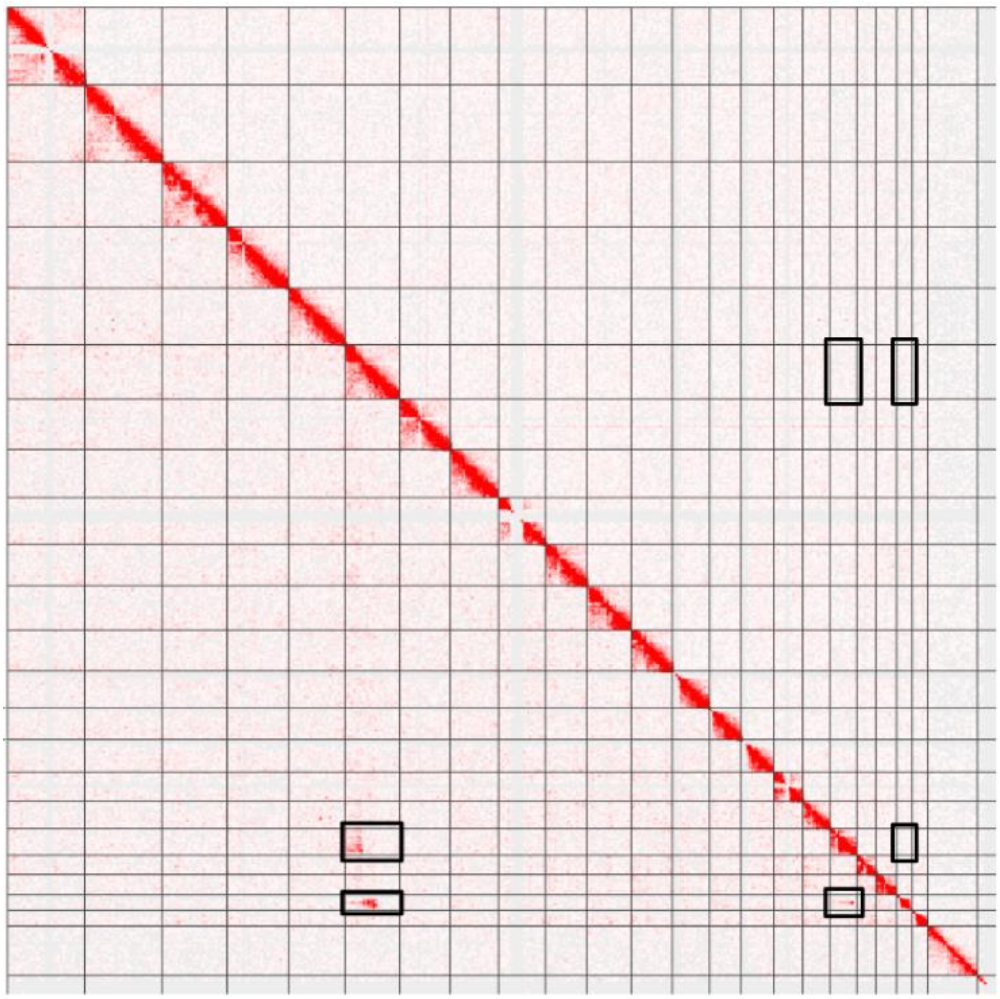

Fig. 1. The heat maps of the Hi-C contacts for embryo Vla1_e below diagonal, above — Sheg1_e as a control. Black rectangles represent unbalanced translocation between chromosomes 6 and 18, and balanced ones between chromosome 6 and 21 and 18 and 21 in Vla1_e sample

Conclusion: The Biop-C protocol allows us to analyze biopsy material of trophectoderm and human embryos and detect aneuploidies, CNVs and translocations, including balanced ones.

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