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Invited Lecture Abstracts

L1

Chromosomes to Circulating DNA

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In recent years, there have been an intense interest in the diagnostic applications of circulating DNA. One source of such interest is in the rapid adoption of noninvasive prenatal testing (NIPT) using cell-free fetal DNA in maternal plasma. One area of focus of my laboratory is to explore the limit of NIPT. In this regard, we have recently completed a 'second generation' noninvasive fetal genome from maternal plasma. For this work, we have sequenced the plasma DNA of a pregnant woman to a depth of 270X haploid genome coverage. This represents the deepest that a single plasma DNA sample has been sequenced to date. Using this approach, together with a novel bioinformatics pipeline, we are able to deduce, for the first time, fetal de novo mutations on a genomewide level with a sensitivity of 85% and a positive predictive value of 74%. We are also able to determine the maternal inheritance of the fetus with a 90-fold increase in resolution when compared with previous attempts. Finally, we have shown that plasma DNA molecules have preferred ending sites. Interestingly, fetal-derived and maternal-derived plasma DNA molecules have different sets of such preferred ending sites. This latter discovery has opened up many new avenues of investigation and has created new applications, e.g. for determining the fraction of fetal DNA without using genetic polymorphisms or DNA methylation markers. NIPT also serves as a model for developing noninvasive diagnostics in many other fields, e.g. oncology and transplantation.

L2

Genomic and functional overlap between somatic and germline chromosomal rearrangements

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Structural genomic variants form a common type of genetic alteration underlying human genetic disease and phenotypic variation. Despite major improvements in genome sequencing technology and data analysis, the detection of structural variants still poses challenges, particularly when variants are of high complexity. Emerging long-read single- molecule sequencing technologies provide new opportunities for detection of structural variants. We demonstrate sequencing of the genomes of two patients with congenital abnormalities using the ONT MinION at 11x and 16x mean coverage, respectively. We developed a bioinformatic pipeline - NanoSV - to efficiently map genomic structural variants (SVs) from the long-read data. Using NanoSV, we readily detected all *de novo* rearrangements involving multiple chromosomes originating from complex chromothripsis events. Genome-wide surveillance of SVs, revealed 3,253 (**33%**) novel variants that were missed in short-read data of the same sample, the majority of which are duplications < 200 bp in size. Long sequencing reads enabled efficient phasing of genetic variations, allowing the construction of genome-wide maps of phased SVs. We employed read-based phasing to show that all *de novo* chromothripsis breakpoints occurred on paternal chromosomes and we resolved the long-range structure of the chromothripsis. Our work demonstrates the value of long-read sequencing for genetic analyses in life sciences research and clinical diagnostics.

L3

Chromosome sequencing: the fifth and final era of cytogenetics

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The modern history of cytogenetics fits into five eras; chromosome spreading, chromosome banding, chromosome painting, chromosome arraying and now chromosome sequencing. T.C. Hsu, the centenary of whose birth we celebrate, was a pioneer of the first. His use of hypotonic fluid to spread chromosomes was key to the emergence of human cytogenetics and to the collection of animal karyotypes published in his Atlas of Mammalian Chromosomes edited with Kurt Benirschke. Forty-five years later, chromosome sequencing achieved the ultimate resolution by defining chromosome disease in terms of base pairs. It relies on sorting and collecting chromosomes in fluid suspension by flow cytometry and, like chromosome painting, on DNA amplification of the sorted samples. Chromosome sorting is currently the most precise method used for measuring chromosome and genome size. Ten thousand cleanly-sorted chromosomes provide sufficient DNA for Next Generation sequencing in both plants and animals. Our collaborations demonstrate the potential of this approach. For example, sequence from sorted gorilla Y chromosomes reveal, remarkably, that human and gorilla Ys are similar and that chimpanzee has lost half the Y genes present in both the other species. In two species of anole lizards, one with large heteromorphic sex chromosomes and the other with small homomorphic sex chromosomes, sequence from the ancestral Y chromosome has been fused with sequence from three microchromosomes to form a large Y chromosome. Sequencing B chromosomes in two deer species demonstrate the inclusion of different

Single-nucleotide polymorphism (SNP)-based noninvasive prenatal testing (NIPT) can be used to screen for a subset of subchromosomal deletions (<10 Mb) associated with severe clinical phenotypes. Over a one-year period of test referrals to Natera, Inc. (San Carlos, CA), 74,938 tests were performed for fetal 22q11.2 deletion syndrome (22qdels) and 39,678 for 1p36, cri-du-chat, Prader-Willi, and Angelman microdeletion syndromes. The screen-positive rate (SPR) for 22qdels was 0.38%. Based on follow-up information on 54% of these cases, the false-positive rate (FPR) was 0.33% and the positive predictive value (PPV) was 15.7%. Six maternal 22qdels were identified. Similarly, for the other four microdeletion syndromes combined, the SPR was 0.59%, there was a 58% positive test follow-up information rate, 0.56% FPR, and 5.3% PPV, with zero maternal deletions. A minimal estimate for the prevalence was approximately 1/1,255 for 22qdels and 1/1,464 for 1p36, cri-du-chat, and Angelman syndromes combined. A protocol improvement was prospectively evaluated. This included reflex re-sequencing of positive call cases at a higher depth of read, which increased the PPV for 22qdels to 44.2% and lowered the FPR to 0.07%. For the other microdeletion syndromes combined, the PPV increased to 31.8%, and the FPR was reduced to 0.07%. Given that the original study was carried out on a high-risk cohort, modelling was performed to estimate PPVs for average-risk populations. The results show that the PPVs would remain similarly high.

The results of this study demonstrate that these microdeletions are relatively common in the test referral population, SNP-based screening is effective and the performance is improved with high-depth resequencing. Invasive testing with microarray analysis is indicated for all women with positive microdeletion screening test results.

3.P7

Detection of cryptic chromosomal abnormalities and fetoplacental discrepancies after cytogenetic study of both placental layers

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The study of chorionic villi samplings (CVS) by conventional cytogenetics reveals chromosomal abnormalities in 12% of cases, and in 1-2% of pregnancies mosaicism is observed. In order to increase the diagnostic yield, new molecular techniques that offer higher resolution have been developed, such as chromosomal microarray-based analysis (CMA). Similar to cytogenetically visible chromosomal abnormalities, cryptic chromosomal abnormalities (CCA) may also be presented as confined placental mosaics, leading to misinterpretations. The purpose of the present work was to establish the frequency of CCA and confined placental mosaicism of CCA in CVS, and to evaluate the reliability of the strategy used.

We performed CMA in CVS of 90 pregnancies with normal karyotype or a balanced familial rearrangement, in both trophoblast and mesenchyme. Thirty-three percent of them belonged to the pathological group as they were referred for ultrasound abnormalities, and the remainder 67% was the control group referred mostly due to abnormal first trimester screening.

The overall frequency of reportable non-mosaic CCA was 7,8%, but only a 6,7% with phenotypic consequences, and in 1% of samples a CCA was only found in trophoblast. Most of the CCA were diagnosed in the control group.

Although the cohort presented is relatively small, it seems that the rate of CCA is higher than other previous prenatal diagnosis reports. Placental mosaicisms of CCA present a frequency similar to that of cytogenetically visible chromosomal abnormalities during the first trimester of pregnancy. However, CCA do not seem to be generally associated with ultrasound abnormalities in the first trimester of gestation. The strategy used is reliable for the detection of placental mosaicisms of CCA.

Partial results from the case study have been previously presented (Eur J Hum Genet 2015, Vol 23 Supp 1, 55)

3.P8

Cystic hygroma in fetuses with normal and aneuploid karyotypes

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Introduction

Cystic hygroma is a vascular-lymphatic malformation and can occur either as an isolated finding or as a part of syndrome (chromosomal abnormality; Noonan, Smith–Lemli–Opitz, Escobar, Fanconi pancytopenia syndromes). The incidence of cystic hygroma is about 1:1000–1:6000 births.

Objective: The analysis of the ultrasonographic and karyotyping data of fetuses with cystic hygroma.

Methods

A complete fetal sonographic examination was performed, followed by fetal karyotyping. For cytogenetic analysis of biopsy samples a direct method of processing the villi was used and for fetal blood a halfmicromethod.

Results

A total of 48 (0,7%) fetuses with cystic hygroma were identified in 6919 high-risk pregnancies referred for fetal karyotyping. Cystic hygroma was diagnosed in 50% of the cases at 12–14 weeks of gestation.

A karyotype abnormality occurred in 29 (60,4%) of fetuses, including trisomy 21 (20,7%), monosomy X (62,1%), trisomy 18 (10,3%), and other (6,9%). Despite well-known association between maternal age and frequency of aneuploidy, there were only 4 (13,8%) pregnant women over 35 years among diagnosed aneuploid cases. The proportion of pregnant women under 25 years was 2 times higher than in other age groups among euploid fetuses with cystic hygroma.

Besides hygroma, associated congenital anomalies were observed in 12 (63,2%) of 19 fetuses with normal karyotype. Among them the most frequently diagnosed were cardiac abnormalities – 10 (83,3%) cases.

Conclusion

Cystic hygroma is associated with high rates of karyotype abnormality, major congenital malformations. Monosomy X was the most common form (62,1%) among aneuploid cases of cystic hygroma (n = 29). Only 7 (14,6%) fetuses were euploid and without ultrasonographic detectable structural anomalies.

3.P9

Transfer of aneuploid embryos following preimplantation genetic diagnosis the added value of a haplotyping based genome wide approach

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Introduction

Embryo selection for monogenic diseases has been mainly performed using targeted disease-specific assays. Recently we have developed haplarithmisis, which is based on genomic haplotype reconstruction of cell(s) biopsied from embryos. This provides information not only about the inheritance of Mendelian disease alleles, but also about numerical and structural chromosome anomalies and