Journal of Molecular and Genetic Medicine

Chetta et al., J Mol Genet Med 2018, 12:4
DOI: 10.4172/1747-0862.1000374

Case Report Open Access

De novo Atypical Chromosome Translocation 46, XY, t(4;13)(q12;p12)dn in Prenatal Diagnosis

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Abstract

Apparently balanced reciprocal translocations are a common type of chromosome rearrangements with an estimate incidence range from about 1 in 500 to 1 in 625 human newborns. Rearrangements were found both in clinically unaffected individuals and patients with phenotypic abnormalities. Most are inherited, but approximately one in five are *de novo* events and introduce a risk of abnormal phenotype in 6.1% of prenatal genetic counseling.

Keywords: Chromosome; Prenatal diagnosis; Genetic material

Introduction

In the present case, we reported the analysis results of the proband for prenatal diagnosis using G-banded karyotype, C-banding, nuclear organizer regions (Ag-NOR) staining and whole genome array methodology (CGH). We documented a *de novo* atypical balanced 46,XY,t(4;13)(q12;p12)dn with an unusual length of chromosome 13 (chr13) satellite stalk [1-5]. Initial chromosome analysis from amniotic fluid cultures samples were performed by standard G-banding of metaphase chromosomes. The karyotype analysis is extended on both parents culturing peripheral blood mononuclear cells in order to elucidate the chromosome rearrangements.

Karyotypes of proband and parents were established according to the International System for Human Cytogenetic Nomenclature (ISCN 2013) [6]. In addition, the proband rearrangement was analyzed using, C-banding, silver staining (Ag-NOR) for nucleolar organizing regions to highlight the unusual length of chr13 satellite stalks. Finally, the Cytogenetic analysis was completed using whole genome array CGH methodology.

Chromosome preparation

Karyotyping was executed on metaphase chromosome preparations from amniotic fluid obtained via amniocentesis (proband) and peripheral blood lymphocytes (parents) using standard G-banded metaphases (400-band level for proband and 550 band resolution for parents) by modifications of the trypsin (GTL) and Giemsa/Leishman staining following standard procedure. Chromosome analysis was accomplished twice on amniotic fluid collected on two separated occasions following the European Cytogenetic guideline [7,8]. Cytogenetic analysis was thorough on amniotic fluid by C-banding and Ag-NOR staining following standard methods. G-banded, AgNOR-stained and C-banding were examined under a light microscope attached to a computerized analysis system to capture grayscale. *tiff images (Zeiss Axio Imager.M2 and digital camera Cool Cube 1 MetaSystems).

Array data and confirmatory analysis

Array data set was analyzed using the Bluefuse Multi software (BlueGnome Ltd. Cambridge, UK), and the reporting threshold was set at 200 kb. All called imbalances detected and copy number changes were compared to known aberrations listed in public available databases - ENSEMBL (Ensembl: http://www.ensembl.org), DECIPHER (http://decipher.sanger.ac.uk) and the Database of Genomic Variants (DGV, http://projects.tcag.ca/variation/) - using NCBI136/hg18 UCSC or GRCh37/hg19 assemblies and were further aligned with the in-house database

Case Report

The proband was a female without detectable fetal morpho-structural evidences or functional alterations after routine ultrasound screening. The age of mother and father are respectively 38 and 29 years old without apparent phenotypic abnormalities. There was no documented family history of known genetic disorder and the parents were in a non-consanguineous marriage. Parents already had two children of 18-month-old and 3-year-old, respectively, without evidence of genetic disorder. The cytogenetic study using G-banded karyotype in proband revealed an atypical translocation 46, XY, t(4;13)(q12;p12)dn with a peculiar length of satellite stalks of chr13. This unusual length of satellite stalks was highlighted using Ag-NOR staining. As shown by AgNOR staining the satellites of chr13 range in size from double to triple (panel. F). The abnormal length of satellite stalks and the consequent distance between the boundaries of the chr13 and chr14 makes the cytogenetic investigation extremely complicated. After obtaining informed consent, the cytogenetic analysis was extended to the parents. Parental origins of the translocation were excluded analyzing karyotyping of both parents at a minimum resolution of 550 band following the European Cytogenetic guideline and defining as *de novo*, the chromosome rearrangements identified. Finally, using array CGH the absence of genetic material lack in proband was confirmed and the non-appearance alterations in parents, corroborating the evidence of *de novo* balanced chromosomal translocation. However, CGH array investigation showed the presence of approximately 1.7 Mb paternal duplication which includes glutamate ionotropic receptor kainate type subunit 2 gene (*GRIK2*) on chr 6 located onto region 6q16.3 (102,337,371-104,071,324). A defect *GRIK2* gene was associated with autosomal recessive mental retardation while there are no clinical evidences attributable to gene duplications (Figure 1).

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Received October 24, 2018; **Accepted** November 05, 2018; **Published** November 08, 2018

Citation: Chetta M, Di-Matteo L, Russo M, Sodano E, Festa M, et al. (2018) *De novo* Atypical Chromosome Translocation 46, XY, t(4;13)(q12;p12)dn in Prenatal Diagnosis. J Mol Genet Med 12: 374 doi:10.4172/1747-0862.1000374

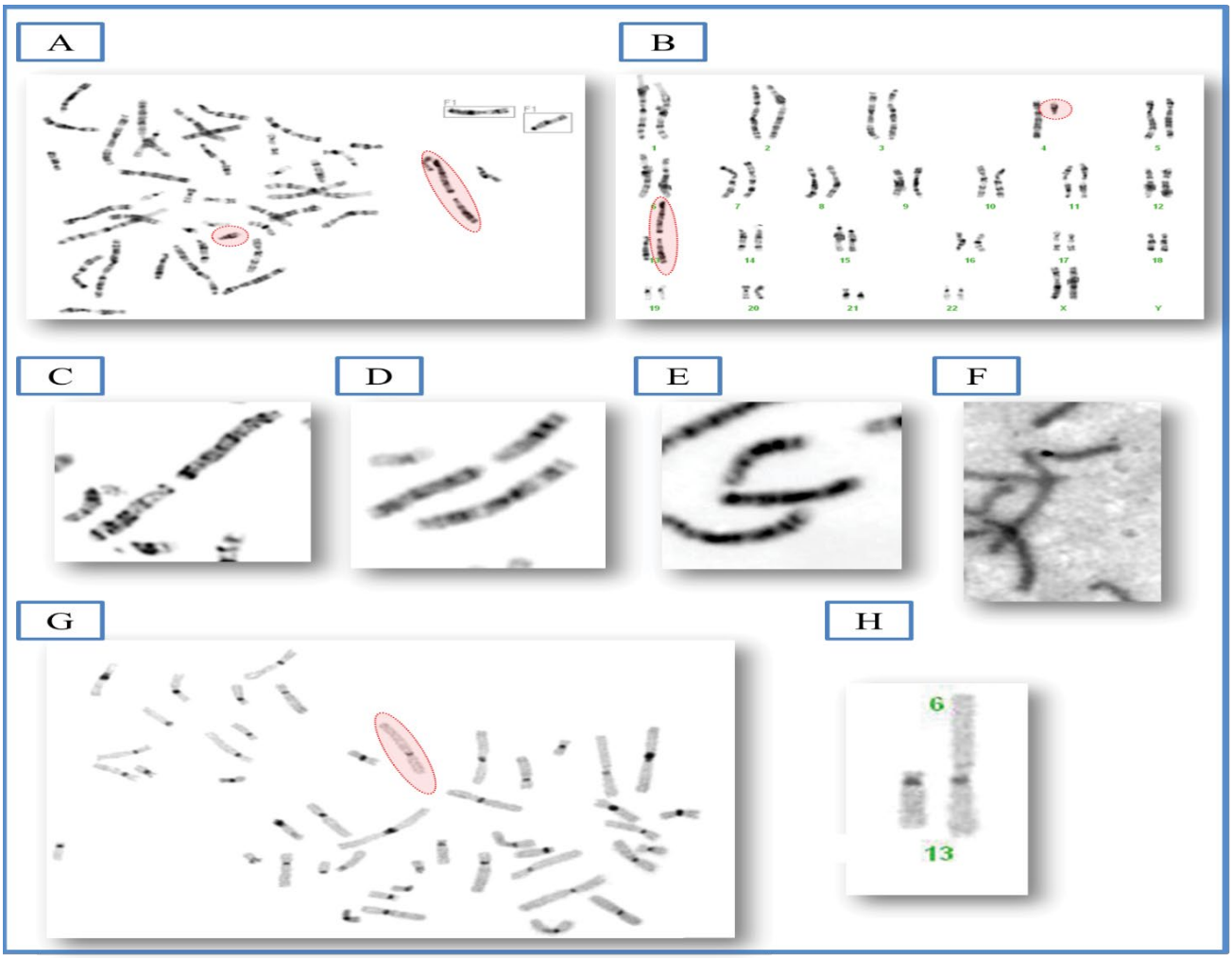

Figure 1: GTG-banding karyotype of amniotic fluid at the 400-band level. The translocation (4;13)(q12;p12)dn are highlighted by red circle (Panel A). Full proband karyogram (Panel B). Detail of translocation in three different metaphases where is clearly visible the peculiar length of satellite stalks of chromosome 13 (Panels C, D, E). Detail of translocation using Ag-NOR (Panel F). Proband metaphase and detail of translocation (4;13)(q12;p12)dn using C-banding (Panel G, H).

Discussion

Although the specific translocation 46, XY, t(4;13)(q12;p12)dn was not described previously there are some indications concerning the region 4q12 and 13p12. In particular the region 4q12 was associated to different kind of tumors. In literature, are reported deletions, duplications and inversions involving the 4q12 region and other portions of the 13 chromosomes (13q14, 13q22, 13q33). In these cases, the patients are affected by lymphoid neoplasms, Hypereosinophilic syndrome (HES), breast cancer and Central nervous system (CNS) tumors. The region 13p12, in the case of deletion or duplication inversion, was associated to prostate cancer [9]. Currently karyotype analysis is the most widespread routine genetic test in the world and continues to offer always new information. Autosomal reciprocal balanced translocations occur in approximately 0.1% of newborns and the estimated frequency of *de novo* balanced rearrangements in the general population from prenatal diagnosis is 0.0283% [10-12].

Conclusion

In our case, results should be interpreted carefulness because we have not information about a possible role of this translocation. We do not exclude the possible transposition of genetic material in active chromatin region, resulting in altered gene expression related to position effect, or presence of distal regulatory i.e., enhancer or silencer elements. Our case should require a cautious proband's follow up to observe possible abnormal phenotype and understand potential molecular features in order to classify specific disease by mapping possible gene breakpoints or position effect.

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