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Young mothers and higher incidence of maternal meiosis-I non-disjunction: Interplay of environmental exposure and genetic alterations during halt phase in trisomy 21

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ABSTRACT

Trisomy 21 is a genetic condition caused when chromosomes fail to separate during meiosis. We have studied conventional karyotype and QF-PCR using STR markers with high polymorphism and heterogeneity and the results were analyzed, to determine the paternal and meiotic origin of trisomy 21. This study was conducted using a detailed questionnaire to include: paternal, maternal, clinical and family history for various confounding factors such as age and regional environmental exposures where the parents resided. Out of 120 samples 95% (N = 114) were of maternal origin, including 92% (N = 105) of meiosis 1 errors and 8% (N = 9) meiosis 2 errors. Paternal origin accounted for 5% (N = 6) and were all due to meiosis-I errors. The higher incidence of maternal meiosis-I observed in the present study suggests that human trisomy 21 non-disjunction is a result of multiple factors contributing to the origin of the genetic condition.

1. Introduction

The possibility of giving birth to a baby with a congenital defect is a major fear among women due to increasing number of such reports [1]. Hence it becomes important to understand the underlying mechanisms of birth defects. The term "trisomy 21" refers to a genetic condition arising due to non-segregation of the chromosome pair during meiosis, popularly known as 'Down Syndrome' (DS). Constitutional free trisomy 21 accounts for 95%, while translocation and mosaicism account for 5% of DS cases [2,3]. The incidence of non-disjunction has also been studied for parental and meiotic origin; more than 90% of recorded cases are of maternal origin i.e., maternal meiosis I [MMI] and Maternal meiosis II [MMII] [4,5].

Meiosis I [MI] occurs when the chromosome pairs fail to separate. Meiosis II [MII] happens when the chromatids fail to separate, and these occur around conception. Understanding the effect of maternal age and environmental factors on the meiotic origin of trisomy 21 could shed light on the stage at which maternal exposures may have taken place if any, apart from the possibility of spontaneous occurrence.

Meiosis I originates around 11–12 weeks of gestation where pairing at the synapse and recombination occurs (prophase I) and halts until ovulation. This "Halt Phase" can extend from 10 to 50 years. At ovulation, the oocyte which is in MI phase enters metaphase II until fertilization to complete the meiotic phase, unlike spermatogenesis which starts at puberty followed by cells entering meiosis phases without delay. This halt phase in oocyte formation may be responsible for increased prevalence of maternal nondisjunction and other meiotic errors [6].

The maternally derived trisomy 21 cases reported are with high mean maternal age for MI and MII errors (MMI 29.5 ± 6.8; &MMII 32.0 ± 7.3, [5], (MMI 31.06 ± 6.69 and MMII 33.84 ± 4.93, [7]. Compared to this, our study indicates a lower mean maternal age (MMI 24.96 ± 4.17 and MMII 27.78 ± 3.00) which raises significant concern regarding the origin of meiotic genetic error in the absence of history of older maternal age. There are certain environmental factors such as toxicants, nutrition, and stress known to induce genetic alteration which are inherited and manifested in the germ cells of the progeny, a phenomenon called transgenerational inheritance. The possibility of transgenerational inheritance of genetic changes is considered in addition to ageing [8].

Hence, like other genetic conditions, DS is expected to be the outcome of genetic, epigenetic, environmental, and stochastic origin making it complex to discriminate each stressor's individual contribution.

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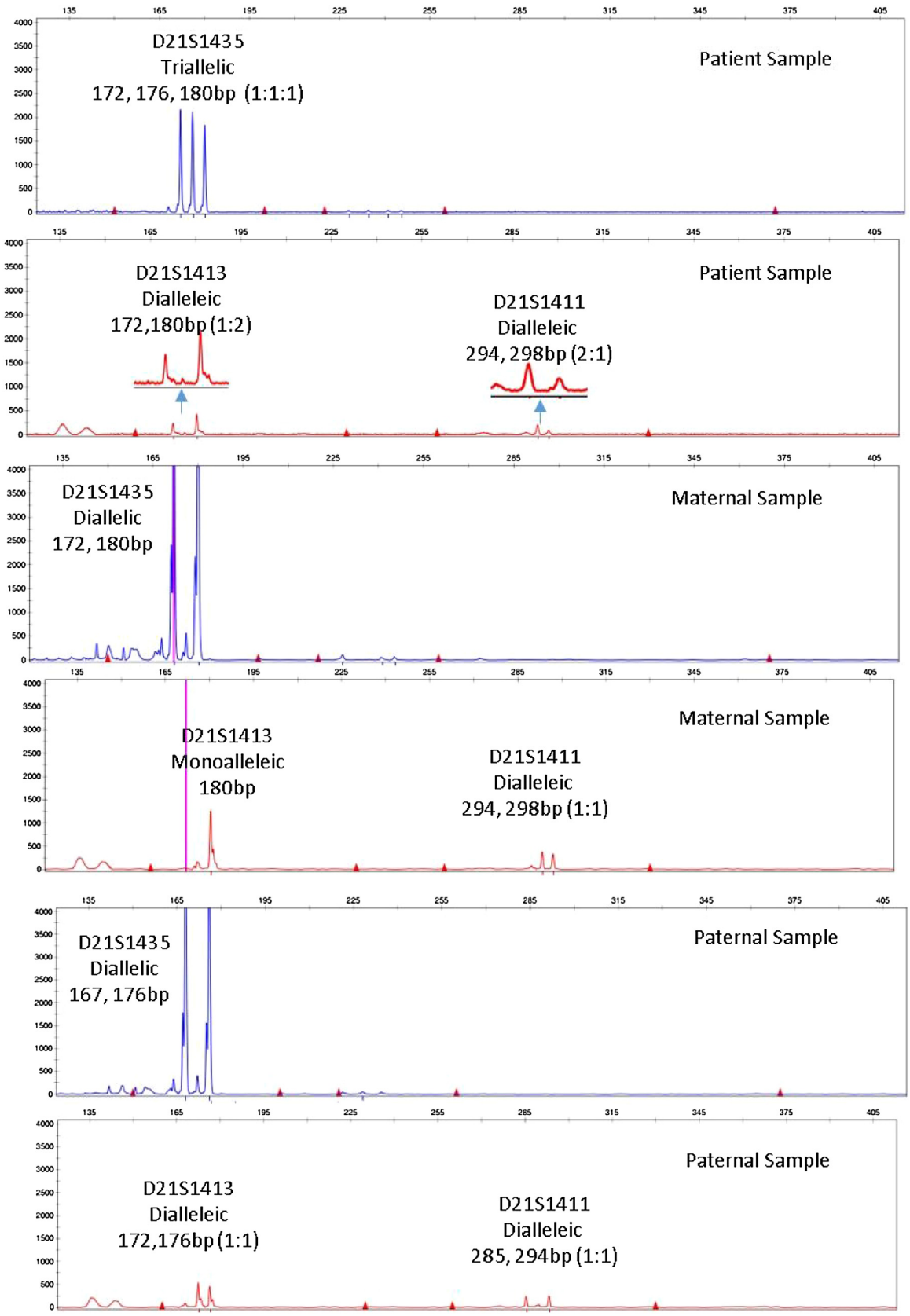

Fig. 1. Figure showing the meiosis one origin of non-disjunction in the patient sample. The marker D21S1435 is showing a triallelic pattern with equal ratio of each alleles representing trisomy of 21st chromosome similarly D21S1435 and D21S1411 marker shows a diallelic trisomy pattern. The alleles 176 of D21S1435 was inherited from father while the remaing two alleles, 172 & 180, were inherited from maternal sample confirming the maternal origin of non-disjunction. The allele 180 of D21S1413 and the allele 294 & 298 was inherited from maternal DNA confirming maternal origin.